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STEROID TOTAL SYNTHESIS—HYDROCHRYSENE APPROACH—XVI[1]

RACEMIC CONESSINE, PROGESTERONE, CHOLESTEROL, AND SOME RELATED NATURAL PRODUCTS

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Abstract—The synthetic work disclosed herein all stems from the previously described tetracyclic hydroxy ketone **4**. In the present study some minor improvements in the preparation of **4** are given.

Part I. The synthesis of *dl*-conessine (**5**) was attacked in two phases. Phase one involved introduction of the 3-dimethylamino group as follows: the alcohol **10**, produced by degradation of natural conessine, was oxidized to the ketone **11** which was converted into the α,β-unsaturated ketone **9** by a conventional bromination-dehydrobromination sequence. The key transformation involved conversion of **9**, by reaction with dimethylamine, into the dienamine **8** which, on treatment with sodium borohydride and acetic acid, was selectively reduced to conessine. In the course of this phase of the work, a new, efficient method for degrading conessine to the α,β-unsaturated ketone **9** was developed; the steps involved conversion of the readily available *N*-desmethylconessine **6** (X=H) into the *N*-chloro substance **6** (X=Cl), dehydrohalogenation to give the Schiff base **7**, and finally hydrolysis of **7**.

Phase two involved the conversion of the hydroxy ketone **4** into **10**. Reaction of **4** with methyllithium afforded the diol **12** (R=H) which was selectively acetylated to give **12** (R=Ac) and this, in turn, was dehydrated with phosphorus oxychloride and pyridine. The resulting product, mainly the acetoxy olefin **13**, was ozonized to give the diketone **14**. On treatment with potassium hydroxide **14** underwent intramolecular aldol condensation to give the unsaturated ketone **15**, hydrocyanation of which afforded a mixture of the 13α (**16**) and 13β (**17**) cyano ketones. The former could be dehydrocyanated by pyrolysis, regenerating unsaturated ketone **15** which could be rehydrocyanated to give more of the desired epimer **17**. These epimeric cyano ketones were submitted to a number of reactions involving the formation of heterocyclic substances, which transformations served to provide proof of their configurations. Attempts to produce the pyrrolidino ring by direct reduction of the cyano ketones were successful in the 13α but failed in the 13β series. Therefore the 13β cyano ketone was converted to the ketal **24** which was reduced with lithium aluminum hydride to give a mixture of the imine **25** and amine **26**. The latter substance, on acid hydrolysis, was converted into the enamine **27**. Catalytic hydrogenation gave the pyrrolidino compound **28** which, on methylation, afforded the desired alcohol **10**. Finally this racemic material was carried through the sequence described above (phase one) to give racemic conessine.

Part II. Racemic progesterone (**31**) was obtained from the aforementioned cyano ketal **24** by selective reduction of the cyano group with LAH to the imino compound which could be treated directly

* It is with real pleasure that we submit this account of our recent steroid total synthesis studies in honor of Sir Robert Robinson. The subject, we feel, is particularly appropriate for the occasion since Sir Robert is well recognized as the father of the field.

[1] Part XV, W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike and W. Bartmann, *J. Amer. Chem. Soc.* **85**, 1409 (1963).

by the Wolff-Kishner method to give the 13β-methyl ketal **33**. Oxidation with Sarett reagent afforded the ketone ketal **35** which, on treatment with bromine in acetic acid, underwent concomitant bromination at C-4 and cleavage of the ketal residue. The resulting bromo ketone, on dehydrohalogenation with benzyltrimethylammonium mesitoate, gave *dl*-progesterone. It is to be noted that acid hydrolysis of the ketone ketal **35** afforded *dl*-pregnane-3,20-dione. Similarly hydrolysis of the ketal **33** gave *dl*-pregnan-3α-ol-20-one.

Some of the reactions described above were applied to the 13α-cyano ketone, and in this way the 13α,17α diketone **39**, among other products, was produced.

In preliminary experiments directed toward the synthesis of *dl*-cholesterol, the 13β-cyano ketone **17** was treated with isohexylmagnesium bromide to give the adduct **40**. Attempts to utilize this product, however, were abandoned when it was found that neither the dehydration product **41**, nor the lactone **42** (formed by the action of phosphoric acid on **40**), could be selectively reduced to the imine or aldehyde respectively for conversion to the 13β-methyl compound. Some attempts also were made to elaborate the side chain *via* the ethoxyacetylene adduct **44**, which was converted to the carboxylic acid derivatives **45** and **46**.

The successful approach involves reaction of the aforementioned hydroxy ketone **47** with isohexyllithium to give, after selective acetylation, the hydroxy acetate **48**. Dehydration with phosphorus oxychloride and pyridine followed by catalytic hydrogenation and saponification afforded *dl*-5β-cholestan-3α-ol (**50**, R = H) along with some of the 20-iso compound. Oxidation of **50** (R = H) gave *dl*-5β-cholestan-3-one (**51**), which was converted by the usual bromination-dehydrobromination sequence into *dl*-Δ^4-cholesten-3-one (**52**). This last substance was transformed, by the action of sodium borohydride and potassium hydroxide on the enol acetate, into *dl*-cholesterol (**32**).

Part III. Considerable attention has been given to an alternative approach to 18-substituted steroids, but this work was terminated short of completion.

Reaction of methacrylonitrile with the furfurylidene derivative **53** of the hydroxy ketone **4** gave the adduct **54**. It was hoped to use this product in a scheme that was elaborated successfully on the model substance **56** which was converted into **63** by the following sequence: **56** → **57** → **58** → **59** (R = OH) → **59** (R = CH_3) → **60** (R = Ac) → **60** (R = H) → **61** → **62** → **63**. However, the early stages of the work in the tetracyclic series failed. Attention was turned to the use of substances derived from **54** by ozonization, e.g., the triacid **72** ($R^1 = R^2 = H$, $R^3 = OH$). After some preliminary model work leading to substances depicted in formulas **64–71**, the aforementioned triacid was converted, by esterification followed by selective saponification, into the diacid ester **72** ($R^1 = H$, $R^2 = CH_3$, $R^3 = OH$). This was transformed into the diketo ester **72** ($R^1 = Ac$, $R^2 = R^3 = CH_3$) which, on Baeyer-Villiger oxidation, afforded **73** ($R^1 = R^3 = Ac$, $R^2 = CH_3$). All attempts to effect selective hydrolysis of the acetate residues led to the lactone **74**. A number of transformations of this lactone were studied: hydride reduction afforded **75** (R = H); oxidation with Sarett reagent followed by ketalization afforded **76** which could be reduced to the diol **77** (R = H), but we were not successful in obtaining the C-13 aldehyde residue, or an appropriate form, e.g., **78**, for closure of ring D. Some further studies on attempts to produce the diolefinic compound **81** are also described.

IN previous papers of this series we have described the total synthesis of racemic forms of the naturally occurring steroids: epiandrosterone,[2] 3β,11β-dihydroxyandrostan-17-one,[3] testosterone,[4] and aldosterone.[1] The starting point for each of these syntheses was the tetracyclic ketone **2**, which is readily accessible from 5-methoxy-2-tetralone by two successive (*in situ*) Robinson annelation reactions, first with ethyl vinyl ketone and then with methyl vinyl ketone.[5] The insoluble ketol **1**[6] is simply filtered from

[2] W. S. Johnson, B. Bannister and R. Pappo, *J. Amer. Chem. Soc.* **78**, 6331 (1956).

[3] W. S. Johnson, R. Pappo and W. F. Johns, *J. Amer. Chem. Soc.* **78**, 6339 (1956).

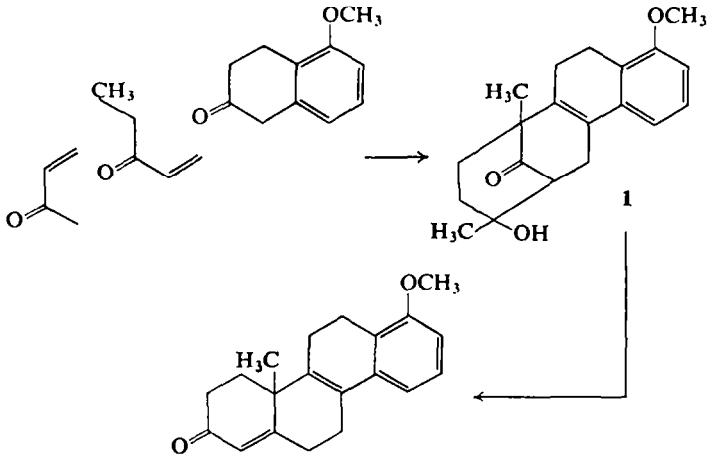
[4a] W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *J. Amer. Chem. Soc.* **78**, 6354 (1956); [b] W. S. Johnson, W. A. Vredenburgh and J. E. Pike, *Ibid.* **82**, 3409 (1960).

[5] W. S. Johnson, J. Szmuszkovicz, E. R. Rogier, H. I. Hadler and H. Wynberg, *J. Amer. Chem. Soc.* **78**, 6285 (1956).

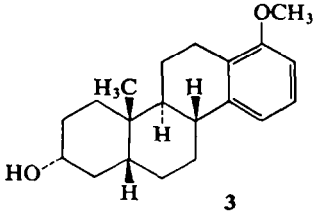
[6] W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, *J. Amer. Chem. Soc.* **82**, 614 (1960).

the reaction mixture, and on treatment with sodium methoxide it is smoothly converted into **2**.

In the present paper we set on record the details of further studies which have culminated in the synthesis of conessine (Part I) and of progesterone and cholesterol, including some other related natural products (Part II), from the tetracyclic ketone **2**. Part III consists of a report of a study of an alternative approach to 18-substituted steroids which has been terminated short of completion. All of this synthetic work



utilizes as an intermediate the 18-nor-D-homo steroid **4** which is available[4b] from the substance **2** by the following stereoselective steps: hydrogenation of the 4,5- (steroid numbering) double bond over palladium to give the A/B *cis* isomer, reduction of the keto group with sodium borohydride in isopropyl alcohol (an improved method described in the present work) giving the 3α-hydroxy compound, and reduction of the 8,9- (styrene) double bond with potassium and alcohol in ammonia to give the A/B/C *cis-anti-trans* anisole compound **3**. Forced Birch reduction of the aromatic nucleus of **3** with lithium-ammonia-alcohol, followed by acid hydrolysis of the enol ether, and hydrogenation of the unsaturated ketone mixture over palladium-on-carbon afforded **4**. In the present work we explored the use of potassium instead of lithium in the Birch reduction of the anisole compound **3**. This study was prompted by the



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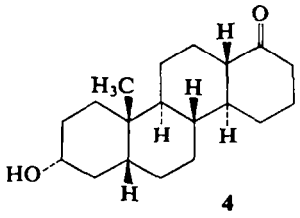

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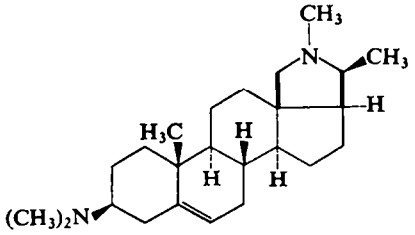
disclosure[7] that the apparent superiority of lithium over potassium (and sodium) in such reactions was due mainly to the relatively rapid consumption of the latter metal by reaction with alcohol, and that this undesired reaction is catalyzed by traces of iron

[7] H. L. Dryden, Jr., G. M. Webber, R. R. Burtner and J. A. Cella, *J. Org. Chem.* **26**, 3237 (1961).

present as an impurity in the ammonia. Indeed with appropriately purified ammonia, satisfactory reduction of **3** with potassium was realized on a 40-g scale. The product was submitted to the further steps described above, and the pure perhydrochrysenone **4** was isolated, after purification *via* the semicarbazone, m.p. 266–267°, in 31% over-all yield. When the two aforementioned potassium-in-ammonia reduction steps were combined, without isolation of **3**, it was more difficult to obtain **4** in a pure condition.

PART I—CONESSINE

The adrenal hormone, aldosterone, was the first steroid to be totally synthesized before it was prepared by partial synthesis. By now there is only one other comparable example, namely conessine (**5**). Thus three total syntheses of this alkaloid were completed[8] before an authentic partial synthesis from 3β-acetoxy-Δ^5-pregnen-20β-ol was developed.[9] The present paper records the details of our total synthesis which has already been delineated in preliminary form.[8a]



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Since we planned to start with the substance **4**, the synthetic project resolved itself into two phases: first, the contraction of ring D and construction of the heterocyclic ring E; and, second, the introduction of the dimethylamino group at C-3. We chose to study the latter problem first in the hope that 5β-conanin-3α-ol (**10**), which is available by degradation of conessine,[10] could in some way be reconverted to conessine, in which case the alcohol **10** could serve as an identification as well as a possible relay point in the complete synthesis. An account of the details of this study follows.

Introduction of the 3-*dimethylamino group*[11]

Conversion of **10** → **5**. The results of previous studies directed toward the stereoselective preparation of a 3β-amino steroid by a direct substitution process, e.g., reaction of dimethylamine with a 3β-*p*-toluenesulfonate of a Δ^5-unsaturated steroid,[12] were not promising. Therefore we elected to study the selective reduction of the dienamine

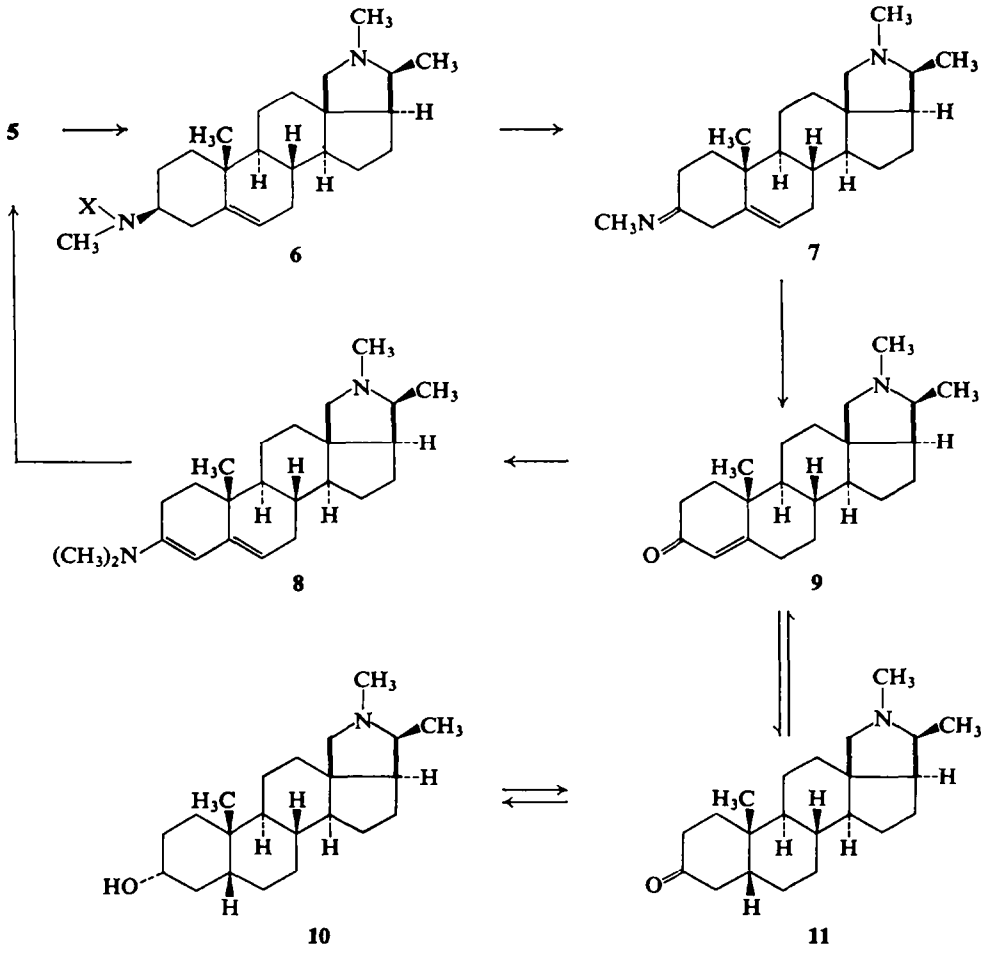
[8] [a] J. A. Marshall and W. S. Johnson, *J. Amer. Chem. Soc.* **84**, 1485 (1962); [b] G. Stork, S. D. Darling, I. T. Harrison and P. S. Wharton, *Ibid.* **84**, 2018 (1962); [c] W. Nagata, T. Terasawa and T. Aoki, *Tetrahedron Letters* 869 (1963).

[9] D. H. R. Barton and A. N. Starratt, *J. Chem. Soc.* 2444 (1965). In this article the previously reported partial synthesis of conessine is invalidated.

[10] R. Pappo, U.S. Patent No. 2,913,455 (1959); R. Pappo and J. Baran, U.S. Patent 2,912,432 (1959); R. Pappo, U.S. Patent No. 3,063,987 (1963).

[11] For a preliminary report, see W. S. Johnson, V. J. Bauer and R. W. Franck, *Tetrahedron Letters* 72 (1961).

[12] E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.* **81**, 5209 (1959).



8 which promised to be readily accessible[13] from Δ^4-conanen-3-one (9). The unsaturated ketone 9 had been produced from conessine by Pappo[10] who devised an ingenious sequence of reactions involving, as the key step, the base-catalyzed internal displacement of the C-3 quaternary ammonium salt derived from 6-ketodihydroconessine to give the 3,5-cyclo-6-keto system. After reduction to the hydroxy compound, a retro *i*-steroid rearrangement, followed by oxidation, yielded 9. In the present work a more direct approach was developed based on the Ruschig method of producing ketones from amines.[14] According to the reported procedure,[15] conessine was converted, by selective reaction with cyanogen bromide, into *N*-cyanoisoconessimine (6, X=CN), which, on treatment with potassium hydroxide, underwent hydrolysis and (on acidification) decarboxylation to yield isoconessimine (6, X=H) in 43% over-all yield. Our purified product melted at 72·5–74° as compared with the reported value of 92°.[15] This desmethyl compound, on treatment with t-butyl hypochlorite, was converted into the *N*-chloro derivative 6 (X=Cl). Treatment with 0·1 M ethanolic

[13] Cf. F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.* **75**, 1918 (1953).
[14] H. Ruschig, W. Fritsch, J. Schmidt-Thome and W. Haede, *Chem. Ber.* **88**, 883 (1955).
[15] S. Siddiqui and R. H. Siddiqui, *J. Indian Chem. Soc.* **11**, 787 (1934).

sodium ethoxide effected dehydrohalogenation to give the unsaturated imine **7** (or the Δ^4 isomer) which, without isolation, was hydrolyzed with sodium acetate in acetic acid[13,16] to give Δ^4-conanen-3-one (**9**). This product was shown by IR spectroscopic and mixture m.p. comparisons to be identical with a sample prepared by the Pappo method.[17] The over-all yield of chromatographed unsaturated ketone **9** was 38%. When *N*-chlorosuccinimide[18] was used in place of t-butyl hypochlorite and the concentration of sodium ethoxide in the dehydrohalogenation step was increased to saturation, the yield was raised to 64%.

When a mixture of the unsaturated ketone **9**, benzene, magnesium sulfate, a trace of *p*-toluenesulfonic acid, and a large excess of dimethylamine was sealed in a tube and agitated for several days at ambient temperature, the extremely air-sensitive, crystalline enamine **8**, m.p. 146–151°, was produced in 54% yield. Purification by recrystallization was difficult, but with careful exclusion of air from the solvents it was possible to obtain a pure specimen, m.p. 150–151°.

Some of our studies of the reduction of dienamine systems like **8** with sodium borohydride and acetic acid have already been published,[19] and suggestive evidence has been advanced to support the hypothesis that the reaction proceeds by attack of hydride (at C-3) on the C-4 protonated form of the dienamine.[19,20] In the present study the dienamine **8** was in this way converted into conessine in 36% yield. This yield can almost certainly be improved, because since the present work we have found[19] that a modified procedure, involving the use of diglyme as solvent, results in the analogous reduction of 3-*N*-pyrrolidyl-3,5-cholestadiene to give the corresponding cholesteryl amine in 60% yield. The improved procedure has not yet been tried in the conessine series.

Prior to the aforementioned work in the conessine series, an exploratory study was carried out with Δ^4-cholesten-3-one, which was converted, by the method described above, into 3-dimethylamino-3,5-cholestadiene, m.p. 97–99°. This dienamine was in turn reduced with sodium borohydride and acetic acid to give the known[21] 3β-dimethylamino-Δ^5-cholestene.

With the conversion of the conanenone **9** into conessine (**5**) in hand, we next turned our attention to the transformation of the alcohol **10** into unsaturated ketone **9**, so as to complete the links in the over-all synthetic sequence **10** → **5**. The general plan was to prepare the alcohol **10** from the unsaturated ketone **9**, then to study the reconversion of the former into the latter. Pappo[10] had already described the preparation of **10**. The first step involved catalytic hydrogenation of the perchlorate salt of **9** to give 5β-conanin-3-one (**11**), m.p. 133–134°, in unstated yield. In the present work the hydrogenation of **9** over Pd-C in benzene–ethanol with a trace of added potassium hydroxide[22] afforded the ketone **11**, m.p. 127–129° (130·5–131° after further purifica-

[16] Cf. M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.* **75**, 5927 (1953).

[17] We wish to thank Dr. R. Pappo for providing us with this material (see Ref. 10).

[18] H. Ruschig and J. Schmidt-Thome, U.S. Patent No. 2,697,107 (1954). See also Ref. 12.

[19] J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963).

[20] Cf. J. Schmitt, J. J. Panouse, A. Hallot, P-J. Cornu, P. Comoy and H. Pluchet, *Bull. Soc. Chim. Fr.* **30**, 809 (1963).

[21] D. P. Dodgson and R. D. Haworth, *J. Chem. Soc.* 67 (1952).

[22] Cf. W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister and H. Wynberg, *J. Amer. Chem. Soc.* **78**, 6289 (1956).

tion) in 68% yield. Pappo [10] effected reduction of the ketone **11** with LAH to give the alcohol **10**, m.p. 132°. Using lithium tri-t-butoxyaluminum hydride, we obtained the alcohol **10**, m.p. 127–131°, in 92% yield. A purified specimen melted at 130·5–131°, resolidified, and remelted at 151–151·5°.

The oxidation of the alcohol **10** to the ketone **11** was complicated by the presence of the amino group. The action of *N*-bromoacetamide gave a non-basic tarry product presumably resulting from attack on the pyrrolidine ring. An attempt to use Jones reagent[23] led to precipitation of the salt of the amino alcohol and inhibition of further reaction. When the alcohol was treated with a mixture of chromium trioxide, acetic acid, and aqueous sulfuric acid, the desired ketone **11** was produced in 55% yield. This yield was raised to 80% in the racemic series (see below) by adding some perchloric acid to the reaction mixture in order to stabilize the pyrrolidine ring by more complete salt formation.

The conversion of the ketone **11** into **9** by the bromination-dehydrobromination sequence was also complicated by the sensitive pyrrolidine ring. By treating the ketone **11** with one mole-equivalent of bromine in dimethylformamide,[24] it was possible to obtain a crude bromo ketone which, without purification, was heated with lithium bromide in dimethylformamide[24] to give, after careful chromatography, the unsaturated ketone **9** in 18% yield. A small improvement in yield (25%) was realized when the bromination was carried out in acetic acid and the dehydrohalogenation was performed with tetramethylammonium mesitoate in acetone.[25] In the racemic series (see below) it was possible to obtain the unsaturated ketone **9** in 25% over-all yield from the alcohol **10**.

Synthesis of the pentacyclic alcohol **10** *and its conversion to racemic conessine*

The first stage in this part of the synthesis involved the contraction of ring D of the hydroxy ketone **4**. This substance, on treatment with excess methyllithium, was converted into the diol **12** (R = H), m.p. 151–153° (purified specimen, 155–156°) in 90% yield. The reaction was highly stereoselective, presumably involving the expected[26] β (equatorial) attack by the reagent to give mainly the C-17a epimer **12** (R = H). Confirmation of this configuration was afforded by the results of the dehydration experiment (see below). Treatment of the diol **12** (R = H) with acetic anhydride and pyridine at room temperature effected selective acetylation to give, in 86% yield, the 3-acetate **12** (R = Ac), m.p. 164–166° (purified specimen, 166–167°). Dehydration of this monoacetate with phosphorus oxychloride and pyridine was more difficult than expected and was only about one-half complete after 24 hr at room temperature. Heating the reaction mixture at 100° for 3 hr afforded an oily mixture of unsaturated compounds which was rich in that isomer, **13**, with the tetrasubstituted ethylenic bond as shown by the weak vinyl hydrogen absorption in the NMR spectrum as well as by the results of ozonolysis (see below). This behavior on dehydration is consistent with a 17aα (axial) configuration of the hydroxyl group in **12** (R = H or Ac).[27] The

[23] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

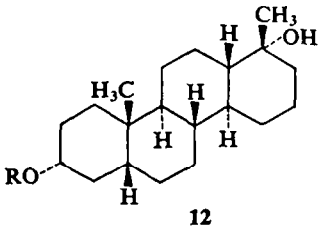
[24] Cf. [a] R. P. Holysz, *J. Amer. Chem. Soc.* **75**, 4432 (1953); [b] P. J. Krapp, Ph.D. Thesis, University of Wisconsin (1961).

[25] W. S. Johnson, J. F. W. Keana and J. A. Marshall, *Tetrahedron Letters* 193 (1963).

[26] Cf. H. O. House and W. L. Respess, *J. Org. Chem.* **30**, 301 (1965).

[27] Cf. D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956); J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *Ibid.* 753 (1957).

17a epimer (equatorial hydroxyl) would be expected to give mainly the product with an exocyclic olefinic bond.[27] We were not able to isolate the pure isomer **13**, or to



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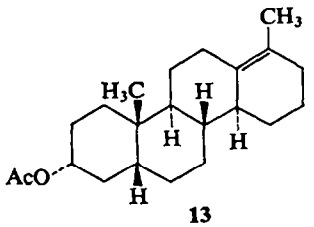

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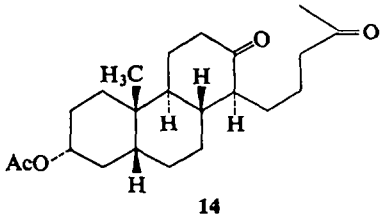
increase the proportion of **13** in the mixture by acid-catalyzed equilibration. Dehydration of **12** (R=Ac) with mineral acid, formic acid, or iodine gave mixtures which contained somewhat less of the isomer **13** as shown by the slight increase in the vinyl hydrogen absorption in the NMR spectra.

Ozonolysis of the aforementioned dehydration product containing **13**, in the presence of pyridine,[28] afforded, after decomposition of the ozonide with formaldehyde, the acetoxy diketone **14**, which could be isolated in crude crystalline form in yields approaching 50%. The purified material melted at 79·5–80·5°. This substance, on treatment with aqueous ethanolic potassium hydroxide, underwent intramolecular aldol condensation and saponification to afford, in 65% yield, the hydroxy unsaturated ketone



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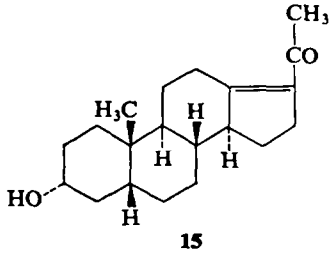

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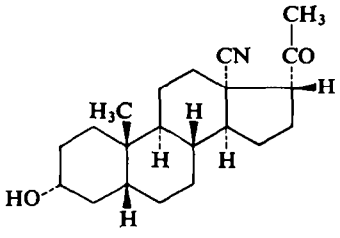
15, m.p. 74–77°. For preparative purposes it was not necessary to purify intermediates. Thus the unsaturated ketone **15**, m.p. 74–78°, could be obtained in 35% over-all yield from the hydroxy ketone **4**.

The unsaturated ketone **15** is a hygroscopic material which, after extensive recrystallization, exhibits capricious double melting point behavior (77–85°; 102–110°), which is apparently due to polymorphism since the spectral characteristics in solution remain unchanged. When sodium methoxide-catalyzed equilibration ($\alpha,\beta \rightleftharpoons \beta,\gamma$ unsaturated tautomers) was attempted,[29] a decrease in the extinction coefficient of the α,β-unsaturated ketone maximum in the ultraviolet absorption spectrum was observed, but this was accompanied also by a hypsochromic shift. This unexpected shift may possibly be the result of retro aldol ring opening promoted by traces of moisture to afford the hydroxy diketone **14** (H in place of Ac) and partial aldol recyclization at the methyl group of the pentanone side chain to give the seven-membered ring

[28] G. Slomp and J. L. Johnson, *J. Amer. Chem. Soc.* **80**, 915 (1958).
[29] Cf. W. L. Meyer and L. F. Wolfe, *J. Org. Chem.* **27**, 3263 (1962).

α,β-unsaturated ketone with no α substituent and accordingly a shorter wavelength maximum in the UV spectrum.

Having realized the contraction of ring D, we turned attention to the introduction of the C-18 group and the elaboration of the pyrrolidine ring E. We proposed to employ the well-known conjugate addition of cyanide ion to the α,β-unsaturated ketone system of **15**, in close analogy to the excellent method developed by Nagata.[30] Following his hydrocyanation procedure,[31] we treated the substance **15** with potassium cyanide and ammonium chloride in dimethylformamide. A mixture consisting of approximately equal amounts of the 13α- and 13β-cyano ketones, **16** and **17**, was thus formed in high yield. The configurational assignments are discussed below. These C-13 epimers could be separated by chromatography in yields of 20–35%; the pure 13α isomer **16** was obtained in two forms melting at 144–145° and at 169–171°, and the 13β isomer melted at 169–171°. In an effort to regenerate the unsaturated ketone **15** from the undesired 13α isomer **16**, alkaline-catalyzed dehydrocyanation[32] was attempted. Treatment with ethanolic sodium hydroxide at room temperature gave, in high yield, a new product, $C_{21}H_{33}O_3N$, m.p. 185–197°, which, because of the characteristic bands in the infrared spectrum (see experimental section), was formulated as the imino lactol (**18a**) and/or the lactamol (**18b**) (perhaps a mixture of C-20 epimers).[33]



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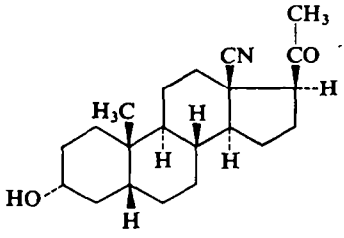

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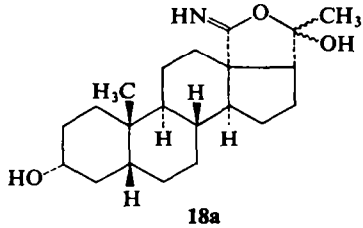
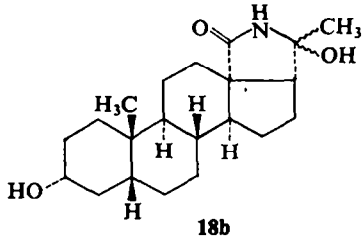


18a



18b

In any event there was no observable dehydrocyanation under these conditions. An attempt to effect dehydrocyanation by treatment with silver oxide led to the same mixture.

The desired dehydrocyanation of the 13α-cyano ketone **16** was finally accomplished by simple pyrolysis. On heating at 320–350° hydrogen cyanide was evolved with concomitant distillation of the cyanide-free product. The distillate consisted of a

[30] See particularly W. Nagata, I. Kikkawa and K. Takeda, *Chem. and Pharm. Bull., Japan* **9**, 79 (1961); and also Ref. 29.

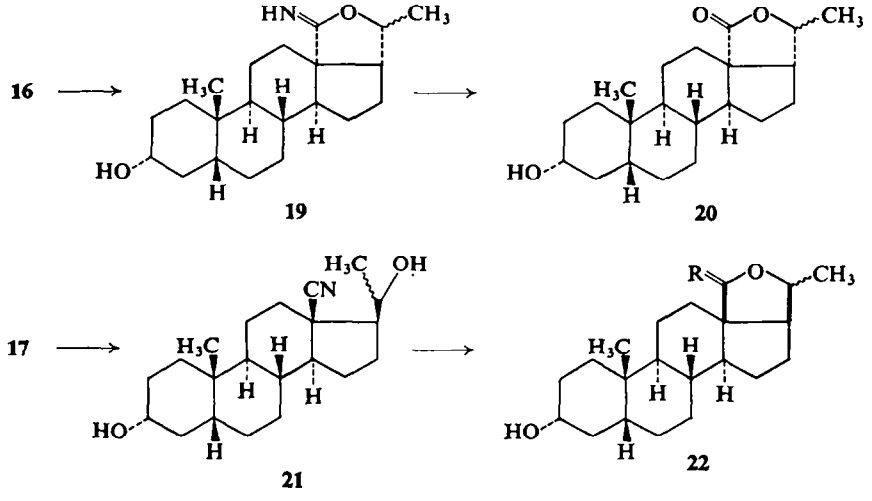
[31] W. Nagata, *Tetrahedron* **13**, 278 (1961).

[32] Cf. W. Nagata, S. Hirai, H. Itazaki and K. Takeda, *J. Org. Chem.* **26**, 2413 (1961).

[33] Nagata (Ref. 32) obtained analogous results after basic treatment of the cyano ketones derived from Δ^4-cholestenone-3.

mixture of α,β- and β,γ-unsaturated ketones in a ratio of about 3:2 as determined by IR and UV spectroscopy. The hypothesis that the high temperature caused bond migration of the initially formed α,β-unsaturated ketone was supported by distilling the pure α,β isomer at 350°. The distillate contained a 2:1 mixture of conjugated and unconjugated isomers. The mixture from the dehydrocyanation reaction was reconverted to a mixture of the 13α- and 13β-cyano ketones. Although the latter isomer was isolated in only 11% yield, this experiment serves to establish in principle the stereo-selectivity of this stage of the synthesis.

When the cyanation was conducted with liquid hydrogen cyanide and triethylaluminum in tetrahydrofuran,[34a] we did, as claimed by Nagata[34a] in a similar case, obtain mainly the desired *trans* (13β) isomer, but in our hands the procedure gave only a 23% yield. Unfortunately we have not been able to realize the high yields reported by Nagata.[34a,b]

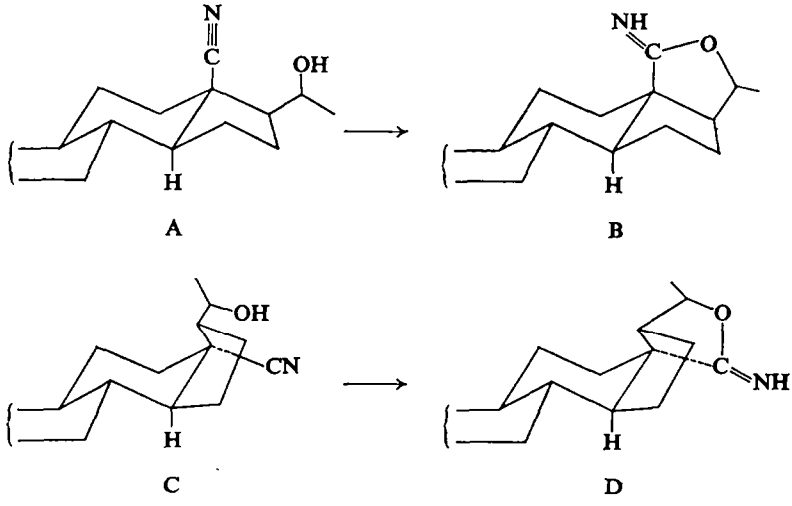


Attention is now turned to the matter of the configuration of the cyanation products **16** and **17**. It was expected that the cyanation conditions were sufficient to effect isomerization of the C-17 acetyl group to give an equilibrium mixture with the more stable epimer in preponderance. By analogy with the known position of the equilibrium in the progesterone series,[35] the C/D *trans* series should exist preferentially with the 17 acetyl group in the β configuration as shown in formula **17**. Inspection of models of the C/D *cis* series, on the other hand, clearly shows that the 17α isomer **16** is the more stable of the two C-17 epimers. That the 145° cyano ketone corresponded to **16** and the 171° isomer to **17** was proved by the following experiments involving selective reduction of the carbonyl group at C-20. Treatment of the 145° cyano ketone with lithium tri-t-butoxyaluminum hydride (conditions which should not effect epimerization at C-17) gave directly, in high yield, the imino lactone **19**, m.p. 211–220°, which was easily hydrolyzed, with aqueous acetic acid, to the lactone

[34] [a] W. Nagata, M. Yoshioka and S. Hirai, *Tetrahedron Letters* 461 (1962); [b] We suspect that the hydrocyanation of **15** would proceed in high yield by the new alkylaluminum cyanide method, W. Nagata and M. Yoshioka, *Ibid.* 1913 (1966).

[35] A. Butenandt, J. Schmidt-Thome and H. Paul, *Ber. Dtsch. Chem. Ges.* **72**, 1112 (1939), and previous papers. Also see L. F. Fieser and M. Fieser, *Steroids*, p. 468. Reinhold, New York (1959).

20, m.p. 195–215°. The broad melting point ranges of these two substances suggest that they are mixtures of epimers at C-20. This facile ring closure to give **19** is to be contrasted with the behavior in the C-13β cyano ketone series. When the 171° cyano ketone was reduced under conditions which effected the conversion of **16** to **19**, no imino lactone was produced but, instead, the expected cyano diol **21** was obtained. This substance could by cyclized to the imino lactone **22** (R=NH), but only after heating with methanol and concentrated hydrochloric acid.[36] Further acid hydrolysis afforded the lactone **22** (R=O), m.p. 180–196° (C-20 epimeric mixture). This difference in behavior of the two cyano ketones is explicable on conformational grounds. The steric expansion resulting from the conversion of —C≡N to —C=NH is a higher energy process in the 13β series (A → B), where the cyano group is *axial* to ring C, than in the 13α series (C → D) where the cyano group is *equatorial.*



A B C D

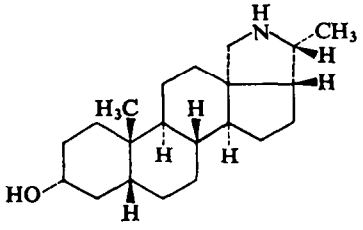
In the attempted base-catalyzed dehydrocyanation reaction described above, the extraordinary ease with which the 13α-cyano ketone **16** underwent ring formation to **18a**/**18b** is similarly consistent with the equatorial (to ring C) conformation of the cyano group. The β-cyano ketone **17**, under identical conditions, was recovered unchanged, which is in accord with the axial conformation of the cyano group and its relative reluctance to undergo steric expansion.

For the completion of ring E, our first plan called for a one-step ring closure by catalytic hydrogenation *via* an intramolecular reductive amination process. The feasibility of this approach is exemplified by Mandell and Singh's[37] production of piperidine rings from γ-cyano ketones in their synthesis of *dl*-matridine. Our initial efforts along this line showed considerable promise. Thus the 13α-cyano ketone **16**, used as a model, was readily transformed, by catalytic hydrogenation in dilute ethanolic

[36] Cf. D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Amer. Chem. Soc.* **82**, 2640 (1960).

[37] L. Mandell and K. P. Singh, *J. Amer. Chem. Soc.* **83**, 1766 (1961); L. Mandell, K. P. Singh, J. T. Gresham and W. J. Freeman, *Ibid.* **87**, 5234 (1965).

perchloric acid over rhodium-on-alumina, into the pyrrolidino compound **23**. It was disappointingly surprising to find, however, that application of this direct hydrogenation approach to the 13β-cyano ketone **17** met with failure. The nitrile remained unchanged, and the ketone group was reduced to hydroxyl. Under a variety of conditions



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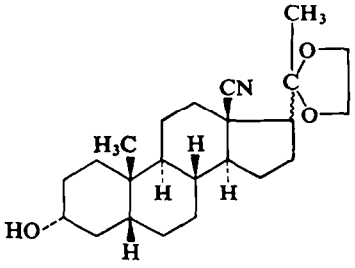

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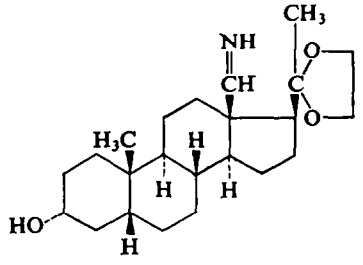

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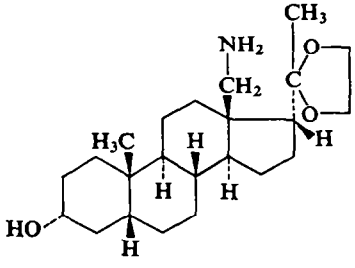


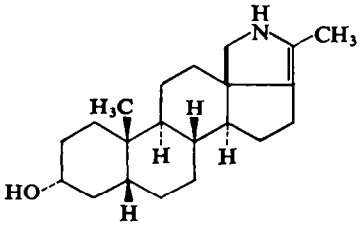
26

examined, reduction of the ketone evidently was always significantly faster than of the nitrile group, thus precluding significant ring formation *via* Schiff base condensation. Apparently the steric hindrance of the axial 13β-cyano group (see above) renders its selective reduction extremely difficult. We turned, therefore, to a less direct approach involving blocking the ketone against reduction by derivative formation.

The β-cyano ketone **17**, on acid-catalyzed reaction with ethylene glycol, was converted into a crystalline ketal **24**, m.p. 125–155°, which was evidently a mixture of C-17 epimers. Treatment of this ketal mixture with excess LAH afforded what appeared, by IR spectroscopy, to be about a 1:1 mixture of the imine **25** and the amine **26**. This ratio appeared to be invariant even though many modifications designed to increase the yield of amine were employed, e.g., increased temperature, prolonged reaction time, addition of fresh reagent, resubmission of the crude product to hydride treatment, and attempted catalytic hydrogenation. We were therefore forced to the conclusion that the imino fraction of the product was unreducible because the C-17 side chain was β oriented (formula **25**), exerting sufficient steric interaction with the C-18 group to prevent the latter from expanding beyond trigonal hybridization. The C-17 side chain of the amine fraction accordingly must be α oriented (formula **26**). These conclusions require that the cyano ketal **24** is also an approximately 1:1 mixture of the C-17 epimers. This may indeed represent the position of equilibrium, since the conditions that were used for the ketalization are probably sufficient for effecting equilibration *via* the enol ether,[38] although the possibility has not been ruled out that

[38] Cf. A. Marquet and J. Jacques, *Bull. Soc. Chim. Fr.* **29**, 90 (1962).

the starting ketone is undergoing equilibration at C-17 and that the ketalization step is kinetically controlled. In any case it is entirely reasonable that the position of the equilibrium between the ketone **17** and its 17α epimer should be shifted away from the 17β epimer in the case of the ketals **24** because of the larger steric requirement of the ketal residue which, when β oriented, would, as shown by models, have more severe non-bonded interactions (involving the hydrogen atoms on the C-21 methyl group and the ethylene bridge) with the 18β-cyano group. Such interactions would be expected to be even more severe with a larger C-18 group than cyano, e.g., methyl. This conclusion leads to the interesting hypothesis that the products of ketalization of 20-keto steroids having a 17 hydrogen atom[39] may favor the 17α rather than the 17β configuration, provided the method of preparation involves equilibrating conditions as in the present case.



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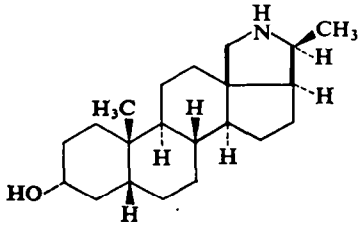

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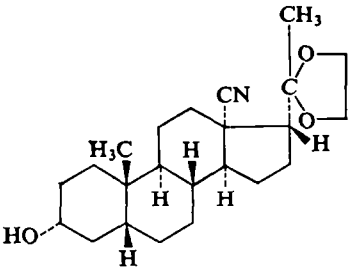
The mixture of ketals **25** and **26**, on treatment with acid in order to cleave the ketal residue, was converted to a neutral fraction (presumably aldehydic material derived from hydrolysis of the imino group of **25**) and a basic fraction which evidently was the enamine **27** (or the isomer with an exocyclic double bond) produced by cyclization of the amino ketone. Catalytic hydrogenation of the crude enamine was difficult, but conditions were found for effecting reaction to give the pyrrolidine derivative **28**. Without purification the latter substance was methylated with formaldehyde and formic acid[40] to give the crystalline racemic form of the alcohol **10**, m.p. 168·5–170°. The solution infrared spectrum of this substance was identical with that of the authentic naturally derived enantiomer described above. The yield of *dl*-**10** was 23% over-all from the cyano ketone **17**.

Since preliminary experiments directed toward the resolution of the racemic alcohol **10** did not look promising, we elected, instead, to complete the synthesis of racemic conessine following the method developed with the natural enantiomer (see above). Oxidation of the *dl*-alcohol **10** with chromium trioxide in aqueous acetic acid and sulfuric acid with added perchloric acid gave crude crystalline *dl*-ketone **11** in 80% yield. The pure product melted at 147–149°. The crude ketone was brominated in acetic acid containing hydrobromic acid, and the product, without purification, was treated with lithium bromide in dimethylformamide to give an α,β-unsaturated ketone fraction amounting to a 25% over-all yield from the alcohol **10**. This product was converted to the crude *dl*-enamine **8** which was reduced with borohydride and

[39] See, for example, the numerous cases cited by J. F. W. Keana in Djerassi's *Steroid Reactions*, pp. 3–22. Holden-Day, San Francisco (1963).

[40] R. Tschesche and A. C. Roy, *Chem. Ber.* **89**, 1288 (1956). M. L. Moore in *Organic Reactions* Vol. V, p. 307. Wiley, New York (1949).

acetic acid to give crude crystalline *dl*-conessine (**5**) in 7·5% over-all yield from the alcohol **10**. The purified material melted at 127–128·5°. On admixture with natural conessine (m.p. 124–125°), the m.p. was 112–126°. The solution infrared as well as the mass spectra of the two materials were identical.



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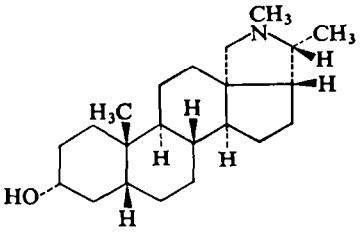

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The formation of the pyrrolidine ring E was also examined in the 13α series. In striking contrast with the work described above, the reactions in this isomeric series proceeded readily, in a straightforward manner which is in keeping with the lower steric hindrance of the angular functional group attached to C-13. Thus the 13α-cyano ketone **16** was converted, in high yield, into a *single* crystalline ketal, m.p. 174–175°, which is regarded as the presumably more stable (see above) C-17α epimer **29**. Reduction of the ketal **29** with LAH proceeded readily and to completion (no imine absorption in the IR spectrum of the crude product). Acid hydrolysis was, as in the 13β series, accompanied by cyclization to give enamine, which was easily hydrogenated to give the pyrrolidino compound, m.p. 195–196·5° (purified sample, 196–197°) in 51% yield. On the basis of steric-approach considerations, this product is assigned the configuration shown in formula **23**. Treatment with formaldehyde and formic acid afforded the *N*-methyl compound **30** which was obtained as an oil after chromatography.

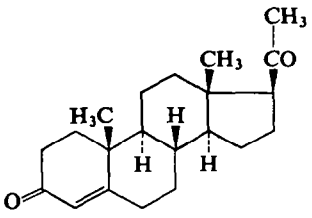
PART II—PROGESTERONE AND CHOLESTEROL

During the past 15 years a variety of totally synthetic approaches to the steroids have been developed.[41] A number of these schemes establish synthetic pathways to progesterone (**31**) and cholesterol (**32**) in the sense that totally synthetic intermediates were produced and these were identified with degradation products from natural materials, which had been interrelated with progesterone and cholesterol through "partial synthesis" techniques. Up to the time of the present work, there had been no published report of a synthesis which was carried all the way through so as to afford totally synthetic progesterone[42] and cholesterol. The present study describes the preparation of the totally synthetic racemic materials, as well as of some other related naturally occurring substances, namely pregnan-3α-ol-20-one (found in the urine of pregnant women), pregnane-3,20-dione (found in the urine of pregnant mares),

[41] See, *inter alia*, I. V. Torgov, *Pure Appl. Chem.* **6**, 525 (1963); L. Velluz, J. Valls and G. Nominé, *Angew. Chem.* (Int. Ed.) **4**, 181 (1965).

[42] However, R. B. Woodward and E. H. White, in unpublished work, had prepared totally synthetic progesterone in 1952; we have had the opportunity of comparing their material with our product (see below). We thank Professor Woodward for apprising us of his work and for providing us with a comparison specimen.

5β-cholestan-3α-ol, 5β-cholestan-3-one, and Δ^4-cholesten-3-one. The last three substances have been found in ambergris and also in the unsaponifiable matter of dogs' feces.[43]



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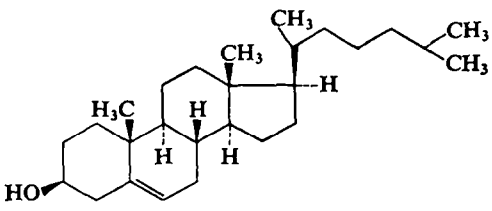


32

Progesterone, pregnan-3α-ol-20-one and pregnane-3,20-dione[44]

We envisaged starting with the 13β-cyano ketal **24**, an intermediate in the conessine synthesis (see above), and applying a method devised by Nagata[30] for conversion of the cyano to methyl group, namely, reduction of the cyano to the imino group, alkaline hydrolysis to the aldehyde, and finally Wolff-Kishner reduction.[45]

As described above (Part I), the method which we employed for the ketalization of the cyano ketone **17** gave a mixture of C-17 epimeric ketals which, on reduction with lithium aluminum hydride, afforded the imine **25** from the 17β and the amine **26** from the 17α epimer. Pursuant to the objective at hand we explored the possibility of selective reaction so that reduction of the 17α epimer would also stop at the imino stage. The best conditions which we found involved a fortuitous concentration of reactants so that the imine complex precipitated as the reduction proceeded. A twenty-fold molar excess of LAH in refluxing tetrahydrofuran for 4·5 hr gave the best yields of imine as estimated by the intensity of the band at 6·1 μ in the IR spectrum. Higher proportions of LAH caused over-reduction. Under milder conditions, reduction was incomplete as shown by the proportionately greater intensity in nitrile absorption at 4·85 μ in the infrared. Although semicrystalline, the imine could not be satisfactorily purified, evidently because of an extreme susceptibility of part of the material (presumably the 17α epimer) to hydrolyze to aldehyde. When the crude imine mixture was subjected to the described[30] conditions for alkaline hydrolysis, only approximately 10% of the material was converted into aldehyde as estimated from the relative intensities of the bands at 6·1 and 5·86 μ in the infrared spectrum. Extended treatment with alkali effected hydrolysis of, at most, one-half of the imine, and this product could not be handled satisfactorily. Finally it was found that the hydrolysis step is unnecessary since, under appropriate conditions, the crude imine can be made to undergo the Wolff-Kishner reduction directly as described below.

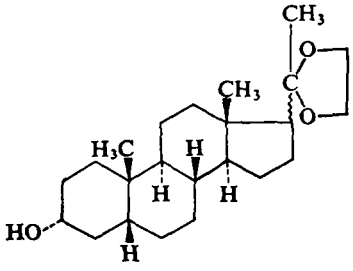
The usual Huang-Minlon procedure for Wolff-Kishner reaction effected negligible reduction of the imine mixture. Reasoning that the imine probably was not appreciably converted into hydrazone under these conditions, we explored the effect of extending the reaction time for hydrazone formation. Thus when the hydrazone-forming stage

[43] C. Riddell and R. P. Cook, *Biochem. J.* **61**, 657 (1955).

[44] For a preliminary report on this work, see Ref. 25.

[45] Since our report (Ref. 25), W. Nagata, T. Terasawa and T. Aoki, *Tetrahedron Letters* 865 (1963), have applied this method to the 5α,3β isomer of **17** and reported high yields for each step.

was carried out for 16 instead of 3 hr at 130°, before raising the temperature to effect decomposition of the derivative, the desired 13β methyl ketal **33** (C-17 epimeric mixture), m.p. 119–127°, was isolated in 50% over-all yield from the cyano ketal **24**. Moreover the latter substance was recovered in 13% yield (even after the strenuous alkaline conditions of the Wolff-Kishner reaction), so that the yield was 63% based on utilized starting material. Hydrolysis of the ketal, presumably with concomitant equilibration of the C-17 epimers, afforded *dl*-pregnan-3α-ol-20-one (**47**), m.p. 171–173°.



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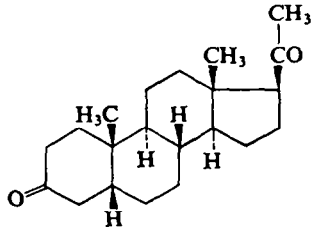

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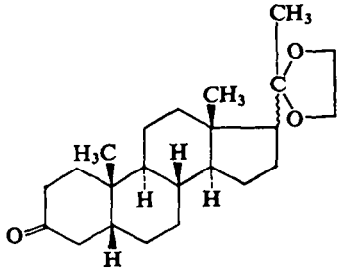

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Oxidation of the hydroxy ketal **33** with Jones reagent,[23] followed by acid-catalyzed hydrolysis, afforded *dl*-pregnane-3,20-dione (**34**), m.p. 111–112°. The solution IR spectrum of this material was identical with that of naturally derived pregnane-3,20-dione.[46] The steps for the conversion of this diketone into progesterone are known;[46,47] however, we elected to follow an alternative, but closely related, pathway to progesterone. The hydroxy ketal **33** was oxidized with Sarett reagent[48] to give the ketal ketone **35**, an apparently pure epimeric form of which, m.p. 168·5–170·5°, was obtained by crystallization. The crude ketal ketone **35** was then treated with bromine in acetic acid[47] which effected selective bromination at C-4 with concomitant cleavage of the C-20 ketal residue and, presumably, equilibration of the C-17 epimers. The dehydrohalogenation of the crude bromo diketone was effected with benzyltrimethylammonium mesitoate in refluxing acetone[25] to give *dl*-progesterone (**31**), m.p. 183·5–185·5°. The solution infrared spectrum of this material was identical with that of authentic progesterone. A sample of *dl*-progesterone prepared by Woodward and

[46] A. Butenandt and J. Schmidt, *Ber. Dtsch. Chem. Ges.* **67**, 1901 (1934).

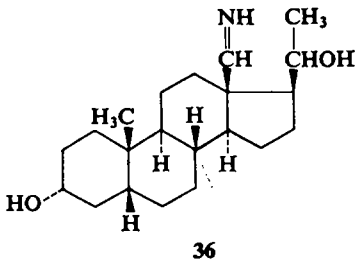
[47] H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 266 (1953).

[48] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**. 422 (1953).

White,[42] after recrystallization from methanol, melted at 183–185°, and showed no m.p. depression on admixture with our material. The IR spectra (KBr) of the two racemic specimens were identical.

The remaining part of this discussion of the progesterone work is devoted to a report of preliminary studies of alternative attempts to effect conversion of the cyano into the methyl group, as well as some experiments in the 13α series leading to the synthesis of 13α,17α-pregnane-3,20-dione (**39**).

It was hoped that the 13β-cyano ketone **17** could be reduced directly to the imine diol **36** which could be converted, as described above, into the 13β-methyl compound. Even under forcing conditions with lithium aluminum hydride, the reaction stopped at the cyano diol stage **21** (see Part I). Apparently the precipitation of the sparingly soluble di-salt of **21** precluded further reduction. In an effort to obviate this difficulty, the 13β-cyano ketone **17** was converted into the tetrahydropyranyl ether, m.p. 166–168°, and this was treated with excess lithium aluminum triethoxy hydride[49] in refluxing tetrahydrofuran; however, the IR spectrum of the product indicated that little if any reduction of the cyano group had occurred. Another approach envisaged selective reduction with lithium aluminum hydride of the lactone **22** (R=O) (see Part I) to give the lactol[1,50] which could then be converted by the Wolff-Kishner reaction into the 13β-methyl compound. Under the conditions examined there was no reduction of the lactone. This is to be compared with the behavior in the 13α series, where attempts to effect reduction of the lactone **20** to the lactol either with LAH or with bis-3-methyl-2-butylborane[51] afforded only completely reduced triol, m.p. 223–224°.



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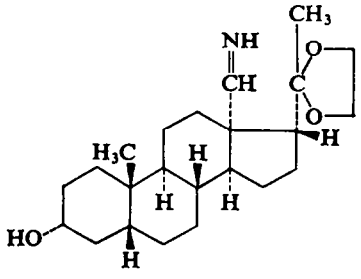


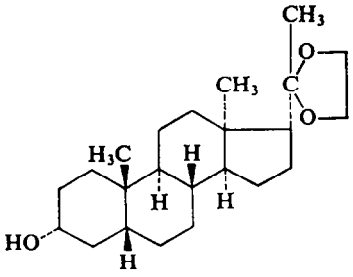
37

The selective reduction of the 13α-cyano ketal **29** (Part I) was facile compared with the behavior in the 13β series, and proceeded with a twofold (instead of twenty-fold) excess of LAH to give the imine **37**. Under these conditions the product was contaminated with unreduced cyano ketal, and under more vigorous conditions some over-reduction to give amine was observed. Unlike the 13β isomer, the imine **37** was relatively easily converted, by hydrolysis with sodium hydroxide, into the aldehyde which was not obtained in a pure form because of contamination with the cyano ketal **29**. The crude imine **37** was carried through the same sequence as described above for the 13β isomer to give the 13α-methyl hydroxy ketal **38**, m.p. 141–142·5°. Oxidation and hydrolysis of the ketal afforded *dl*-13α,17α-pregnane-3,20-dione (**39**),

[49] H. C. Brown, C. J. Shoaf and C. P. Garg, *Tetrahedron Letters* No. 3, 9 (1959).

[50] Cf. G. E. Arth, *J. Amer. Chem. Soc.* **75**, 2413 (1953); J. v. Euw, R. Neher and T. Reichstein, *Helv. Chim. Acta* **38**, 1423 (1955).

[51] H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.* **83**, 486 (1961).



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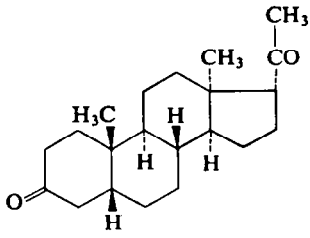
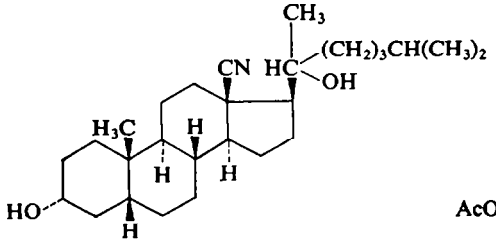


39

m.p. 138–142·5°. These steps were performed only once and no effort was made to vary conditions in order to maximize yields. The configuration of the dione **39** at C-17 is presumed to be α on conformational grounds (see Part I).

Cholesterol, 5β-cholestan-3α-ol, 5β-cholestan-3-one and Δ⁴-cholesten-3-one

With cholesterol as the ultimate synthetic objective, we decided first to examine the possibility of introducing the isohexyl side chain into the 13β-cyano ketone **17** (Part I) prior to conversion of the angular cyano to the methyl group. Reaction of the cyano ketone **17** with excess isohexylmagnesium bromide, in the presence of magnesium bromide to minimize reduction,[52] afforded the adduct **40** as an oil in 52% yield. The product of reduction, namely the diol **21** described in Part I, was also isolated in 30% yield. There was no evidence of reaction with the cyano group. When isohexyllithium was used instead of the Grignard reagent, the desired adduct **40** was obtained in only 19% yield. The remainder of the product consisted of starting cyano ketone (probably formed *via* enolization) and an oily substance showing imine absorption at 6·1 μ in the IR spectrum which probably resulted from addition of the isohexyllithium to the nitrile as well as to the keto group.



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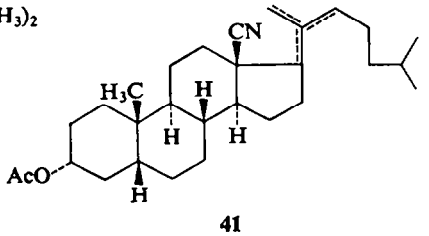

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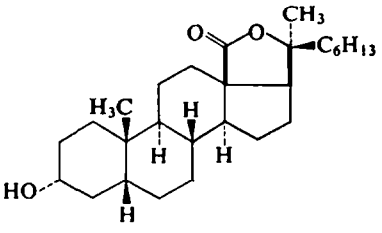
Reaction of the diol **40** with acetic anhydride in pyridine at room temperature gave the 3-mono acetate, which on treatment with phosphorus oxychloride in pyridine underwent dehydration to produce a mixture of olefinic isomers **41**. Attempts to hydrogenate the olefinic bonds selectively failed. We were also unable to realize hydrolysis of the cyano group on treatment with potassium hydroxide in triethylene glycol or with 85% phosphoric acid. The action of LAH yielded a mixture of starting material and amine accompanied by trace amounts of the desired imine as determined by IR spectroscopy. Further studies with **41** were, therefore, abandoned forthwith, and

[52] C. G. Swain and H. B. Boyles, *J. Amer. Chem. Soc.* **73**, 870 (1951).

attention was turned to the diol **40**, in the hope that hydrolysis of the cyano group would be facilitated by the neighboring C-20 hydroxyl group. Indeed, treatment of the diol **40** with an aqueous mixture of propionic and phosphoric acid afforded a mixture of the oily lactone **42** and the imino lactone **43**, m.p. 219·5–220·5°. When the latter substance was resubmitted to the same treatment, it was recovered essentially unchanged. Evidently one of the two C-20 epimers of the imino lactone undergoes hydrolysis to the lactone very much faster than the other. On this basis we tentatively



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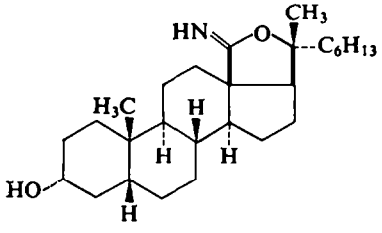

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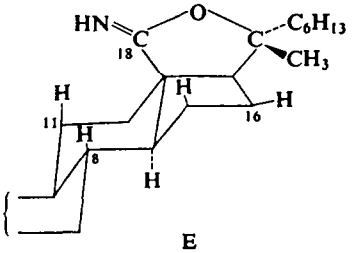

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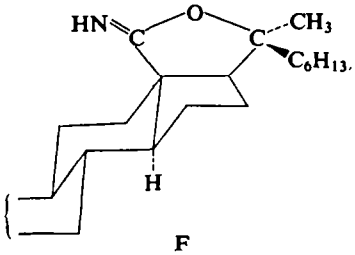


F

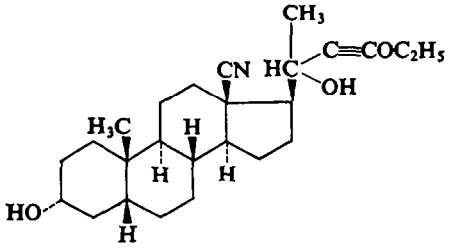
assign the configuration E to the hydrolysis-resistant epimer and F to the reactive epimer. Models suggest that nucleophilic attack by water at the carbon atom of the protonated form of the imino group from the front face would be hindered in both epimers by the ring hydrogens, particularly those at C-8 and at βC-16. Therefore that epimer with the larger amount of hindrance to the nucleophilic attack at the rear of the molecule, namely E with the isohexyl group shielding the rear side, would be expected to be the less reactive. Accordingly the lactone and imino lactone are tentatively assigned the configurations shown in formulas **42** and **43**, respectively.

Since the lactone **42** could be obtained in 47% yield, some preliminary investigations were conducted to see if it promised to be useful. The following exploratory reactions were performed. Oxidation with Jones reagent gave the 3-keto lactone which was converted to the 3-ethylene ketal. Treatment of the ketal with LAH effected reduction of the lactone to the ketal diol. Preliminary attempts to perform appropriate selective reactions on this diol did not look promising, and the study was suspended at this stage.

Another approach, which was given some attention, envisaged synthesizing lithocholic acid for further conversion to cholesterol. The 13β-cyano ketone **17** readily underwent condensation with lithium ethoxyacetylide, affording the adduct **44** which, although not obtained in a pure state, could be converted, by treatment with ethanolic hydrogen chloride,[53] into an oily mixture of geometric isomers of the unsaturated

[53] Cf. H. Heusser, K. Eichenberger and P. A. Plattner, *Helv. Chim. Acta* **33**, 1088 (1950).

ester **45** ($R=C_2H_5$). Hydrogenation of this mixture over palladium-on-carbon afforded a crystalline ester **46** ($R=C_2H_5$), m.p. 144–145°. The configuration of this ester at C-20 is open to question. When the mixture of unsaturated esters **45** ($R=C_2H_5$) was saponified, a mixture of unsaturated acids **45** (R=H) was produced from which



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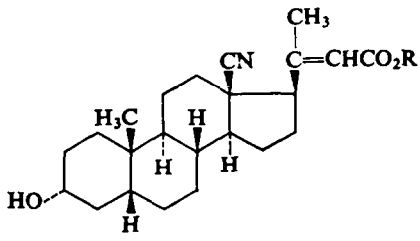

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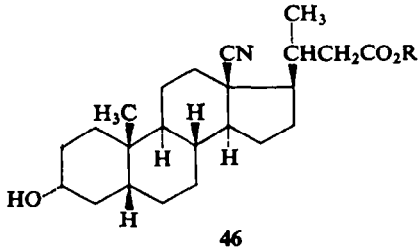
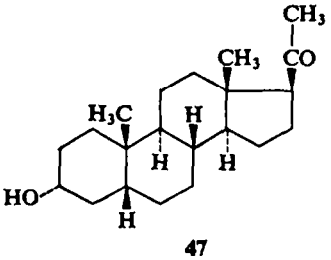


46

it was possible to isolate, in low yield after chromatography and recrystallization, one of the isomers, m.p. 223–225°. Hydrogenation of this substance over platinum oxide in acetic acid afforded a mixture (C-20 epimers) of saturated acids **46** (R=H) from which a form, m.p. 244–249°, was isolated by repeated recrystallizations. This same saturated acid was obtained on saponification of the saturated ester **46** ($R=C_2H_5$) melting at 144–145°. Since the foregoing experiments failed to afford both C-20 epimers and gave no clue as to the configuration of the one in hand, it was decided to explore a route with precedent for producing the product of desired configuration.



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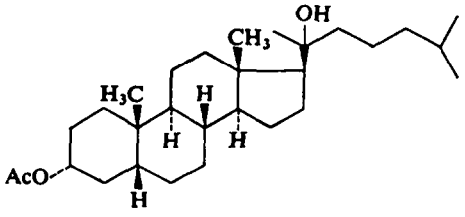
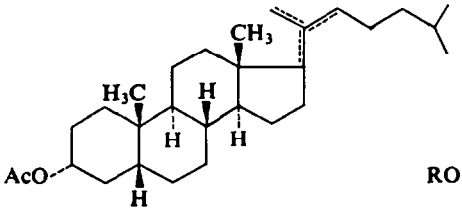


48

The following sequence is an adaptation of the general method of Woodward[54] for the elaboration of the cholesterol side chain. The hydroxy ketone **47**, obtained on hydrolysis of the ketal **33** (see above), was treated with isohexyllithium to give a mixture of C-20 epimeric diols which, on treatment with acetic anhydride and pyridine,

[54] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952).

was selectively acetylated to produce the crystalline hydroxy acetate **48**. By repeated recrystallizations, one of the epimers, m.p. 151–153°, was isolated. This 153° isomer appeared to be the preponderant product which, according to Cram's rule, would be expected to have the C-20 α configuration.[55] The crude epimeric mixture of hydroxy acetates, on dehydration with phosphorus oxychloride and pyridine, was transformed into a mixture of unsaturated compounds **49** containing a substantial amount of the $\Delta^{20,21}$ isomer as indicated by pronounced absorption for the terminal methylene group at 6·10 and 11·2 μ in the IR spectrum. Comparable olefinic mixtures have been hydrogenated over Pt in acetic acid to give mixtures of saturated isomers in which the natural 20β epimer was preponderant.[54,56] Hydrogenation of our hydroxy olefin **49** under these conditions with an added trace of perchloric acid afforded a semi-crystalline product in an over-all yield of 72% from the ketone **47**. A form, m.p. 122·5–124·5°, was readily isolated by four recrystallizations, and this was presumed,



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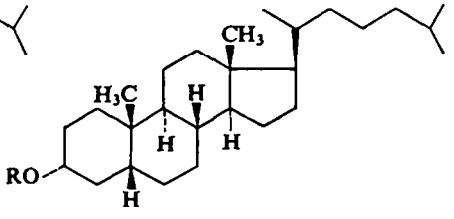
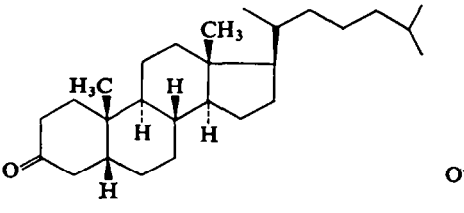


50

by analogy,[54,56] to be the desired epimer **50** (R = Ac). Saponification of this isomer afforded *dl*-5β-cholestan-3α-ol (**50**, R = H), which exhibited a variable melting point, presumably due to polymorphism.

The substance **50** (R = H), on oxidation with Jones reagent, was converted into *dl*-5β-cholestan-3-one (**51**), m.p. 75–78°. The solution infrared spectrum was identical with that of the naturally derived enantiomer. However, since these spectra were also indistinguishable from those of the racemic 20-iso epimer, the question of identity required further consideration (see below). The ketone **51** was transformed into the



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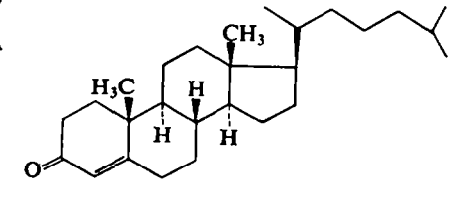


52

unsaturated ketone **52** by selective bromination at C-4 with pyridine hydrobromide perbromide in acetic acid,[57] followed by reaction with semicarbazide,[58] and then

[55] L. F. Fieser and M. Fieser, *Steroids* p. 344. Reinhold, New York (1959).
[56] F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.* **80**, 3087 (1958).
[57] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.* **70**, 417 (1948).
[58] V. R. Mattox and E. C. Kendall, *J. Biol. Chem.* **188**, 287 (1951); T. H. Kritchevski, D. L. Garmaise and T. F. Gallagher, *J. Amer. Chem. Soc.* **74**, 483 (1952).

cleavage of the resulting unsaturated semicarbazone with pyruvic acid. Thus *dl*-Δ^4-cholesten-3-one (**52**) was obtained in two interconvertible dimorphic forms, m.p. 113–115° and 120–121°.

Treatment of the cholestenone **52** with acetyl chloride and acetic anhydride[59] gave the enol acetate which, without purification, was reduced[60] with sodium borohydride and potassium hydroxide in aqueous isopropyl alcohol to yield *dl*-cholesterol (**32**), m.p. 149–149·5°. A mixture of this racemic product with natural cholesterol (m.p. 148·5–149·5°) melted at 143·5–148°. The solution infrared, mass and NMR spectra of the two substances were identical respectively. An attempt to resolve the totally synthetic, racemic product by selective precipitation with digitonin[54] failed. We considered it necessary, therefore, to obtain conclusive evidence that we were not dealing with the 20-iso series.

From the mother liquor, which afforded the first crop of crude crystalline 5β-cholestan-3α-ol acetate (**50**, R = Ac), there was obtained, after saponification, an oily product which was rich in the 20-iso epimer. Jones oxidation of this material afforded an oily specimen containing 20-iso-5α-cholestan-3-one, the infrared spectrum of which was, as noted above, indistinguishable from that of the C-20 epimer. Fortunately the enigma was solved by NMR spectroscopy. The spectra of the crystalline racemic ketone **51** and of the naturally derived material were identical. In particular, the signals for the hydrogens of the C-20 methyl group appeared as a doublet centered at $\delta = 0{\cdot}91$ ppm. In contrast the C-20 signal in the spectrum of the oily ketone appeared as a doublet centered at 0·83 ppm. These data leave no doubt about the identity of the crystalline ketone and, in turn, of the racemic form of cholesterol described above.

PART III—STUDIES OF AN ALTERNATIVE APPROACH TO 18-SUBSTITUTED STEROIDS

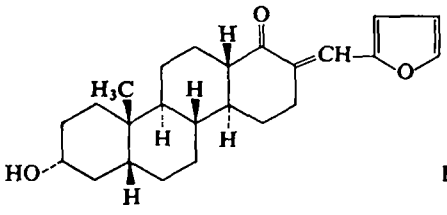
Prior to the investigations described in the preceding sections, considerable effort was expended in a study of an alternative approach to 18-substituted steroids. Although abandoned short of completion in favor of the successful approach described above, these incomplete studies are being recorded here because we feel that they not only have interest *per se* but they constitute a promising potential for the production of these types of steroids.

The general approach envisaged application of the basic scheme for constructing the D ring that was employed in the synthesis of aldosterone.[1] In the present case we planned to start with the furfurylidene derivative **53** of the tetracyclic ketone **4**. Previous studies[1,61] have demonstrated that alkylation of systems like the enolate anion of **53** invariably involves preferential attack (at C-13) on the α side of the molecule to yield the C/D *cis* ring fusion. We proposed to use methacrylonitrile for alkylation with the expectation that the adduct **54** would be formed. The carbon atom of the cyanoisopropyl residue attached to C-13 was envisaged as becoming C-17, while the carbonyl group was destined to become C-18 of the steroid nucleus. The hypothetical oxidation product of **54**, with the groups arranged in the appropriate position for the elaboration of ring D, is shown in formula G.

[59] U. Westphal, *Ber. Dtsch. Chem. Ges.* **70**, 2128 (1937).

[60] W. G. Dauben and J. F. Eastham, *J. Amer. Chem. Soc.* **73**, 4463 (1951).

[61] W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen and R. Pappo, *J. Amer. Chem. Soc.* **84**, 2181 (1962).



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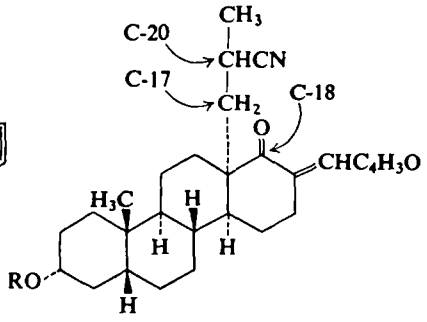

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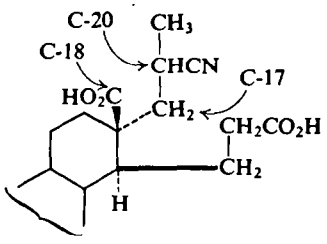

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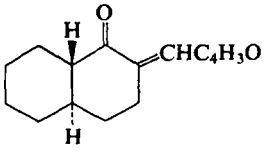

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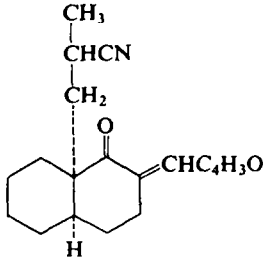

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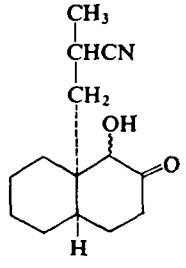

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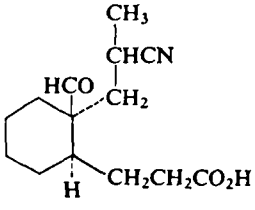

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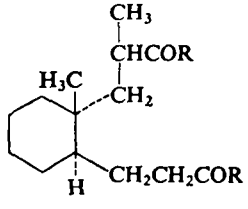

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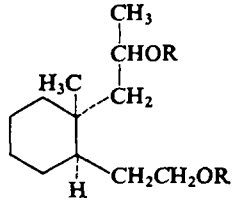

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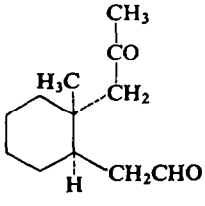

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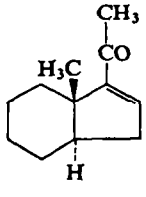

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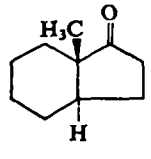


63

First, a model study was undertaken in order to see if 1-decalone could in this way be converted into a *trans*-fused hydrindane system carrying an angular substituent.[62]

The details of the preparation of the diacid **59** (R = OH) have already been described.[1] These involve the Michael condensation of *dl*-2-furfurylidene-1-decalone (**55**) with methacrylonitrile. The carbonyl group of the resulting adduct **56** was selectively reduced to the alcohol with sodium borohydride, and this in turn was converted to the tetrahydropyranyl ether which was oxidatively cleaved and then hydrolyzed to give the hydroxy ketone **57**. Periodate oxidation of this last substance afforded the aldehydo cyano acid **58**, which, under Wolff-Kishner conditions, was converted into the diacid **59** (R = OH). This diacid (mixture of epimers at carbon corresponding to C-20 steroid numbering) was converted, by the acylmalonic ester method,[63] into the diketone **59** ($R = CH_3$) which was in turn rearranged, by treatment with trifluoroperacetic acid,[64] into the diacetate **60** (R = Ac). Saponification afforded the diol **60** (R = H) which was transformed, by oxidation in two stages—first with *N*-bromoacetamide (to oxidize the secondary hydroxyl), then with Sarett reagent[48]—into the keto aldehyde **61**. Without purification, this last substance was cyclized directly with aqueous potassium hydroxide to yield the bicyclic unsaturated ketone **62**, λ_{max}^{ether} 233 mμ. The structure and configuration were established by Beckmann rearrangement of the oxime of **62** followed by hydrolysis[65] to give the known *dl*-8-methyl-*trans*-hydrindan-1-one (**63**), isolated as the 2,4-dinitrophenylhydrazone. This derivative was identified with authentic material[66] by mixture melting point and infrared spectral comparison.

The conversion **55** → **62** constitutes a model for converting the tetracyclic substance **53** into the pregnane series. Treatment of the furfurylidene ketone **53** with methacrylonitrile in methanol containing sodium methoxide gave, in 85% yield, a crystalline mixture of epimeric adducts **54** (R = H) which was composed of approximately 3 parts of isomer A, m.p. 208–209°, and 5 parts of isomer B, m.p. 256·5–258°. Isomer A, on treatment with potassium ethoxide in ethanol, was converted, in part, into isomer B, thus demonstrating that these isomers were, as expected, epimeric about the carbon atom (C-20) holding the cyano group. Treatment of isomers A and B with sodium borohydride gave the products (epimeric mixture) of reduction of the keto group. Preliminary experiments on protection of the hydroxyl groups as the tetrahydropyranyl ethers followed by ozonization and hydrolysis gave disappointingly low yields of neutral material; therefore further attempts to obtain the ketol (corresponding to **57**) were abandoned. An unsuccessful attempt also was made to hydroxylate the olefinic bond of the borohydride reduction product and to cleave what was presumed to be the resulting tetrahydroxy ketone with periodic acid in the hope of effecting conversion directly to the aldehydo acid (corresponding to **58**). The work up to this point, beginning with substance **53**, was carried out by John E. Pike. In view of these unpromising results, attention was turned to a study of the direct oxidation of the cyanopropyl furfurylidene ketone, without prior reduction, with the aim of producing substances with the angular carboxyl instead of aldehyde group.

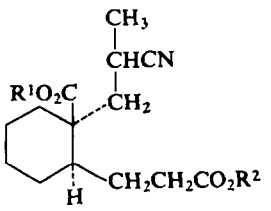
[62] A preliminary account of this work has been published: W. S. Johnson, D. G. Martin, R. Pappo, S. D. Darling and R. A. Clement, *Proc. Chem. Soc.* 58 (1957).

[63] R. E. Bowman, *J. Chem. Soc.* 325 (1950).

[64] Cf. W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.* 77, 2287 (1955).

[65] Cf. G. Rosenkranz, O. Mancera, F. Sondheimer and C. Djerassi, *J. Org. Chem.* 21, 520 (1956).

[66] W. S. Johnson, *J. Amer. Chem. Soc.* 66, 215 (1944).



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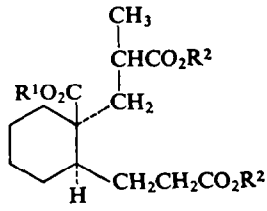

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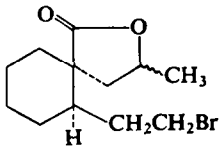

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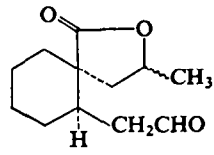
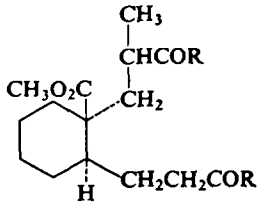


67

Some exploratory studies were conducted in the model series. Ozonization of **56** followed by treatment with hydrogen peroxide afforded the nitrile diacid **64** ($R^1=R^2=H$). This product was obtained as a mixture of epimers about the carbon atom holding the cyano group. All of the products described below that were derived from this nitrile diacid were also mixtures of epimers, although in some instances a single form was separated. An attempted Stephen reduction[67] of the cyano diester **64** ($R^1=R^2=CH_3$) failed. It was noted that this cyano diester underwent selective saponification to give the half-ester **64** ($R^1=CH_3$, $R^2=H$). Exhaustive alkaline hydrolysis of the nitrile diacid afforded the triacid **65** ($R^1=R^2=H$). The corresponding trimethyl ester ($R^1=R^2=CH_3$) could be selectively saponified to the ester diacid **65** ($R^1=CH_3$, $R^2=H$). In order to degrade this substance appropriately for completion of the fused five-membered ring, it was necessary to eliminate both carboxyl groups which we hoped could be effected by the Hunsdiecker reaction.[68] The product of treatment of the disilver salt of **65** ($R^1=CH_3$, $R^2=H$) with bromine afforded a mixture which evidently contained



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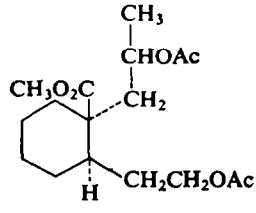

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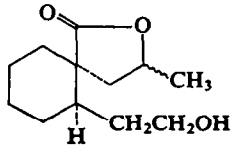

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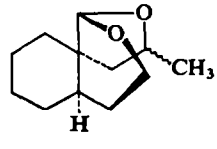

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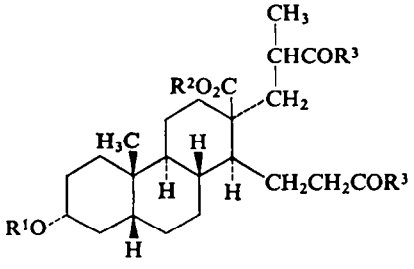
[67] See E. Mosettig, *Organic Reactions* Vol. III, p. 248. Wiley, New York (1954).
[68] See R. H. Johnson and R. K. Ingham, *Chem. Rev.* **56**, 219 (1956).

the bromo lactone **66**,[69] since it could be converted, by treatment with potassio 2-nitropropane,[70] into the aldehydo lactone **67** isolated as its 2,4-dinitrophenylhydrazone, m.p. 191·5–194°. This aldehyde has potential for use in a scheme related to that described above for the production of **62**; however, in view of the low yields, we turned our attention to other methods of degradation.

The low-temperature Rosenmund reduction[1] of the acid chloride **68** (R = Cl) derived from **65** ($R^1 = CH_3$, $R^2 = H$) proceeded readily to give an ester dialdehyde, characterized as the bis-2,4-dinitrophenylhydrazone, m.p. 218–220·5°. The acid chloride was prepared under conditions that do not promote rearrangement;[71] however, there was no assurance that some or even extensive rearrangement did not occur during the reduction step. Therefore the ester dialdehyde may have been the substance **68** (R = H) and/or the isomer in which the ester and aldehyde (attached to the branched carbon) groups of **68** (R = H) are interchanged. In any case, preliminary attempts to degrade this material by conversion to the bis-enamine, followed by ozonization,[72] were unsuccessful, and this study was abandoned.

A high-yield degradation was realized by a sequence like that used with **59** (R = OH) (see above). The diacid chloride **68** (R = Cl) was converted into the diketo ester **68** ($R = CH_3$) and this, in turn, was submitted to the Baeyer-Villiger oxidation to give the diacetate **69**. We hoped that it would be possible to hydrolyze the acetate residues selectively to give the corresponding dihydroxy ester which could then be oxidized and cyclized as in the preparation of **62** described above. However, under all conditions examined, only the hydroxy lactone **70** was produced. Since it seemed



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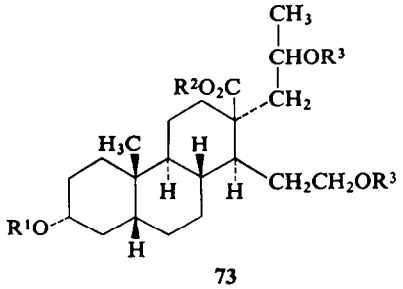

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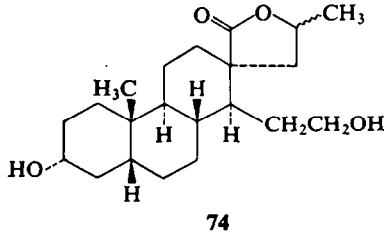

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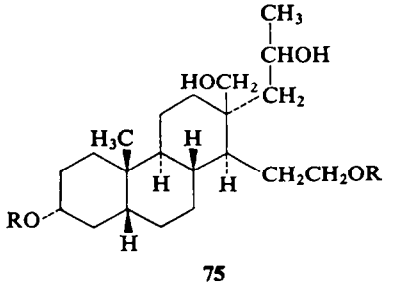

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[69] Cf. the lactone formation in the Hunsdiecker reaction with a glutaric half-ester system, K. Ziegler, G. Schenck and E. W. Krockow, *Naturwiss.* **29**, 390 (1941); *Leibigs Ann.* **551**, 1 (1942).

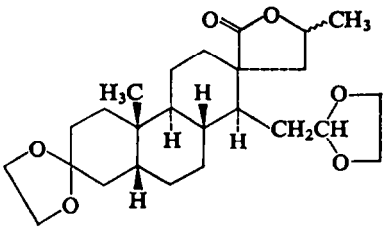
[70] Cf. [a] S. V. Lieberman, *J. Amer. Chem. Soc.* **77**, 1114 (1955); [b] H. B. Hass and M. L. Bender, *Ibid.* **71**, 1767, 3482 (1949).

[71] J. Cason, *J. Org. Chem.* **13**, 227 (1948), and Refs. cited.

[72] Cf. M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.* **74**, 3627 (1952).

likely that this type of structure could be manipulated successfully, we discontinued the model study and turned our attention to the parent series. One other experiment in the model series deserves mention; namely, the selective reduction of the lactone ring of **70** to the aldehyde stage of oxidation.[50] The product finally isolated from the mixture appeared to be the internal acetal **71**.

The aforementioned cyano furfurylidene ketone **54** (R = H) was converted to the acetate **54** (R = Ac) (isomer B, m.p. 188–189·5°), which was treated with ozone, then with hydrogen peroxide followed by exhaustive saponification to yield the hydroxy triacid **72** ($R^1 = R^2 = H$, $R^3 = OH$) in 80% over-all yield. The mixture of epimers could be roughly separated by crystallization, and treatment of these isomer-enriched fractions with diazomethane gave the hydroxy trimethyl esters **72** ($R^1 = H$, $R^2 = CH_3$, $R^3 = OCH_3$) which were easily purified: isomer A, m.p. 131–132°, and isomer B, m.p. 90–92°. It is to be noted that ozonization of isomer B-rich furfurylidene ketone afforded hydroxy triacid rich in the higher-melting epimer which was therefore considered to be in the same (B) stereochemical series. The stereochemical integrity of the A and B series appears to be maintained throughout the transformations described below. Conditions were developed for the selective saponification of the triester to the hydroxy diacid ester **72** ($R^1 = H$, $R^2 = CH_3$, $R^3 = OH$): isomer A, m.p. 120–120·5°, and isomer B, m.p. 215·2–218°. Acetylation of the 3-hydroxy group was effected by direct esterification with acetic acid and hydrogen chloride to yield the acetoxy diacid ester **72** ($R^1 =$ Ac, $R^2 = CH_3$, $R^3 = OH$): isomer B, m.p. 245·3–246·3°. This substance, on treatment by the Bowman method (see above), was converted into the diketo ester **72** ($R^1 = Ac$, $R^2 = R^3 = CH_3$): isomer A, m.p. 132·2–133·2°, and isomer B, m.p. 102–104·3°. Even though these isomers are readily interconverted by heating with sodium acetate in methanol, the conditions for the Bowman synthesis are so mild that a specimen of diacid ester rich in one epimer leads to diketo ester which is also predominantly one isomer, in the same epimeric series. As in the aldosterone series,[1] the Baeyer-Villiger oxidation of the diketo ester was stereospecific, the A series leading to a triacetate, m.p. 117·7–118·7°, and the B to triacetate, m.p. 121·4–122·7°, **73** ($R^1 = R^3 = Ac$, $R^2 = CH_3$). Each of these products, on mild saponification, was transformed into the respective dihydroxy lactones **74**, A, m.p. 220–221°, and B, m.p. 216–218°. As in the model series, attempts to effect selective saponification of the acetate residues without lactone formation were unsuccessful. Methanolic hydrochloric acid treatment also gave only lactonic material. Mercedes Velasco carried the sequence through with the ethyl instead of methyl ester hoping that the carboethoxyl group of **73** ($R^1 = R^3 = Ac$, $R^2 = C_2H_5$) would be sufficiently more resistant than the carbomethoxyl group to cleavage so that the desired selective hydrolysis could be realized. However, this substance, on saponification under such mild conditions that the acetate residues were not entirely removed, was converted into a product containing a high proportion of lactone. Preliminary attempts to convert the lactone, by treatment with alkali, into the salt of the hydroxy acid, and either to alkylate or oxidize this salt looked very unpromising, apparently because of the extraordinary stability of the lactone ring even under fairly strong alkaline conditions. Attempts to effect selective reduction of the bis-tetrahydropyranyl ether of the lactone **74** to the lactol stage failed. With bis-3-methyl-2-butylborane, there was no reaction; while with one equivalent of lithium aluminum hydride, a mixture of lactone and completely reduced tetraol derivative **75** (R = tetrahydropyranyl) was produced.



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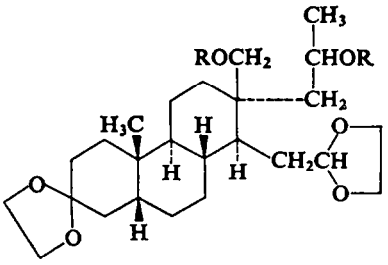

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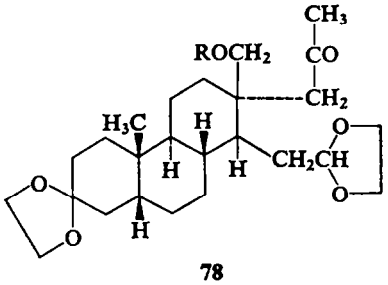

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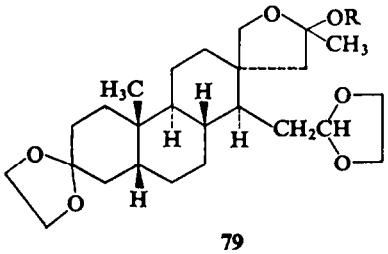

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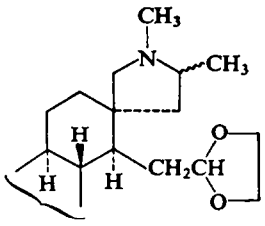
Another attempt to put the readily accessible dihydroxy lactone **74** to synthetic use involved oxidation with Sarett reagent[48] and conversion of the resulting keto aldehyde, by reaction with ethylene glycol, into the ketal acetal lactone **76**. This transformation occurred in 58% yield in both series. Pure isomer A melted at 167·2–168·6°, and B at 194–195·5°. These epimers were readily reduced, with LAH, to the corresponding diols **77** (R=H): isomer A, m.p. 185·3–186·4° (diacetate, **77** (R=Ac), m.p. 116·8–118·2°), and isomer B, m.p. 171–171·5° (diacetate **77** (R=Ac), m.p. 123–125·7°). We hoped that, by analogy to previous work,[1,73,74] *N*-bromoacetamide in t-butyl alcohol and pyridine would effect selective oxidation of the secondary hydroxyl group of **77** (R=H) giving the keto alcohol **78** (R=H) which in turn could be cyclized (as in the case of **61** → **62**) after hydrolysis of the acetal residue. The desired oxidation proceeded in at least 36% yield in the B series and to a lesser extent in the A series. A similar difference in behavior of the two epimers was noted in the aldosterone series.[1] The crude product from the *N*-bromoacetamide oxidation would not crystallize, perhaps because it existed as a tautomeric mixture of hydroxy ketone **78** (R=H) and lactol **79** (R=H), predominantly the latter as suggested by the weak carbonyl absorption in the IR spectrum. An attempt to effect closure of the D ring by treatment of this substance with hydrogen chloride in acetic acid[8b] led to a product showing no absorption for an α,β-unsaturated ketone in the ultraviolet spectrum. We hoped that acetylation would occur preferentially at the primary alcoholic group of the form **78** (R=H), thus shifting the equilibrium with the production of **78** (R=Ac). Unfortunately, the only crystalline product isolated, in 36% over-all yield, was the lactol acetate **79** (R=Ac). The pure substance melted at 182·3–183·3°. Preliminary attempts were made to effect cyclization of ring D, after saponification of the acetate

[73] M. Ehrenstein, G. W. Barber and M. W. Gordon, *J. Org. Chem.* **16**, 349 (1951).
[74] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1165 (1949).

and acid hydrolysis of the acetal residue; however, treatment with sodium acetate in acetic acid[1] or with aqueous potassium hydroxide[75] gave no evidence of the formation of the desired product, and this approach was not pursued further.



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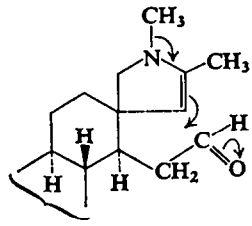
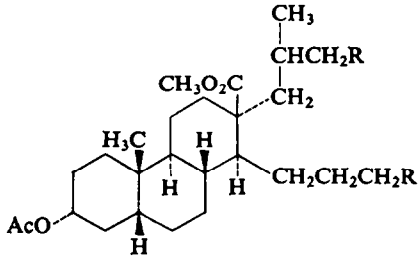


I

Another scheme, which envisaged the use of the diol acetal ketal 77 (R = H), was its conversion into the ditosylate 77 (R = Ts) which, by treatment with methylamine, should give the product H with the pyrrolidine ring. Mercuric acetate oxidation and hydrolysis of the acetal residue should afford the product I which it was hoped would cyclize as suggested by the arrows in formula I. The scheme has been carried only to the stage of the ditosylate which was prepared in 90% yield by Armin Kreutzer from 77 (R = H), isomer A. The pure diester melted at 140–142°. This product was in hand at the time of the completion of the synthesis of conessine as described in Part I of the present paper; hence the work, although promising to this stage, was carried no further.



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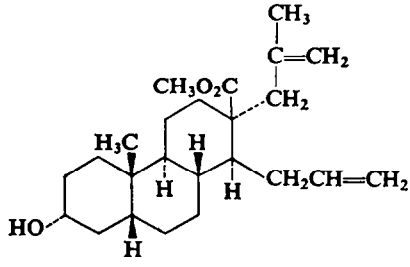

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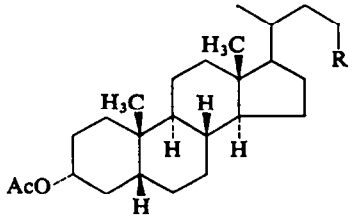

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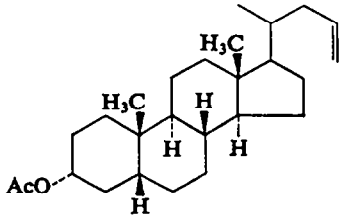


83

Another approach to the degradation of the side chains of the diacid 72 (R^1 = Ac, R^2 = CH_3, R^3 = OH) was explored. The carboxyl groups of this substance were

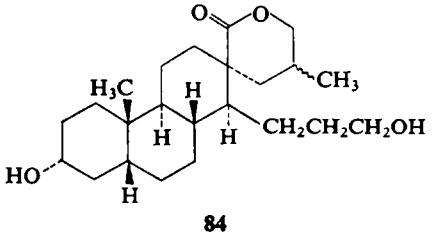
[75] Cf. G. I. Poos, W. F. Johns and L. H. Sarett, *J. Amer. Chem. Soc.* 77, 1026 (1955).

selectively reduced by the action of diborane;[76] thus the diol **80** (R = OH) was produced: isomer B, m.p. 98·5–100°. The plan envisaged the conversion of this substance, by one of a variety of elimination processes, into the diene **81** which on ozonolysis should yield the keto aldehyde desired for cyclization of ring D. Model studies for olefin formation were performed with lithocholic acid 3-acetate **82** ($R = CO_2H$). Reduction with diborane[76] afforded the hydroxy acetate **82** ($R = CH_2OH$), m.p. 62–64°. Pyrolysis of the boric ester[77] prepared either *in situ* by reduction of the acid (see above) or from the crystalline hydroxy acetate, afforded an oil which, as shown by infrared spectroscopy, contained some of the desired olefinic compound **83**. However, vapor phase chromatography indicated the presence of seven major components. The tosylate **82** ($R = CH_2OTs$), m.p. 116–117°, was prepared, but attempts to convert it, by direct elimination, into **83** met with failure. Success was finally realized by the Cope method.[78]

The tosylate was converted, by displacement with dimethylamine, into the dimethylamino compound **82** ($R = CH_2N(CH_3)_2$) which was transformed, with peracetic acid,

$$R = CH_2\overset{\overset{O}{\uparrow}}{N}(CH_3)_2$$

into the *N*-oxide **82** ($R = CH_2\overset{\overset{O}{\uparrow}}{N}(CH_3)_2$) and this in turn was pyrolyzed, giving the desired olefinic acetate **83**, m.p. 111–112°. We then tried to apply the scheme to **80** (R = OH). Tosylation followed by treatment with dimethylamine gave the crystalline diamine **80** ($R = N(CH_3)_2$), isomer B, m.p. 96–97°. Treatment of this product with peracetic acid followed by pyrolysis, however, gave a low yield of a fraction of appropriate volatility for **81**, and the infrared spectrum of this product exhibited only weak absorption in the 11 μ region. Evidently the reaction had taken an abnormal course, and this approach was abandoned.



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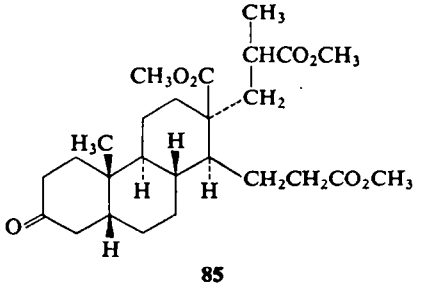

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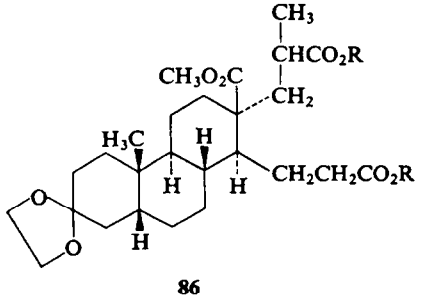

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[76] H. C. Brown and W. Korytnyk, *J. Amer. Chem. Soc.* **82**, 3866 (1960).
[77] W. Brandenberg and A. Galat, *J. Amer. Chem. Soc.* **72**, 3275 (1950).
[78] A. C. Cope and E. M. Acton, *J. Amer. Chem. Soc.* **80**, 355 (1958) and previous papers.

In the course of the study mentioned directly above, it was noted that when the diol **80** (R = OH) was submitted to mild saponification with one mole-equivalent of potassium hydroxide, instead of simply effecting hydrolysis of the acetyl group, the treatment resulted in concomitant lactonization to give the substance **84**. An epimer, m.p. 213–216°, was isolated. We also examined the oxidation of the hydroxy triester **72** (R^1 = H, R^2 = CH_3, R^3 = OCH_3) to the keto triester **85**, isomer A, m.p. 89·5–90·5°. This substance was converted into the ethylene ketal **86** (R = CH_3): isomer A, m.p. 138–139°, and isomer B, m.p. 87–88°. Selective saponification afforded the diacid ketal ester **86** (R = H): isomer B, m.p. 119–126° (mixture of dimorphic forms). Attempts to convert this substance by selective reduction with diborane (see above) into the diol ketal ester gave unpromising results.

EXPERIMENTAL

dl-cis-1-*Methoxy*-8α-*hydroxy*-10a-*methyl*-5,6,6a,7,8,9,10,10a,11,12-*decahydrochrysene*

A mixture of 40·0 g *cis*-1-methoxy-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysen-8-one,[4b] m.p. 119·5–120·6°, and 5·1 g $NaBH_4$ in 950 ml anhyd. isopropyl alcohol was stirred in an atmosphere of N at room temp. for 6 hr. Both the ketone and $NaBH_4$ were powdered prior to addition in order to accelerate dissolution in the isopropyl alcohol. Approximately 50 ml water was added to the clear reaction mixture; then most of the alcohol was removed under reduced press. at steam-bath temp. The solid residue was mixed with 200 ml 5% NaOH aq and extracted thoroughly with benzene. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The benzene soln was concentrated under reduced press. until the volume was approximately 100 ml; then 400 ml hot hexane was added. On cooling, the soln deposited 33·2 g (82% yield) product, m.p. 154–157°.

dl-3α-*Hydroxy*-D-*homo*-18-*noretiocholan*-17a-*one* (**4**)

To a mixture of 40·0 g of **3**,[4b] m.p. 156–158°, 2·2 l. anhyd. ammonia (redistilled from K), and 1·6 l. abs. EtOH was added with stirring a total of 300 g of K metal in 1- to 2-g portions over a period of several hr. The blue color which developed on the addition of a piece of K was allowed to disappear before another portion of the metal was introduced. After the addition of the metal was complete, the NH_3 was allowed to evaporate through a Hg bubbler for protection against atmospheric O, and the colorless residual soln was diluted with ice water and extracted with benzene and ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on removal of the solvent under reduced press. was hydrolyzed by heating for 1 hr under reflux (N atm.) with 300 ml 95% EtOH and 40 ml 10% HCl aq. Most of the EtOH was removed by distillation under reduced press. at steam-bath temp. The residue was diluted with water and extracted thoroughly with 1:3 ether-benzene. The combined organic layers were washed with water, sat. $NaHCO_3$ aq, and then with sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was hydrogenated at atm. press. in 500 ml abs. EtOH containing 6 g KOH over 4 g 10% Pd-C. The reaction was complete in 2 hr with the absorption of 70% of the theoretical amount of H. The mixture was filtered, the filtrate neutralized with AcOH, and most of the solvent removed at reduced press. The residue was diluted with water and extracted with benzene. The combined extracts were washed with water, sat. $NaHCO_3$ aq, followed by sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was dissolved in 150 ml 95% EtOH containing 30 ml water; then 65 ml 2·0 M aqueous semicarbazide hydrochloride and 20 ml pyridine were added. The resulting thick white suspension was heated at steam-bath temp. for 30 min, cooled in ice, and filtered to give the crude semicarbazone, m.p. 265–267°. A small sample of the *semicarbazone* on recrystallization from 95% EtOH was obtained as colorless microcrystals, m.p. 266–267°. (Found: C, 68·85; H, 9·6; N, 12·0. $C_{20}H_{33}O_2N_3$ requires: C, 69·12; H, 9·57; N, 12·01%).

The remainder of the semicarbazone was hydrolyzed by heating under reflux (N atm.) with 150 ml 95% EtOH and 50 ml 10% HCl aq for 2 hr. The warm soln was diluted with water to the point of incipient cloudiness and seeded with authentic ketone. On cooling, the soln deposited 8·73 g (23%

yield) of product, m.p. 145–147°. An additional 2·9 g (8% yield), m.p. 142–146°, was obtained as a second crop from the mother liquors.

The *acetate*, prepared with pyridine–Ac_2O, was obtained as colorless crystals from hexane, m.p. 135–136°. (Found: C, 75·6; H, 9·7. $C_{21}H_{32}O_3$ requires: C, 75·86; H, 9·70%).

PART I. CONESSINE

Isoconessimine (6, X=H)

Conessine, m.p. 121–122° (L. Light and Co., Ltd.), was converted to 6 (X=CN).[15] Our product melted at 183–185° (reported[15] 182–183°). A soln of 2·02 g of 6 and 3 g 85% KOH aq in 25 ml abs. EtOH was heated at reflux under N for 60 hr. The solvent was removed by distillation at reduced press., the solid residue was treated with 75 ml ether, and the mixture filtered. The ether soln was extracted thoroughly with 20% AcOH aq. The acidic aqueous solns were combined, chilled in ice, and made basic with excess cold conc. KOH aq. The alkaline mixture was thoroughly extracted with 1:1 benzene–ether. The combined organic layers were washed with water, followed by sat. brine and, after back-extraction of the aqueous layers, were dried over K_2CO_3 under an atm. of N. The semi-solid residue obtained on evaporation of the solvent at reduced press. was crystallized from aqueous MeOH to give 1·32 g (first crop), m.p. 68–70°, and 0·23 g (second crop), m.p. 66–70°. Repeated recrystallizations from aqueous MeOH afforded a mixture of colorless rods and platelets, m.p. 72·5–74° (reported[15] 92°). (Found: C, 80·6; H, 11·4; N, 8·0. $C_{23}H_{37}N_2$ requires: C, 80·64; H, 11·18; N, 8·18%).

Δ^4-Conanen-3-one (9)

A soln of 1·25 g isoconessimine, m.p. 68–70°, in 20 ml anhyd. ether was mixed with 0·50 g N-chlorosuccinimide (Matheson Coleman and Bell) that had been freshly recrystallized from chf. The mixture was allowed to stand at room temp. in an atm. of N for 45 min, during which period the crystalline chlorosuccinimide gradually changed into an opaque white powder (succinimide). The mixture was filtered, the filtrate diluted to 50 ml with ether, and then it was washed with water, followed by sat. brine. The residue (the N-chloramine) obtained by evaporation of the solvent at reduced press. and room temp. was dissolved in 10 ml anhyd. ether and added to a sat. EtONa soln in 20 ml abs. EtOH. After 1 hr the reaction mixture gave a negative starch-iodide test. A mixture of 3 g AcOH, 3 g AcONa, and 3 ml water was added, and most of the ether was removed by distillation to give a homogeneous soln which was heated at reflux under N for 2 hr. The soln was cooled, made basic with conc. KOH aq, and extracted thoroughly with 1:1 benzene–ether. The combined organic layers were washed with water, followed by sat. brine and, after the usual back-extraction, were dried over K_2CO_3 under N. The brown oily residue obtained on evaporation of the solvent at reduced press. was chromatographed on 60 g of Woelm alumina activity II. The fraction eluted with 25% ether in benzene amounted to 0·74 g of colorless needles, m.p. 99–105°, λ_{max}^{chf} 5·97 μ. Repeated recrystallizations of a specimen from pentane gave transparent needles, m.p. 107–108° (reported[10] 108–110°), $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ϵ 16,000). (Found: C, 80·5; H, 10·2; N, 4·3. $C_{22}H_{33}ON$ requires: C, 80·68; H, 10·16; N, 4·28%).

The m.p. of a mixture of the analytical sample with authentic Δ^4-conanen-3-one, m.p. 109–110°, obtained from Dr. Pappo, showed no depression. The IR spectra of the two specimens were identical.

In an experiment designed to test the efficacy of potassium t-butoxide as the dehydrohalogenating agent, a portion of crude chloramine was divided into two equal parts and treated in parallel experiments with sat. EtONa in EtOH on the one hand and potassium t-butoxide in t-butyl alcohol on the other. Both experiments were conducted as in the example described above, and the resulting crude products were analyzed by UV spectroscopy. In the EtONa–EtOH case the absorption, $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ϵ 11,000), was consistent with the yield in the foregoing example. The product of the potassium t-butoxide–t-butyl alcohol experiment showed a $\lambda_{max}^{95\%\ EtOH}$ 243 mμ (ϵ 3300) corresponding to the considerably lower yields of conanenone.

5β-Conanin-3-one (11)

A soln of 0·370 g of 9, m.p. 99–105°, in 5 ml thiophene-free benzene and 2 ml abs. EtOH containing a drop of 15% KOH aq was hydrogenated at atm. press. and room temp. over 0·10 g 10% Pd-C (Engelhard Industries). Gas uptake was complete within 10 min. The mixture was filtered, diluted with ether, and washed with water, followed by sat. brine. The oily residue obtained on evaporation

of the solvent at room temp. was triturated with hexane to yield 0·320 g of crystals, m.p. 115–125°. Recrystallization from hexane afforded 0·250 g, m.p. 127–129°, λ_{max}^{chf} 5·82 μ. Repeated recrystallizations of a sample from hexane gave colorless transparent chunky prisms, m.p. 130·5–131° (reported[10] 133–134°). (Found: C, 80·0; H, 10·6; N, 4·1. $C_{22}H_{35}ON$ requires: C, 80·19; H, 10·71; N, 4·25%).

5β-Conanin-3α-ol (**10**)

A soln of 0·096 g of **11**, m.p. 127–129°, in 5 ml anhyd. THF was added to a soln of 1·4 g of lithium tri-t-butoxyaluminum hydride (Metal Hydrides Inc.) in 5 ml THF. After 90 min at room temp., the soln was diluted with ether; then 0·5 ml water and 0·4 ml 10% KOH aq were carefully added with cooling. After the resulting ppt became granular it was separated by filtration. The residue obtained on evaporation of the filtrate at reduced press. was chromatographed on 5 g Woelm alumina activity II. The fraction eluted with 25% ether in benzene amounted to 0·088 g of colorless transparent plates, m.p. 127–131°. Repeated recrystallizations of a sample from pentane afforded material m.p. 130·5–131°, resolidifying at 132–135° and remelting at 151–151·5° (reported[10] 132°). In later experiments only the higher-melting modification was obtained. (Found: C, 79·6; H, 11·2; N, 4·5. $C_{22}H_{37}ON$ requires: C, 79·70; H, 11·25; N, 4·23%).

5β-Conanin-3-one (**11**) *from 5β-conanin-3α-ol* (**10**)

A soln of 0·250 g CrO_3 in 0·7 ml conc. H_2SO_4 was diluted to a volume of 10 ml with water; then a 1·50-ml portion of it was added with cooling to a soln of 0·103 g of the aforementioned conaninol, m.p. 127–131°, in 4 ml glacial AcOH containing a drop of conc. H_2SO_4. The reaction mixture was maintained at ice-bath temp. for 1 hr, and then was treated with a drop of EtOH in order to consume excess oxidant. The soln was diluted with water, made basic with conc. KOH aq, and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. was chromatographed on 7 g Woelm alumina activity II. The fraction eluted with 5% ether in benzene amounted to 0·570 g ketone, m.p. 125–128°. Recrystallization from hexane afforded material, m.p. 128–130°, undepressed on admixture with the authentic **11**. The IR spectra of the two materials were identical.

Δ⁴-Conanen-3-one (**9**) *from 5β-conanin-3-one* (**11**)

Method A. A soln of 0·023 g Br in 0·6 ml anhydrous dimethylformamide was added slowly at room temp. (N atm.) with stirring to a soln of 0·050 g of **11**, m.p. 127–129°, and 0·04 g *p*-toluenesulfonic acid monohydrate in 2 ml anhydrous dimethylformamide. The addition required 3·5 hr since drops were added only after the previous drop had completely reacted, as determined by disappearance of color. An additional 0·05 g of *p*-toluenesulfonic acid monohydrate was added during this addition period in order to maintain a reasonable rate of reaction. After the addition was complete, the soln was stirred for 30 min, chilled in ice, diluted with water, and made basic with conc. KOH aq. The mixture was extracted with 1:1 benzene–ether, and the combined organic layers were washed with water, followed by sat. brine, and dried over K_2CO_3. The yellow oily residue obtained on removal of the solvent was kept in a desiccator at 0·1 mm for 8 hr, and then was used without further purification. A soln of this bromo ketone in 2 ml anhydrous dimethylformamide containing 0·193 g anhydrous LiBr was stirred and heated at 100° for 10 hr. The mixture was cooled, diluted with water, made basic with cold conc. KOH aq, and extracted with 1:1 benzene–ether. The combined organic layers were washed with water, followed by sat. brine, and dried over K_2CO_3. The oily residue, $\lambda_{max}^{95\%\ EtOH}$ 239 mμ (ϵ 4200), obtained on evaporation of the solvent at reduced press. was chromatographed on 2 g Woelm alumina activity II. The first fraction eluted with 25% ether in benzene afforded 0·006 g crude **11**, m.p. 103–130°. The next fraction yielded an oil which could not be induced to crystallize. The following fractions afforded 0·009 g of **9**, m.p. 103–105°. Recrystallization from pentane gave colorless crystals, m.p. 105–106°, undepressed on admixture with the authentic conanenone described above. The IR spectra of the two specimens were identical.

Method B. A soln of 0·016 g Br in 0·25 ml AcOH was added with stirring at room temp. to a soln of 0·036 g of **11**, m.p. 127–129°, in 1 ml glacial AcOH containing a drop of 48% HBr. Upon completion of the addition, which took 10 min, a compound, possibly the amine hydrobromide, crystallized from the soln. The mixture was neutralized with sat. $NaHCO_3$ aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The oily

residue obtained on evaporation of the solvent was dissolved in 2 ml reagent-grade acetone, 0·059 g tetramethylammonium mesitoate (dried at 100° and 0·1 mm for 2 hr) was added, and the mixture was heated at reflux under N for 1 hr. The mixture was cooled, made basic with sat. $NaHCO_3$ aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was chromatographed as described in the preceding experiment to give a total of 0·009 g of **9**, m.p. 100–105°.

3-Dimethylamino-$\Delta^{3,5}$-conadiene (**8**)

A Carius tube was charged with 0·040 g anhyd. $MgSO_4$, 0·01 g *p*-toluenesulfonic acid monohydrate, 0·075 g of **9**, m.p. 100–105°, and 2 ml benzene; then anhydrous dimethylamine was distilled from KOH pellets through a soda-lime tube into this mixture. After the entire system was saturated with the amine at room temp., the tube was chilled in a Dry Ice–acetone bath and distillation was continued until approximately 1 ml dimethylamine had condensed. The tube was sealed and agitated for 7 days at room temp. The tube was opened, the dimethylamine evaporated under a stream of dry N, and the benzene solution was filtered through a pad of BaO in order to remove the $MgSO_4$ and the *p*-toluenesulfonic acid. The residue obtained on removal of the solvent under a stream of N amounted to 0·075 g yellow crystals. Recrystallization from degassed (i.e., air was removed and replaced by N) acetone under N yielded 0·044 g of buff-colored crystals, m.p. 146–151°, λ_{max}^{ether} 271 mμ (ε 18,000). Repeated recrystallizations from degassed acetone afforded buff-colored rods, m.p. 150–151°, λ_{max}^{ether} 271 mμ (ε 18,400). (Found: C, 81·0; H, 10·8; N, 8·0. $C_{24}H_{37}N_2$ requires: C, 81·30; H, 10·80; N, 7·90%).

Conessine (**5**) *from the dienamine* **8**

A soln of 0·052 g crude **8**, λ_{max}^{ether} 271 mμ (ε 18,000), in 5 ml anhydrous degassed dioxan (under N) was added to a suspension of 0·11 g $NaBH_4$ in dioxan. The mixture was allowed to stand for 2 days;[79] then a soln of 0·5 ml AcOH in 1 ml water was added, and the mixture was heated at reflux for 1 hr. The soln was cooled, diluted with water, made basic with cold conc. KOH aq and extracted with 1:1 benzene–ether. The combined organic layers were washed with water, followed by sat. brine, and after the usual back-extractions were dried over K_2CO_3. The residue obtained on removal of the solvent at reduced press. was chromatographed on 2 g Woelm alumina activity II. The fraction eluted with 25% ether in benzene amounted to 0·038 g crystals, m.p. 80–115°. Recrystallization from acetone afforded 0·018 g conessine, m.p. 119–121°. Material of comparable quality from another experiment on further recrystallization from acetone yielded colorless plates, m.p. 124·5–125°, undepressed on admixture with natural conessine. The IR spectra of the two specimens were identical.

3-Dimethylamino-$\Delta^{3,5}$-cholestadiene

A mixture of 0·40 g anhyd. $MgSO_4$, 0·01 g *p*-toluenesulfonic acid monohydrate, and 0·196 g Δ^4-cholesten-3-one,[80] m.p. 78–80°, in 2 ml benzene was treated as described above with anhyd. dimethylamine. After 4 days at room temp., the product was isolated as described above to give 0·20 g crude oily dienamine which, on trituration with acetone, was converted into yellow crystals, m.p. 60–80°, λ_{max}^{ether} 271 mμ (ε 18,000). Repeated recrystallizations from acetone afforded buff-colored rods, m.p. 99–100°, λ_{max}^{ether} 271 mμ (ε 19,000). (Found: C, 84·1; H, 11.7; N, 3.9. $C_{29}H_{49}N$ requires: C, 84·60, H, 12·00; N, 3·40%).

3β-Dimethylamino-Δ^5-cholestene

A soln of 0·180 g crude dienamine, λ_{max}^{ether} 271 mμ (ε 18,000), described in the preceding experiment, in 20 ml anhydrous degassed dioxan was treated with 0·10 g $NaBH_4$ and then with 0·5 ml AcOH in 1 ml water as described in the prep. of conessine. The crude semicrystalline product which was isolated as described was chromatographed on 7 g Woelm alumina activity II. The fractions eluted with 25% benzene in 60–68° pet. ether amounted to 0·055 g colorless crystals, m.p. 138–151°. Recrystallization from ether afforded colorless plates, m.p. 148–151° (reported[21] 151°).

[79] As shown in later work (ref. 19) there was no reaction during this operation which, therefore, is unnecessary.

[80] L. F. Fieser, *Organic Syntheses* **35**, 43 (1955).

dl-17$\alpha\beta$-*Methyl*-D-*homo*-18-*noretiocholane*-3α,17aα-*diol* (**12**, R = H).

MeLi was prepared[81] by the dropwise addition of 40·8 ml MeI to a stirred suspension of 410 cm Li wire, cut into 10-cm lengths, in 600 ml anhydrous ether. After the addition was complete, the mixture was stirred and heated at reflux for 2 hr; then it was cooled, and the excess Li wire was carefully removed. A soln of 11·60 g of **4**, m.p. 144–146°, in 600 ml anhydrous ether was slowly added with stirring to the aforementioned MeLi soln. After addition was complete (ca. 30 min), the mixture was stirred and heated at reflux for 3 hr; then it was cooled and treated with excess cold $Na_2S_2O_3$ aq. The aqueous layer was extracted with ether, and the combined organic layers were washed with $Na_2S_2O_3$ aq, water, sat. brine, and were dried over Na_2SO_4. Removal of the solvent at reduced press. left 11·90 g colorless solid which was suitable for use in subsequent transformations. Recrystallization from acetonitrile afforded 10·0 g (first crop), m.p. 152–154°, and 1·52 g (second crop), m.p. 120–134°. A sample of the first-crop material on two recrystallizations from ether afforded colorless needles, m.p. 155–156°. (Found: C, 78·5; H, 11·2. $C_{20}H_{34}O_2$ requires: C, 78·38, H, 11·18%).

In another experiment carried out as described above, there was obtained from 15·60 g of **4**, m.p. 144–146°, a crude product which on recrystallization from acetonitrile afforded 14·77 g (first crop). m.p. 151–153°, and 1·4 g (second crop), m.p. 125–135°. The first-crop material, amounting to a 90% yield, was used for the preparation of the acetate described below.

dl-17$\alpha\beta$-*Methyl*-D-*homo*-18-*noretiocholane*-3α,17aα-*diol 3-acetate* (**12**, R = Ac)

A soln of the aforementioned 14·77 g of diol **12** (R = H), m.p. 151–153°, in 120 ml anhyd. pyridine containing 25 ml Ac_2O was allowed to stand at room temp for 12 hr. The mixture was then heated on a steam bath for 30 min, cooled, poured into a large volume of ice and water, and extracted thoroughly with ether. The combined organic layers were washed in turn with water, 2% H_2SO_4 aq, water, 5% $NaHCO_3$ aq, sat. brine, and were finally dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was satisfactory for the dehydration experiment described below. Crystallization from acetonitrile gave 14·39 g (first crop), m.p. 164–166°, and 0·62 g (second crop), m.p. 150–158°. Recrystallization of a sample of the first-crop material from acetonitrile gave colorless heavy needles, m.p. 166–167°. (Found: C, 75·9; H, 10·6. $C_{22}H_{36}O_3$ requires: C, 75·81; H, 10·41%).

Dehydration of the hydroxy acetate **12** (R = Ac)

The dehydration of the hydroxy acetate as well as the succeeding ozonolysis experiment appeared to give essentially the same results irrespective of whether crude or purified starting material was employed. A soln of 5·22 g hydroxy acetate, m.p. 130–145°, in 50 ml anhyd. pyridine and 6·0 ml $POCl_3$ was heated at 100° under N for 3 hr. The soln was then cooled, poured onto cracked ice and extracted with ether. The combined organic layers were washed with water, 2% H_2SO_4 aq, again with water, 5% $NaHCO_3$ aq, sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. amounted to 5·01 g yellow oil which was of sufficient purity for use in subsequent reactions. A 0·200-g sample of this oil was chromatographed on 13 g Florisil. The major product was eluted with 50% hexane in benzene, giving 0·195 g colorless oil. The IR spectra of the first and last fractions were identical with that of the crude unchromatographed product. Evaporative distillation at 105° (0·05 mm) afforded 0·175 g colorless oil consisting of dl-17a-*methyl*-D-*homo*-18-*nor*-$\Delta^{13,17a}$-*etiocholen*-3α-*ol acetate* (**13**) contaminated with double-bond isomers. (Found: C, 79·7; H, 10·2. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·37%).

The 60-mc NMR spectrum of this product in CCl_4 (TMS internal standard) showed a total absorption for approximately 0·25 vinyl hydrogen at $\delta = 5{\cdot}2$–$5{\cdot}3$ ppm. The remainder of the spectrum was consistent with the structure **13**, showing in particular absorption at 1·59 ppm for the 17a-methyl protons. The absorption for the C-19 methyl protons appeared partly at 0·84 and partly at 0·88 ppm, presumably due to the mixture of bond isomers.

An attempt to effect the dehydration with $POCl_3$ in pyridine at 5° for 16 hr failed; the hydroxy acetate was completely recovered. Treatment for 24 hr at room temp. or for 30 min at 100° effected dehydration of approximately one-half of the material.

Treatment of the hydroxy acetate with 98% formic acid or with iodine[82] gave olefinic mixtures

[81] Cf. G. Stork and F. H. Clarke, *J. Amer. Chem. Soc.* **83**, 3114 (1961).
[82] M. S. Newman and S. Otsuka, *J. Org. Chem.* **23**, 797 (1958).

which contained somewhat more vinyl hydrogen as estimated by the NMR spectrum. The yield of diketone **14** obtained on ozonolysis of these products was decreased somewhat.

dl-4bβ-*Methyl*-1β-(4-*ketopentyl*) 2-*keto*-7α-*acetoxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**14**)

A soln of 0·260 g of the aforementioned colorless evaporatively distilled dehydration product containing **13** in 5·0 ml anhydrous CH_2Cl_2 containing 0·15 ml anhydrous pyridine, was treated at −70° with O_2 containing O_3. As the reaction proceeded, the color of the solution first changed to a bright yellow, then gradually faded, becoming colorless. At this point the flow of O_3 was stopped, and 0·5 ml 36% aqueous HCHO was added with thorough mixing. The cold soln was allowed to warm to room temp. over a 2-hr period. It was then diluted and extracted with ether. The combined organic layers were washed with water, 2% H_2SO_4 aq, a dil. $FeSO_4$ aq in 2% H_2SO_4 aq, water, dil. $KHCO_3$ aq, sat. brine, and finally were dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. amounted to 0·262 g yellow oil, λ_{max}^{film} 2·90 μ (OH), 3·72 (aldehyde CH), 5·78 (ester C=O), 5·87 (aldehyde and ketone C=O), and 8·05 (acetate). Material of this quality could be used directly in the cyclization reaction described below.

An 80-mg specimen of the crude diketo acetate was chromatographed on 6 g silica gel. The fraction eluted with 10–25% ether in benzene gave a total of 41 mg crystalline **14**. Repeated recrystallizations from ether–pet. ether afforded colorless short, flat blades, m.p. 79·5–80·5°, λ_{max}^{chf} 5·78 μ (ester C=O) 5·87 (ketone C=O) and 8·05 (acetate). The 60-mc NMR spectrum in CCl_4 of this material (TMS standard) showed absorption for 1 proton at δ = 4·4–4·8 ppm (CHOAc), for 3 protons at 2·03 (MeC=O), for 3 protons at 1·92 ($MeCO_2$) and 0·88 (angular Me). (Found: C, 72·9; H, 9·6. $C_{22}H_{34}O_4$ requires: C, 72·89; H, 9·45%).

In another experiment a 0·985-g specimen of total crude dehydration product (from 1·05 g of **12**, m.p. 164–166°) was evaporatively distilled at 120° (0·07 mm) and ozonized as described above in 25 ml CH_2Cl_2 containing 0·6 ml pyridine. Recrystallization of the chromatographed product gave 0·303 g diketone, m.p. 76–79°. Recrystallization from ether–pet. ether gave 0·269 g, m.p. 78–80°.

dl-3α-*Hydroxy*-18-*nor*-"$\Delta^{13(17)}$"-*pregnen*-20-*one* (**15**)

A mixture of 49 mg of **14**, m.p. 79·5–81°, 4·00 ml 95% EtOH, 1·00 ml water, and 56 mg 85% KOH aq was allowed to stand at room temp. At various intervals 25-μl aliquots were withdrawn, diluted to 10 ml with 95% EtOH, and the extinction coefficient at 257 mμ in the UV spectrum was observed. After 1 hr, ε = 5700; 2 hr, 8000; 12 hr, 11,300; and 22 hr, 11,300. The soln was neutralized with AcOH, diluted with water, and extracted with ether. The combined organic layers were washed with water, 5% $NaHCO_3$ aq, sat. brine, and were dried over Na_2SO_4. The colorless solid residue obtained on removal of the solvent at reduced press. was recrystallized from aqueous EtOH to give 25 mg of the unsaturated ketone, m.p. 77–79°. An additional 6 mg, m.p. 64–68°, was obtained from the mother liquors by extraction and crystallization from acetonitrile. Repeated recrystallizations of the first-crop material from aqueous EtOH gave colorless hygroscopic needles, m.p. 72–74°, on slow heating, $\lambda_{max}^{95\%\ EtOH}$ 257·5 mμ (ε 13,500). The 60-mc NMR spectrum of this substance in chf soln (TMS standard) showed absorption at δ = 3·2–3·7 ppm (C-3 H), 2·20 (C-21 Me) and 0·93 (C-19 Me). (Found: C, 79·2; H, 10·2. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%).

The m.p. recorded above was not always observed since this material appeared to exist in two forms, the m.p.s of which seemed to depend on the state of hydration and hence on the rate of heating. Thus m.p.s ranging from 72–78° and 102–110° were observed.

In a somewhat simplified version of the foregoing experiment, a 0·250-g specimen of the acetoxy diketone, m.p. 78–80°, was treated with 20 ml 95% EtOH, 5 ml water, and 0·280 g KOH as described above. After 22 hr the mixture was diluted with water to the point of incipient cloudiness, and a seed of the unsaturated ketone was added. On cooling there was obtained 0·135 g colorless needles, m.p. 74–77°.

In one experiment a 15·6-g specimen of **4**, m.p. 144–146°, was carried through the reaction sequence involving addition of MeLi, acetylation, dehydration, ozonolysis, and cyclization without purification of intermediates. The crude **15** was purified by chromatography on Florisil. The fraction eluted with 25% ether in benzene to pure ether on crystallization from aqueous EtOH gave 3·14 g hydroxy ketone, m.p. 74–78°. This represents a 35% over-all yield for the five reactions.

Hydrocyanation of the unsaturated ketone **15**

(*a*) *By the potassium cyanide–ammonium chloride method.*[31] A soln of 0·540 g of the aforementioned unsaturated ketone, m.p. 76–78°, 0·200 g KCN, and 0·120 g NH_4Cl in 11·0 ml dimethylformamide (distilled from BaO) and 1·4 ml water was stirred at 100° for 8 hr. The mixture was then cooled, diluted with water, and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. amounted to 0·594 g crude cyano ketone mixture, λ_{max}^{film} 2·90 μ (OH), 4·48(C≡N), and 5·88 (ketone C=O). TLC on silica gel with a 1:1 AcOEt–ether solvent system showed two spots, R_f 0·23 and 0·42.

The crude product was chromatographed on 50 g silica gel, and sixteen 100-ml fractions were collected by elution with 35–50% ether in benzene. Fractions 1–3 showed only one spot at R_f 0·42 on TLC and were combined and crystallized from AcOEt–heptane to give 0·136 g dl-3α-*hydroxy*-18-*nitrilo*-13α,17α-*pregnan*-20-*one* (**16**) as colorless plates, m.p. 142–145°. Repeated recrystallizations from AcOEt-heptane raised the m.p. to 144–145°. (Found: C, 76·4; H, 9·4; N, 4·4. $C_{21}H_{31}NO_2$ requires: C, 76·55; H, 9·48; N, 4·25%).

Fractions 6–16, showing on TLC a major spot at R_f 0·23 and a minor spot at R_f 0·42, were combined and crystallized from AcOEt to give 0·145 g dl-3α-*hydroxy*-18-*nitrilopregnan*-20-*one* (**17**), m.p. 155–167°. Recrystallization from AcOEt gave 0·124 g colorless prisms, m.p. 168–172°. Repeated recrystallizations gave material, m.p. 169–171°. (Found: C, 76·7; H, 9·4; N, 4·5. $C_{21}H_{31}NO_2$ requires: C, 76·55; H, 9·48; N, 4·25%).

In later experiments the 13α-cyano ketone was obtained in another crystalline form, namely prisms, m.p. 169–171°, by slow crystallization from AcOEt. This material exhibited the same TLC behavior as the 144–145° modification. On admixture the two forms melted at 165–170°.

The intermediate fractions from the chromatogram described above and the mother liquors from the crystallizations were combined and rechromatographed on 20 g silica gel. By combination of the appropriate fractions as ascertained by TLC and recrystallization, an additional 44 mg of the 13α-cyano ketone, m.p. 140–144°, and 42 mg. of the 13β-cyano ketone, m.p. 167–175°, were obtained.

(*b*) *By the hydrogen cyanide–triethylaluminum method.*[34a] A 0·20-ml portion of a soln of 2·5 ml anhyd. liquid HCN in 5·0 ml anhyd. THF was mixed with 1 ml anhyd. THF containing a 0·80-ml portion of a mixture prepared by mixing 13·5 ml 25% Et_3Al in heptane (Texas Alkyls) with 20·0 ml anhyd. THF. This hydrocyanation reagent was then added to a soln of 0·101 g of **15**, m.p. 73–77°, in 3 ml THF, and the mixture was stirred at 25° for 20 hr. The gelatinous reaction mixture was diluted with ice-cold 2N NaOH and extracted with ether. The combined organic layers were washed with water, cold 2N NaOH, water, 10% HCl, water, sat. brine, and were dried over Na_2SO_4. The residue obtained on evaporation of the solvent was chromatographed on 10 g silica gel. The early fractions eluted with 20–30% ether in benzene appeared (by TLC) to consist of an inseparable mixture of 13α-cyano ketone and starting unsaturated ketone which could not be crystallized. The fraction eluted with 35% ether in benzene upon recrystallization from AcOEt–hexane afforded 25 mg 13β-cyano ketone, m.p. 174–177°.

Dehydrocyanation of the 13α*-cyano ketone* **16** *and reconversion to the* 13β *isomer* **17**

A 0·125-g sample of the 13α-cyano ketone, m.p. 165–169°, was distilled by heating at 350° in a short-path apparatus under a slight positive press. of N. Gas (HCN) was evolved during the heating, and the distillate amounted to 0·102 g pale yellow oil, $\lambda_{max}^{95\%\ EtOH}$ 257 mμ (ϵ 8000). The UV extinction coefficient corresponded to 60% of the α,β-unsaturated ketone. The remaining 40% of the material was presumably the β,γ-unsaturated isomer.

Hydrocyanation of the aforementioned crude distillate according to the procedure described above (Part *a*), followed by chromatography on silica gel, gave 24 mg of **16**, m.p. 165–170°; 14 mg of **17**, m.p. 166–173°; 14 mg of a mixture of the two cyano ketones (TLC, R_f 0·2 and 0·4); and 28 mg oily unconjugated ketone which was probably the β,γ-tautomer of **15**.

A 25 mg sample of **15**, m.p. 74–78°, was distilled as above at 350°. The oily distillate (23 mg) showed $\lambda_{max}^{95\%\ EtOH}$ 257 mμ (ϵ 9700), indicating 67% of the α,β-unsaturated ketone. Redistillation afforded material with $\lambda_{max}^{95\%\ EtOH}$ 257 mμ (ϵ 7400) corresponding to 51% of α,β-unsaturated ketone.

Attempted dehydrocyanation with alcoholic sodium hydroxide

A soln of 60 mg of **16**, m.p. 167–171°, in 3·5 ml 95% EtOH and 0·6 ml 10% NaOH aq was allowed

to stand at room temp. for 2 hr. The soln was then diluted with water and extracted with AcOEt. The combined organic layers were washed with water, followed by sat. NaCl aq, and dried over Na_2SO_4. The colorless solid residue obtained on evaporation of the solvent at reduced press. showed λ_{max}^{chf} 2·89–3·0 μ (OH, NH), and 5·95 (imino lactone or lactam). Crystallization from AcOEt gave 36 mg (first crop), m.p. 182–192°, and 26 mg (second crop), m.p. 174–191°. Repeated recrystallization from AcOEt afforded small colorless needles, m.p. 185–197°, formulated as the C-20 epimeric mixture of either dl-3α,20,20-*trihydroxy*-18-*acido*-13α,17α-*pregnan*(18 → 20)*iminolactone* (**18a**) and/or dl-3α,20-*dihydroxy*-20-*amino*-18-*acido*-13α,17α-*pregnane*(18 → 20)*lactone* (**18b**). (Found: C, 72·9; H, 9·6; N, 3·8. $C_{21}H_{33}O_3N$ requires: C, 72·58; H, 9·57; N, 4·03%).

Reduction of the 13α-*cyano ketone* **16** *to give the imino lactone* **19** *and conversion of the latter to the lactone* **20**

A soln of 60 mg 13α-cyano ketone, m.p. 171–173°, in 4 ml anhyd. THF containing 0·287 g lithium tri-t-butoxyaluminum hydride was stirred at 0° for 1·5 hr. The soln was then poured into water and extracted with 1:1 benzene–ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 58 mg crystalline imino lactone, λ_{max}^{chf} 2·7–3·1 μ (OH, NH) and 5·98 (C=N). Repeated recrystallizations from benzene–hexane gave colorless prisms, m.p. 211–220°, regarded as the C-20 epimeric mixture of dl-3α,20-*dihydroxy*-18-*acido*-13α,17α-*pregnan*(18 → 20)*iminolactone* (**19**). (Found: C, 76·3; H, 10·3; N, 4·1. $C_{21}H_{33}O_2N$ requires: C, 76·08; H, 10·03; N, 4·23%).

The same product could be isolated when LAH or $NaBH_4$ was used as the reducing agent.

The hydrolysis of **19** to **20** was carried out as follows. A mixture of 41 mg of crude crystalline **19**, 5 ml AcOH, 5 ml water, and 1 ml 85% H_3PO_4 was heated at reflux under N for 24 hr. The soln was then cooled, poured into water, and extracted with 1:1 benzene–ether. The combined organic layers were washed with water, 10% $KHCO_3$ aq, sat. brine, and were dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 38 mg of a semicrystalline solid, λ_{max}^{chf} 2·8 μ (OH), 5·72 (γ-lactone C=O) and 5·78 (ester C=O). The last-mentioned band in the IR spectrum indicated that the 3-acetate had been formed, at least in part. This crude product was saponified by heating with 0·5 ml 10% NaOH aq in 4 ml 95% EtOH at 50° under N for 1 hr. The crude product, isolated as described directly above, amounted to 31 mg crystalline lactone. Recrystallization from benzene–hexane gave colorless prisms, m.p. 95–215°, regarded as the C-20 epimeric mixture of dl-3α,20-*dihydroxy*-18-*acido*-13α,17α-*pregnane*(18 → 20)*lactone* (**20**). (Found: C, 75·8; H, 9·75. $C_{21}H_{32}O_3$ requires: C, 75·86; H, 9·70%).

Hydride reduction of the 13β-*cyano ketone* **17** *to give* **21** *and conversion of the latter to the imino lactone and lactone*

To a soln of 61 mg 13β-cyano ketone, m.p. 168–171°, in 4·0 ml anhyd. THF was added 0·73 ml of LAH in THF (concentration 10 mg per ml). A heavy suspension rapidly formed, and the mixture was stirred at 25° for 2 hr and then heated at gentle reflux for 0·5 hr. The mixture was then cooled, treated with a few drops of water, shaken, centrifuged, and the supernatant liquid was decanted and evaporated to dryness, affording a total of 59 mg crystalline cyano diol, λ_{max}^{chf} 2·7–2·9 μ (OH), 4·48 (C≡N), and no absorption from 5·0 to 6·5 μ. Repeated recrystallizations from benzene afforded colorless prisms, m.p. 225–233°, which on TLC (silica gel) showed two spots, R_f 0·18 and 0·23 (1:1 benzene–AcOEt). This material is regarded as the C-20 epimeric mixture of dl-18-*nitrilopregnane*-3α,20-diol (**21**). (Found: C, 75·95; H, 10·0; N, 4·0. $C_{21}H_{33}O_2N$ requires: C, 76·08; H, 10·03; N, 4·23%).

A soln of 38 mg of **21**, m.p. 219–235°, in 5 ml MeOH was treated with 1 ml conc HCl, and the resulting mixture was heated at gentle reflux under N for 3·5 hr. The colorless soln was then cooled and poured over ice. Chilled 1:1 benzene–ether was added with swirling, followed by chilled 10% K_2CO_3 aq. The cold aqueous layer was rapidly extracted with chilled benzene. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 38 mg of crude **22** (R=NH), λ_{max}^{chf} 2·8–3·1 μ (OH, NH) and 6·01 (C=N). This product was hydrolyzed by heating with 2 ml AcOH, 2 ml water, and 0·5 ml 85% H_3PO_4 at 110° under N for 12 hr. The product was then isolated as described above for **20** to give 37 mg colorless oil showing absorption for ester carbonyl in the IR. The material was saponified by heating under gentle reflux with 5 ml MeOH and 1 ml 10% KOH aq. The crude product

isolated as described above amounted to 37 mg semicrystalline lactone showing the characteristic absorption at 5·72 μ in the IR. Crystallization from AcOEt–hexane afforded 15 mg colorless prisms, m.p. 213–215°, regarded as the C-20 epimeric mixture of dl-3α,*20-dihydroxy*-18-*acidopregnane*-(18 → 20)*lactone* (**22**, R = O). (Found: C, 76·1; H, 9·8. $C_{21}H_{32}O_3$ requires: C, 75·86; H, 9·70%).

Ketalization of the 13β-*cyano ketone* **17**

A mixture of 0·130 g 13β-cyano ketone, m.p. 168·5–172°, 0·11 ml ethylene glycol, and 5 mg *p*-toluenesulfonic acid monohydrate in 40 ml benzene was heated at reflux under N for 12 hr. During this process, water was continuously removed by the agency of a Dean-Stark separator. The colorless reaction mixture was then cooled and poured into excess sat. $NaHCO_3$ aq. The organic layer was washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. amounted to 0·140 g crystalline **24**. Recrystallization from AcOEt–hexane gave 0·129 g, m.p. 112–152°. Two more recrystallizations afforded small colorless needles, m.p. 125–155°, regarded as the C-17 epimeric mixture of dl-20-*ethylenedioxy*-18-*nitrilopregnan*-3α-*ol* (**24**). (Found: C, 73·7; H, 9·5; N, 3·5. $C_{23}H_{35}O_3N$ requires: C, 73·95; H, 9·45; N, 3·75%).

The 60-mc NMR spectrum ($CDCl_3$ soln, TMS standard) showed absorption at $\delta = 4·0$ ppm (OCH_2CH_2O), 1·30 (C-21 CH_3), 0·94 (C-19 CH_3). The 3-*acetate* was prepared by the pyridine–Ac_2O method in 90% yield. It crystallized from AcOEt–hexane in the form of colorless flat prisms, m.p. 172–177°. (Found: C, 72·1; H, 8·75; N, 3·2. $C_{25}H_{37}O_4N$ requires: C, 72·25; H, 8·98; N, 3·37%).

dl-5β-*Conanin*-3α-*ol* (**10**)

A mixture of the crude ketal, prepared as described above from 87 mg 13β-cyano ketone, m.p. 169–171°, in 10 ml anhyd. THF and 0·220 g LAH was stirred and heated at reflux for 24 hr. The mixture was then cooled, cautiously treated with 0·44 ml water, followed by 0·35 ml 10% NaOH aq, and diluted with 15 ml anhyd. ether. The granular ppt was removed by filtration, and the filtrate was evaporated at reduced press. to give 98 mg of the imine-amine mixture **25** and **26**, λ_{max}^{film} 2·96 μ (OH, NH) and 6·12 (C=N).

The following modifications did not increase the amount of amine relative to imine as estimated by the relative intensity of the IR absorption band at 6·12 μ and by the amount of neutral material isolated from the subsequent hydrolysis: (1) increasing the heating time to 48 hr; (2) treating the crude isolated amine-imine mixture with an additional fiftyfold excess of LAH after 48 hr and refluxing for an additional 24 hr; (3) using 1:1 dioxan–THF as a solvent to increase the reflux temp.; (4) introducing an additional fiftyfold excess of LAH after 48 hr and refluxing for a further 12 hr; (5) increasing or decreasing the concentration of the cyano ketal while keeping the LAH concentration constant.

In an attempt to effect (a) hydrolysis of the ketal and (b) reductive amination to give **28**, the aforementioned crude imine-amine ketal mixture was dissolved in 4 ml 95% EtOH, and 1 ml 5% aqueous perchloric acid was added. This mixture was then treated with H at atm. press. and room temp. over 0·12 g PtO_2 catalyst. After 20 hr the mixture was filtered, the filtrate diluted with 10% HCl, and extracted with benzene–ether. The combined organic layers were washed with water, followed by saturated brine, and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. amounted to 32 mg neutral material, λ_{max}^{film} 2·92 μ (OH) and 5·87 (C=O), presumed to be a product mixture derived from hydrolysis of the imine portion of the reactant.

The aqueous acidic soln and the aqueous washes were combined and made basic with 10% NaOH aq and extracted with ether–benzene. The combined organic layers were washed with water and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. amounted to 56 mg material which appeared to contain a considerable amount of **27** (or the isomer with an exocyclic double bond) as estimated by the strong absorption at 6·05 μ in the IR spectrum. This product therefore was resubmitted to hydrogenation in 3 ml 95% EtOH containing 0·5 ml 5% aqueous perchloric acid over 0·10 g PtO_2. After 20 hr the product was isolated as described above to give 40 mg crude basic material, λ_{max}^{film} 3·0 μ (OH, NH), containing **28**.

In subsequent experiments the imine-amine ketal mixture was hydrolyzed and the neutral material removed by extraction prior to hydrogenation. The hydrogenation usually failed on first trial even when the crude **27** was first treated with W-2 Raney Ni in EtOH in order to remove any catalyst poisons. In all cases, however, the second reduction attempt with fresh catalyst was successful. In one experiment the hydrogenation, conducted under a pressure of 45 psi, proceeded satisfactorily on the first attempt.

The aforementioned crude **28** was methylated by heating at steam-bath temp. with 0·70 ml 36% aqueous HCHO and 0·20 ml 90% HCOOH according to a previously described procedure.[40] The mixture was cooled, made basic with 10% NaOH aq and extracted with ether–benzene. The combined organic layers were washed with water, followed by sat. brine, and dried over $NaSO_4$. The residue obtained on removal of the solvent under reduced press. was chromatographed on 3 g Woelm alumina activity II. The fraction eluted with 25–35% ether–hexane amounted to 24 mg crystalline solid. Recrystallization from ether–hexane gave 16 mg colorless prisms, m.p. 168·5–170°. (Found: C, 79·45; H, 11·0; N, 4·5. $C_{22}H_{37}ON$ requires: C, 79·70; H, 11·25; N, 4·23%).

The IR spectrum, as well as the mass spectral fragmentation pattern, was identical with that of the natural enantiomer of **10**.

dl-5β-*Conanin*-3-*one* (**11**)

A mixture of 0·149 g of the aforementioned *dl*-5β-conanin-3α-ol, m.p. 168–171°, and 5 ml glacial AcOH was stirred with cooling (ice bath) while 0·25 ml 60% aqueous perchloric acid was added. This was followed by the addition of 1·51 ml of a solution prepared from 0·250 g CrO_3 and 0·75 ml conc. H_2SO_4 diluted to 10 ml with water. The mixture was stored at 0° for 30 min; then a few drops 95% EtOH was added to destroy excess oxidizing agent. The green soln was made basic with 10% NaOH aq, saturated with NaCl and extracted with ether. The combined organic layers were washed with saturated brine and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was chromatographed on 14 g Woelm alumina activity II. The fraction eluted with 3–10% ether in hexane amounted to 0·120 g crystalline ketone, the IR spectrum of which was identical with that of the natural enantiomer of conaninone described above. Further elution with ether gave 15 mg recovered starting alcohol identified by IR comparison. Repeated recrystallizations of the ketone from hexane gave colorless plates, m.p. 147–149°. (Found: C, 80·1; H, 10·8. $C_{22}H_{35}OH$ requires: C, 80·19; H, 10·71%).

dl-*Conessine*

A 0·112-g sample of the crude chromatographed **11** was brominated in 7 ml glacial AcOH containing 0·08 ml 48% HBr with 0·64 ml 0·53M Br in AcOH as described above for the natural enantiomer. The crude bromo ketone, isolated as described above, was dehydrohalogenated with 4 ml dimethylformamide and 0·20 g LiBr as described above. The crude **9**, $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (ε 10,000), isolated as in the case of the natural enantiomer, was chromatographed on 14 g Woelm alumina activity II, affording a total of 36 mg unsaturated ketone, $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ε 16,700–20,000). This product was dissolved in 1·0 ml anhyd. benzene, a soln of 4 mg *p*-toluenesulfonic acid in 0·5 ml anhyd. benzene and 1·5 ml anhyd. dimethylamine was added, and the mixture was chilled in a tube containing 0·30 g anhyd. powdered $MgSO_4$. The tube was then placed in a high-press. hydrogenation bomb and rocked for 48 hr at 45°, opened at −70°, and the product was isolated as described above for the natural enantiomer. The UV spectrum showed λ_{max}^{ether} 268 mμ (ε 9900). The crude enamine in 1·2 ml anhyd. dioxan was stirred for 5 min with 3 mg pulverized $NaBH_4$; then 0·5 ml anhyd. glacial AcOH was added over a 10-min period. The soln was heated at reflux for 1 hr, and the product was isolated as described above for the natural enantiomer. Chromatography of the crude material on 5 g Woelm alumina activity II yielded, in the fractions eluted with 25–50% ether in benzene, 12 mg crude *dl*-conessine. Recrystallization from acetone afforded 7 mg colorless needles, m.p. 121·5–124·5°. The IR spectrum (CCl_4) as well as the mass spectrum of this material was identical with that of natural conessine. Repeated recrystallizations from acetone raised the m.p. to 127–128·5°. (Found: C, 80·8; H, 11·5. $C_{24}H_{40}N_2$ requires: C, 80·84; H, 11·31%).

A mixture of the analytical sample with natural conessine (m.p. 124–125°) melted at 112–126°.

dl-20-*Ethylenedioxy*-18-*nitrilo*-13α,17α-*pregnan*-3α-*ol* (**29**)

A 0·575-g specimen of **16**, m.p. 169–171°, was ketalized with 0·65 ml ethylene glycol and 5 mg *p*-toluenesulfonic acid monohydrate in 50 ml benzene under the conditions described above for the 13β isomer. The crude product isolated as described above amounted to 0·650 g solid cyano ketal, λ_{max}^{film} 2·98 μ (OH) and 4·49 (C≡N). A 50-mg sample of this product on two recrystallizations from AcOEt–hexane gave 30 mg colorless plates, m.p. 174–175°. (Found: C, 74·2; H, 9·6; N, 4·0. $C_{23}H_{35}O_3N$ requires: C, 73·95; H, 9·45; N, 3·75%).

dl-N-*Desmethyl*-5β,13α,17α-*conanin*-3α-*ol* (**23**)

(*a*) *By the reduction of the cyano ketal* **29**. A soln of crude **29** (the total product prepared just as described above from 0·575 g 13α-cyano ketone, m.p. 169–170°), 1·5 g LAH in 50 ml anhyd. THF, and 12 ml anhyd. dioxan was heated at reflux for 24 hr. An additional 0·5 g LAH was added, and heating was continued for 6 hr. The mixture was then cooled, carefully treated with 4·0 ml water, followed by 3·6 ml 10% NaOH aq, diluted with 50 ml anhydrous ether, stirred for 6 hr and filtered. Removal of the solvent at reduced press. gave the crude amino ketal showing no absorption for the cyano group in the IR spectrum. This material was heated with 10 ml 95% EtOH and 10 ml 5% aqueous perchloric acid at steam-bath temp. for 10 min. The soln was then cooled, diluted with HCl aq, and washed with ether. The aqueous acidic soln was made basic with cold 10% NaOH aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 0·400 g solid enamine, λ_{max}^{chf} 3·10 μ (OH, NH) and 6·08 (enamine double bond). The aforementioned crude enamine in 15 ml 95% EtOH containing 3·0 ml aqueous perchloric acid was hydrogenated at atm. press. and room temp. over 0·50 g PtO_2 which had been prereduced in 5 ml 95% EtOH containing 1·0 ml 5% perchloric acid. After 12 hr, 81% of the theoretical amount of H had been absorbed. The mixture was filtered, the filtrate diluted with 1% HCl aq, and washed with ether. The aqueous acid soln was made basic with 10% NaOH aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was recrystallized from MeOH–AcOEt to give 0·200 g colorless needles, m.p. 195–196·5°. Recrystallization raised the m.p. to 196–197°. (Found: C, 79·1; H, 10·9; N, 4·3. $C_{21}H_{35}ON$ requires: C, 79·44; H, 11·11; N, 4·41%).

(*b*) *By catalytic hydrogenation of the* 13α-*cyano ketone* **16**. A soln of 0·108 g 13α-cyano ketone, m.p. 168–172°, in 4 ml 95% EtOH containing 1 ml 5% aqueous perchloric acid was hydrogenated over 55 mg 5% rhodium-on-alumina at 45 psi and room temp. for 24 hr. The mixture was filtered, the filtrate made basic with 10% NaOH aq, and the mixture extracted with benzene. The combined organic layers were washed with sat. brine and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was crystallized from AcOEt to give 49 mg crude pyrrolidino compound, m.p. 179–186°. The IR spectrum of this specimen was identical with that of the pure material described above in Part *a*. Evaporation of the mother liquor from the crystallization gave 40 mg solid which showed weak nitrile absorption at 4·48 μ and weak ketone absorption at 5·85 μ in the IR spectrum.

PART II

dl-20-*Ethylenedioxypregnan*-3α-*ol* (**33**)

To a soln of 89 mg of **24**, m.p. 95–108°, in 1·8 ml anhyd. THF was added with cooling and stirring 13·8 ml 0·17M LAH in THF. The resulting slightly cloudy soln was heated under gentle reflux with stirring under N in an oil bath maintained at 90° for 4·7 hr. During this period a light gray ppt was deposited on the inside of the flask. The mixture was then cooled, and several drops of water were cautiously added with stirring. This mixture was rinsed with water into excess aqueous 10% KOH aq and thoroughly extracted with AcOEt. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 90 mg colorless semicrystalline solid, λ_{max}^{chf} 2·7–3·1 μ (OH, NH) and 6·10 (C=N).

A mixture of 0·156 g of the crude imino compound prepared as described directly above, 5 ml triethylene glycol, 0·62 g 85% KOH pellets, and 3 ml 100% hydrazine hydrate was heated with stirring under N in an oil bath at 130° for 16 hr. The temp. of the bath was then gradually increased to 220° as the excess hydrazine and water were allowed to distill with the aid of a slow stream of N flowing through the system. After a total of 2 hr heating at the higher temp., the pale yellow reaction mixture was cooled, diluted with water and extracted with ether. The combined organic layers were washed with water, followed by brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 0·145 g oil which was chromatographed on 12 g silica gel. The fraction eluted with 8% ether in benzene, a colorless crystalline solid, was recrystallized from hexane, affording 67 mg product, m.p. 119–125°. A combined second and third crop obtained from the mother liquors amounted to 11 mg, m.p. 121–127°. Two additional recrystallizations of the first-crop material from hexane gave colorless prisms, m.p. 121·5–124°. (Found: C, 76·1; H, 10·5; N, 0·0. $C_{23}H_{38}O_3$ requires: C, 76·20; H, 10·56; N, 0·00%).

In the chromatogram described above, later fractions eluted with 50% ether in benzene through pure ether gave 21 mg crude crystalline starting **24** identified by IR comparison.

In another experiment with 0·165 g cyano ketal, m.p. 100–110°, carried out as described above, there was obtained, after chromatography and a single crystallization from hexane, 79 mg (49% yield) of product, m.p. 123–129°.

dl-*Pregnan*-3α-*ol*-20-*one* (**47**)

A soln of 82 mg of **33**, m.p. 123–129°, in 2 ml MeOH was treated with 0·2 ml 5% HCl aq and warmed on a steam bath for 0·5 hr. The soln was concentrated to about one-half the original volume and allowed to cool, whereupon 60 mg hydroxy ketone separated as colorless needles, m.p. 172–173°. An additional 8 mg, m.p. 168–171°, was obtained from the mother liquors. The first-crop material was recrystallized from hexane, affording colorless needles, m.p. 171–173°. (Found: C, 79·1; H, 10·6 $C_{21}H_{34}O_2$ requires: C, 79·19; H, 10·76%).

dl-*Pregnane*-3,20-*dione* (**34**)

A soln of 12 mg of **33**, m.p. 119–123°, in 5 ml acetone (distilled from $KMnO_4$) was treated with 0·1 ml 1N CrO_3–HSO_4[23] and stirred at 29° for 3 min. A few drops of MeOH was added, and the mixture was centrifuged. To the clear supernatant liquid were added 1 ml water, several drops of AcOH, and 1 drop 85% H_3PO_4. This soln was allowed to stand for 4 hr with occasional warming, then poured into excess sat. $NaHCO_3$ aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 10 mg colorless oil which was chromatographed on 1 g silica gel. The fraction eluted with 1:2 ether in benzene amounted to 6 mg crude crystalline dione. Recrystallization from hexane gave 4 mg colorless prisms, m.p. 111–112°. The soln (CS_2) IR spectrum of this specimen was identical with that of the naturally derived[46] enantiomer, m.p. 119–122°. The sample employed for the IR comparison was recovered and recrystallized from hexane, giving colorless prisms, m.p. 109–111°. (Found: C, 79·5; H, 10·3. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%).

dl-20-*Ethylenedioxypregnan*-3-*one* (**35**)

A soln of 66 mg of **33**, m.p. 119–123°, in 1·2 ml anhyd. pyridine was added to a mixture of 0·7 ml pyridine and 67 mg CrO_3.[48] The mixture was stirred at 25° for 18 hr, then cooled in ice as about 8 ml of AcOEt was slowly added. After the addition was complete, the mixture was stirred for 10 min at 25°, filtered through sintered glass, and the ppt was rinsed thoroughly with AcOEt. The combined filtrate and washings were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 72 mg crystalline solid which was chromatographed on 5 g silica gel. The fraction eluted with 5–10% ether in benzene amounted to 54 mg ketal ketone. Two recrystallizations from hexane gave colorless crystals, m.p. 168·5–170·5°. (Found: C, 76·4; H, 9·9. $C_{23}H_{36}O_3$ requires: C, 76·62; H, 10·06%).

In other experiments carried out as described above, it was possible to obtain in 80–85% yield material, m.p. 163·5–166°, after chromatography and a single recrystallization from hexane.

dl-*Progesterone* (**31**)

A soln of 33 mg of **35**, m.p. 163·5–166°, in 1·0 ml AcOH containing 1 drop 48% HBr was stirred and maintained at a temp. of 10° under an atm. of N while 0·71 ml 0·134M Br in AcOH was added dropwise over a 10-min period. After the addition was complete, the soln was stirred for 5 min; then 38 mg AcONa was added, and stirring was continued for an additional 10 min. The mixture was diluted with AcOEt, washed with 5% $KHCO_3$ aq, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was dissolved in 1·5 ml acetone, 75 mg benzyl trimethylammonium mesitoate was added, and the mixture was heated at reflux under N for 1 hr. The mixture was then cooled, diluted with AcOEt, washed with water, then with sat. $KHCO_3$ aq, followed by sat. brine, and dried over Na_2SO_4. The yellow oily residue obtained on evaporation of the solvent at reduced press. was chromatographed on 4 g silica gel. The fraction eluted with 10–25% ether in benzene amounted to 15 mg crude crystalline progesterone. Recrystallization from hexane gave 4 mg colorless prisms, m.p. 182–185°. (Found: C, 80·2; H, 9·7. $C_{21}H_{30}O_2$ requires: C, 80·21; H, 9·62%).

A sample recrystallized 3 times from MeOH and once from hexane melted at 183·5–185·5°. The IR spectrum of this material in chf solution was identical with that of natural progesterone. The mass spectral fragmentation patterns of the two substances were also identical. The comparison of our racemic product with that of Woodward and White[42] is described in the discussion.

dl-18-*Nitrilopregnan-3α-ol-20-one 3-tetrahydropyranyl ether*

The following is an adaptation of a published procedure.[83] To a soln of 0·302 g 13β-cyano ketone, m.p. 171–177°, in 9·0 ml abs. THF were added 0·6 ml dihydropyran and 12 small drops $POCl_3$. The soln was stored under N at 25° for 15 hr. The resulting dark soln was diluted with 150 ml 5% $NaHCO_3$ aq and extracted with benzene. The dark red oily residue obtained on evaporation of the solvent at reduced press. was chromatographed on 45 g Florisil. The fractions eluted with 20% ether in benzene amounted to 0·381 g crystalline tetrahydropyranyl ether. Recrystallization from ether afforded 0·328 g, m.p. 165–168°. Two more recrystallizations from ether afforded colorless prisms, m.p. 166–168°. (Found: C, 75·4; H, 9·5; N, 3·4. $C_{26}H_{39}O_3N$ requires: C, 75·50; H, 9·50; N, 3·39%).

Attempted selective reduction of the lactone **20**

Preparation of dl-13α,17α-*pregnane-3α,18,20-triol.* A soln of bis-3-methyl-2-butylborane in diglyme was prepared from 5·8 g 2-methylbutene-2, 1·2 g $NaBH_4$, and 5·9 g borane trifluoride etherate in 20 ml of diglyme according to the procedure of Brown.[51]

A 1·3-ml portion of the bis-3-methyl-2-butylborane soln was added with stirring to a cold (0°) soln of 52 mg of **20**, m.p. 196–208°, in 1 ml anhyd. diglyme and 1 ml anhyd. THF. The cloudy soln was allowed to warm to 25°, stirred for 15 hr, then cooled to 0°, and a soln of 3 drops of 0·1N NaOH in 0·6 ml 30% H_2O_2 was rapidly added with stirring. This mixture was diluted with water and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 53 mg of a glass, the IR spectrum of which was almost identical with that of the starting lactone. This material therefore was retreated as described above using 2 ml anhyd. THF and 8·5 ml 3-methyl-2-butylborane soln. The reaction mixture was heated with stirring at 80° for 4 hr. The crude product isolated as described directly above showed no carbonyl absorption in the IR spectrum. Chromatography on 5 g silica gel gave, on elution with 50% ether in hexane through 100% ether, 37 mg oil which was treated in the usual manner for a Huang-Minlon reduction (except that the hydrazone formation period was extended to 22 hr) with 3 ml triethylene glycol, 1 ml 100% hydrazine hydrate, and 0·10 g 85% KOH aq in order to convert any lactol into C-18 methyl compound. The crude product isolated from this treatment amounted to 26 mg from which 12 mg triol remained after trituration with ether. Two crystallizations of this product from AcOEt gave short colorless needles, m.p. 223–224°. (Found: C, 74·7; H, 10·7. $C_{21}H_{36}O_3$ requires: C, 74·95; H, 10·78%).

An attempt was made to effect selective reduction of 50 mg of **20**, m.p. 170–205°, in 0·5 ml anhyd. THF with a total of 1·74 ml 0·31M LAH in THF. After a total of 4 hr at 25°, the mixture was treated with dil. HCl aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The semi-solid residue obtained on evaporation of the solvent at reduced press. was triturated with AcOEt, leaving 16 mg triol, m.p. 213–222°. Evaporation of the mother liquor left an oil which was mainly the starting lactone as shown by IR comparison.

dl-20-*Ethylenedioxy*-13α,17α-*pregnan-3α-ol* (**38**)

A soln of 0·102 g of **29**, m.p. 171–173°, 6·5 ml anhyd. THF, and 1·2 ml 0·35M LAH in THF was heated at gentle reflux under N for 4 hr. The mixture was then cooled, treated with wet ether and centrifuged. Removal of the solvent from the supernatant liquid gave crude **37**, contaminated with cyano ketal, as a colorless solid, λ_{max}^{chf} 2·7–3·1 μ (OH, NH), 4·48 (C≡N), and 6·14 (C=N). It is to be noted that material prepared in this manner on treatment with methanolic NaOH according to Nagata's procedure[30] was indeed hydrolyzed to a crude product showing a strong absorption for the aldehyde carbonyl group at 5·88 μ in the IR spectrum.

A mixture of the crude imine, 3·5 ml triethylene glycol, 1·5 ml 100% hydrazine hydrate, and 85 mg 85% KOH aq was heated at 130° for 18 hr. The temp. was raised to 210° while the excess water and hydrazine were allowed to distill, and it was maintained at 210° for 3 hr. The mixture was then cooled, diluted with water and extracted with ether. The combined organic layers were washed with water,

[83] S. P. Barton, D. Burn, G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.* 1957 (1959).

followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. was chromatographed on 13 g Florisil. The fraction eluted with 5% acetone in hexane amounted to 18 mg of crude crystalline **38**, m.p. 136–142°. Three recrystallizations from hexane gave colorless prisms, m.p. 141–142·5°. (Found: C, 76·1; H, 10·55. $C_{23}H_{38}O_3$ requires: C, 76·20; H, 10·56%).

Further elution of the chromatogram with 10% acetone in hexane afforded 60 mg crude crystalline starting cyano ketal identified by IR comparison.

dl-13α,17α-*Pregnane*-3,20-*dione* (**39**)

To a soln of 19 mg of **38**, m.p. 136–142°, in 3 ml acetone was added, with stirring, 0·19 ml 1N CrO_3–H_2SO_4.[23] After 3 min the mixture was treated as described above for the preparation of **34**. The crude product amounted to 16 mg colorless oil which was chromatographed on 2 g Florisil. Elution with 2% acetone in hexane afforded 14 mg of crude crystalline **39**. Recrystallization of 6 mg of this material from hexane gave 3 mg colorless prisms, m.p. 138–142·5°. (Found: C, 80·0; H, 10·3. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%).

dl-18-*Nitrilo*-5β-*cholestane*-3α,20-*diol* (**40**)

Anhyd. $MgBr_2$ was prepared[52] from 55 mg triply sublimed Mg metal turnings and 0·20 ml ethylene bromide in 3 ml anhyd. THF by stirring under N at 50° for 0·5 hr. A soln of 93 mg of **17**, m.p. 175–178°, in 1 ml THF was then added to the cooled suspension, followed by stirring for 1 hr at 25°. This mixture was added to the Grignard reagent prepared from 69 mg Mg and 0·39 ml isohexyl bromide in 3 ml THF. After stirring for 5 hr at 25°, the reaction mixture was poured into dil. HCl aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 0·131 g colorless oil, λ_{max}^{chf} 2·7–3·1 μ (OH), 4·48 (C≡N), and a weak peak at 5·88 (ketone C=O). This material was chromatographed on 10 g silica gel. The fractions eluted with 50% ether in hexane, all showing a single spot on TLC (R_f 0·51 in 1:2 benzene–ether), amounted to 61 mg colorless oil. (Found: C, 77·7; H, 10·9; N, 3·5. $C_{27}H_{45}O_2N$ requires: C, 78·02; H, 10·91; N, 3·37%).

Later fractions in the chromatogram, eluted with 100% benzene to 100% AcOEt, were combined and crystallized from AcOEt to give 28 mg of **21**, m.p. 177–209°, recognized by IR spectroscopy and by TLC. When 85 mg 13β-cyano ketone, m.p. 174–177°, in 14 ml ether was treated with isohexyllithium prepared[84] from 5 cm Li wire, 0·6 ml isohexyl bromide, and 5 ml ether. There was isolated, after a reaction period of 1 hr at 0°, 0·105 g yellow oil which showed 3 major spots on TLC (1:2 benzene–AcOEt): R_f 0·29 (starting cyano ketone), 0·51 (desired product), and 0·65 (imine). This product was chromatographed on 10 g silica gel. The fraction eluted with 20% ether in hexane amounted to 30 mg, R_f 0·65, showing a peak of moderate intensity at 6·1 μ (imine) in the IR spectrum. Treatment of this material with refluxing ethanolic KOH aq converted it into a substance showing no absorption at 6·1 μ but instead a new band at 5·7–5·9 μ, indicating conversion to ketone. The fractions eluted with 50% ether in hexane amounted to 21 mg of **40**. In the later fractions of the chromatogram there was a total of 30 mg starting cyano ketone.

dl-18-*Nitrilo*-5β-*cholestane*-3α,20-*diol* 3-*acetate*

A soln of 61 mg of **40**, showing a single spot on TLC, 1·5 ml anhyd. pyridine, and 0·8 ml Ac_2O was allowed to stand at 25° for 22 hr; then it was poured into water and extracted with ether. The combined organic layers were washed with water, cold 2% H_2SO_4 aq, water, sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. amounted to 69 mg colorless oil which was chromatographed on 6 g silica gel. The fraction eluted with 20% ether in hexane amounted to 64 mg mono acetate which could not be induced to crystallize. (Found: C, 75·9; H, 10·35; N, 3·3. $C_{29}H_{47}O_3N$ requires: C, 76·10; H, 10·35; N, 3·06%).

Dehydration of dl-18-*nitrilo*-5β-*cholestane*-3α,20-*diol* 3-*acetate*

A soln of 62 mg chromatographed hydroxy acetate prepared as described in the preceding experiment, 5 ml anhyd. pyridine, and 0·5 ml $POCl_3$ was heated for 5·5 hr under N in a bath maintained

[84] R. G. Jones and H. Gilman, *Organic Reactions* VI, p. 352. Wiley, New York (1951).

at 135°. The dark reaction mixture was cooled to 0°, poured cautiously over ice, and extracted with ether. The combined organic layers were washed with cold 2% H_2SO_4, water, sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 60 mg which was chromatographed on 6 g silica gel. The fraction eluted with 4% ether in hexane amounted to 54 mg of an oily mixture of dehydration products **41**, λ_{max}^{film} 4·50 μ (C≡N), 5·78 (acetate C=O), 5·95–6·15 (C=C), 11·1 and 11·3 (terminal methylene) and 12·0 (trisubstituted C=C). (Found: C, 79·4; H, 10·4. $C_{29}H_{45}O_2N$ requires: C, 79·22; H, 10·32%).

dl-3α,20-*Dihydroxy*-18-*acidocholestan*(18 → 20)*iminolactone* (**43**) *and the corresponding lactone* **42**

A soln of 96 mg of chromatographed **40** in 10 ml propionic acid containing 5 ml water and 5 ml 85% H_3PO_4 was heated for 17 hr under N in a bath maintained at 145°. The reaction mixture was cooled, poured into water, and extracted with ether. The combined organic layers were washed with 5% NaOH aq, water, sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. was saponified by heating at reflux with 5 ml 10% KOH aq in 20 ml MeOH for 1·3 hr. The mixture was cooled, poured into water, and extracted with 1:1 benzene–ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. amounted to 79 mg oil which was chromatographed on 8 g silica gel. The fractions eluted with 22–25% ether in hexane amounted to 45 mg oil (single spot on TLC, R_f 0·55, 1:2 benzene–AcOEt) which showed strong lactone absorption at 5·75 μ in the IR spectrum and was therefore regarded as **42**. The fractions eluted with 75–100% ether in hexane amounted to 23 mg crystalline **43**, λ_{max}^{chf} 5·98 μ (C=N). Repeated recrystallizations from AcOEt afforded colorless prisms, m.p. 219·5–220·5°. (Found: C, 77·8; H, 10·7; N, 3·6. $C_{27}H_{45}O_2N$ requires: C, 78·02; H, 10·91; N, 3·37%).

The combined mother liquors from the preparation of the analytical specimen were concentrated, affording 10 mg, m.p. 211–218°. This material was resubjected to the acid-catalyzed hydrolysis conditions described above for a period of 67 hr, followed by saponification. The IR spectrum of the total crude product showed no absorption for lactone in the 5·75 μ region. Crystallization from AcOEt afforded 6 mg of **43**, m.p. 214–220°.

dl-18-*Nitrilo*-20-*ethoxyethynylpregnane*-3α,20-*diol* (**44**)

A soln of PhLi was prepared from 9 cm Li wire, 5·0 ml bromobenzene, and 15 ml anhyd. ether. This mixture was cooled to 0° and, with vigorous stirring, a soln of 6·0 ml ethoxyacetylene (Pfister Chemical Works) in 10 ml anhyd. THF was added slowly over a 15-min period. The resulting tan suspension was stirred at 0° for 1 hr and then cooled to −70°. To this mixture was added, with vigorous stirring, a soln of 0·153 g of **17**, m.p. 171–176°, in 9 ml anhyd. THF over a period of 10 min. After stirring for 8 hr at −70°, the mixture was allowed to warm slowly to 25°. The resulting dark red reaction mixture was poured over a mixture of ice and ether, and the aqueous layer was thoroughly extracted with ether. The combined organic layers were washed with water, sat. $KHCO_3$ aq, sat. brine, and dried over Na_2SO_4. The dark red viscous oily residue obtained on evaporation of the solvent at reduced press. amounted to 3·8 g which was chromatographed on 10 g Florisil. The fractions eluted with 6–28% acetone in hexane amounted to 0·429 g crude viscous oily mixture which contained the desired adduct showing on TLC a spot at R_f 0·41 (1:1 ether–AcOEt). One of the center fractions of the chromatogram partially crystallized on trituration with ether. Further trituration gave material, m.p. 134–138°, λ_{max}^{chf} 2·7–3·0 μ (OH), 4·40 (C≡C), and as a shoulder 4·48 (C≡N). This specimen and the mother liquors were combined with all of the other fractions containing the desired adduct and were used in the next step described below. Repeated recrystallizations from ether of comparable material from another run gave colorless prisms, m.p. 136·5–140°, for which a satisfactory analysis was not obtained.

dl-3α-*Hydroxy*-18-*nitrilonorcholanic acid ethyl ester* (**46**, R = Et)

A soln of the aforementioned 0·429-g specimen of crude **44** in 20 ml abs. EtOH was cooled to −20° and saturated with anhyd. HCl gas. After standing for 1·5 hr at 0°, the reaction mixture was poured onto ice and extracted with 1:1 benzene–ether. The aqueous phase was made alkaline by the addition of solid Na_2CO_3 and re-extracted with 1:1 benzene–ether. The combined organic layers were washed with water, 5% $NaHCO_3$ aq, sat. brine, and dried over Na_2SO_4. The dark red oily residue

obtained on removal of the solvent under reduced press. amounted to 0·362 g which was chromatographed on 15 g Florisil. The fractions eluted with 6–10% acetone in hexane amounted to 0·148 g and were shown by TLC to contain **45** (R = Et), R_f 0·61 (1:1 ether–AcOEt). The IR spectrum (chf soln) showed all of the expected absorption bands for this substance, in particular one at 5·88 μ for the unsaturated ester C=O. In addition there were bands at 6·1, 6·3 and 6·4 μ, presumably due to polymeric contaminant. Rechromatography of a 33-mg sample of comparable material from another experiment on 4 g silica gel gave, on elution with 2–4% ether in benzene, 24 mg pale yellow oil which could not be induced to crystallize.

A mixture of the aforementioned 24 mg rechromatographed unsaturated ester, 8 ml AcOEt, and 43 mg 10% Pd-C catalyst was hydrogenated at atm. press. and 14° for 10 hr. The mixture was filtered, and the filtrate evaporated at reduced press. to give 24 mg colorless oil, λ_{max}^{chf} 2·7–3·0 μ (OH), 4·48 (C≡N), and 5·78 (ester C=O). Chromatography on 3·5 g silica gel gave, in the fractions eluted with 10–25% ether in benzene, 20 mg crystalline solid. Recrystallization from AcOEt–hexane afforded 11 mg, m.p. 139–143°. Two additional recrystallizations from the same solvent pair afforded colorless prisms, m.p. 144–145°. (Found: C, 74·8; H, 9·9; N, 3·7. $C_{25}H_{39}O_3N$ requires: C, 74·77; H, 9·79; N, 3·49%).

dl-3α-*Hydroxy*-18-*nitrilo*-$\Delta^{20,22}$-*norcholenic acid* (**45**, (R = H)

A soln of 0·175 g of crude chromatographed **45** (R = Et) in 5 ml MeOH and 5 ml 2% KOH aq was heated at gentle reflux under N for 1 hr. The reaction mixture was diluted with water and washed with ether, acidified with a mixture of ice and 10% H_2SO_4, and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 91 mg orange oil which was chromatographed on 5 g silica gel. A center fraction of those eluted with 45% ether in hexane to pure ether amounted to 55 mg crystalline material. Two recrystallizations from AcOEt gave 13 mg, m.p. 223–225°, which was used for the hydrogenation experiment described below. Another sample of the unsaturated acid after two recrystallizations was obtained as colorless prisms, m.p. 203–223° $\lambda_{max}^{95\%\ EtOH}$ 213 mμ (ϵ 9300). (Found: C, 73·75; H, 8·9. $C_{23}H_{33}O_3N$ requires: C, 74·36; H, 8·95%).

dl-3α-*Hydroxy*-18-*nitrilonorcholanic acid* (**46**, R = H)

(*a*) *By hydrogenation of the unsaturated acid* **45** (R = H). A mixture of the aforementioned 13 mg of the unsaturated acid, m.p. 223–225°, 5 ml AcOH and 36 mg PtO_2 was hydrogenated at 1 atm press. and 17° for 1·5 hr. The mixture was filtered and the combined filtrate and washings were evaporated. The residue was saponified by heating at 70° with 2 ml MeOH and 0·5 ml 5% KOH aq for 0·5 hr. The reaction mixture was poured into water and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was triturated with ether to give 8 mg, m.p. 218–234°. Three recrystallizations from AcOEt gave colorless plates, m.p. 244–249°. (Found: C, 73·8; H, 9·6. $C_{23}H_{35}O_3N$ requires C, 73·95; H, 9·45%).

(*b*) *By saponification of the saturated ester* **46** (R = Et). A mixture of 25 mg of the aforementioned saturated ester, m.p. 143–145°, 5 ml MeOH, and 3 ml 2% KOH aq was heated under gentle reflux in an atm. of N for 1 hr. The crude product isolated as described in the preceding experiment amounted to 21 mg, m.p. 227–237°. Recrystallization of a sample from MeOH gave material, m.p. 242–248°, undepressed on admixture with the analytical specimen described above in Part *a*. A further recrystallization of the material, m.p. 242–248°, from MeOH raised the m.p. to 246–250°.

dl-5β-*Cholestane*-3α,20-*diol* 3-*acetate* (**48**)

Isohexyllithium was prepared[84] from 0·4 ml isohexyl bromide and excess Li wire in 3·0 ml anhyd. ether. To this reagent was added a soln of 68 mg of **47**, m.p. 168–173°, in 17 ml anhyd. ether. The mixture was stirred for 2 hr at 0°; then after warming slowly to 24°, stirring was continued at the higher temp. for another 2 hr. The reaction mixture was decanted from unreacted Li metal into water, and the aqueous phase was extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and were dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 96 mg semicrystalline diol. Attempts to recrystallize this material failed. A soln of the crude diol in 7 ml anhydrous pyridine and 0·6 ml Ac_2O was allowed

to stand at 25° for 10 hr. The reaction mixture was poured into cold water and extracted with ether. The combined organic layers were washed with cold 2% H_2SO_4 aq, cold water, and were dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent at reduced press. amounted to 0·108 g crude mono acetate which was adequate for use in subsequent experiments. A sample of comparable material from another experiment slowly crystallized upon standing. It was recrystallized from hexane, affording colorless needles, m.p. 130–147°. Three additional recrystallizations from hexane gave colorless needles, m.p. 151–153°. (Found: C, 77·8; H, 11·1. $C_{29}H_{50}O_3$ requires: C, 77·97; H, 11·28%).

dl-5β-*Cholestan*-3α-*ol acetate* (**50**, R = Ac)

A soln of the 0·108-g specimen of the crude acetoxy alcohol described in the preceding experiment in 8 ml anhyd. pyridine containing 0·7 ml $POCl_3$ was heated at 135° under N for 4 hr. The dark soln was cooled to 0°, added slowly to ice water and extracted with ether. The combined organic layers were washed with cold 2% H_2SO_4 aq, water, sat. brine, and dried over Na_2SO_4. The oily residue obtained on removal of the solvent at reduced press. amounted to 90 mg, λ_{max}^{film} 5·78 μ (ester C=O), 5·86 (a weak ketone C=O), 6·10 (C=C), and 11·2 (C=CH_2). This product was chromatographed on 7 g silica gel. The fractions eluted with 1–2% ether in hexane amounted to 66 mg clear colorless oily mixture of **49**. The fraction eluted with 50% ether in hexane amounted to 10 mg crude crystalline acetylated starting ketone.

A mixture of the 66-mg specimen of the chromatographed acetoxy olefin mixture, 6 ml AcOH, 67·6 mg PtO_2, and 1 drop of a soln prepared by the addition of 1 drop 60% perchloric acid to 1 ml AcOH was hydrogenated at atm. press. and 15°. After 2 hr the reaction had ceased, 106% of the theoretical amount of gas having been absorbed. The mixture was diluted with benzene, filtered, the filtrate evaporated at 80° under reduced press., and the final traces of AcOH were removed at 80° under a rapid stream of N. The residue was dissolved in hexane, centrifuged to remove traces of catalyst and evaporated under reduced press. at 100° to give 69 mg semicrystalline product. Two recrystallizations from MeOH gave 34 mg, m.p. 109–121°. Two more recrystallizations from MeOH afforded 26 mg colorless needles, m.p. 122·5–124·5°. Material for analysis obtained from a previous experiment melted at 113–121°. (Found: C, 80·6; H, 11·9. $C_{29}H_{50}O_2$ requires: C, 80·87; H, 11·70%).

Evaporation of the mother liquor from the crystallization affording the first crop of the crude acetoxy compound described above gave an oily residue which was rich in dl-20-*iso*-5β-*cholestan*-3α-*ol acetate*. This material was used for oxidation to the 20-iso ketone described below.

dl-5β-*Cholestan*-3α-*ol* (**50**, R = H)

A soln of 50 mg of the aforementioned acetate, m.p. 123–125°, in 6 ml MeOH containing 0·3 ml 10% KOH aq, was warmed close to boiling temp. for 0·5 hr. The mixture was centrifuged, and the supernatant liquid concentrated and allowed to cool, whereupon 42 mg colorless needles separated m.p. 148–157°. Recrystallization from AcOEt–MeCN gave long white needles, m.p. 110–125°, evidently a mixture of polymorphic forms. (Found: C, 82·9; H, 12·3. $C_{27}H_{48}O$ requires: C, 83·43; H, 12·45%).

dl-5β-*Cholestan*-3-*one* (**51**)

A soln of 42 mg of **50** (R = H) prepared as described in the preceding section, m.p. 100–120°, in 6 ml acetone was titrated with a soln prepared by adding 0·2 ml 8N CrO_3–H_2SO_4[23] to 1 ml acetone. After the color of the reaction mixture turned to a permanent yellow, the soln was stirred for 5 min, 5 drops of isopropyl alcohol was added, and the resulting green suspension was poured into water and extracted with ether. The combined ether layers were washed with water, followed by sat. brine, and were dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 42 mg oily ketone which was chromatographed on 1 g silica gel. The fraction eluted with 1% ether in hexane amounted to 41 mg semicrystalline product. Recrystallization from ether–MeOH afforded 21 mg colorless prisms, m.p. 75–78°. (Found: C, 84·2; H, 11·5. $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%).

The IR spectrum of this product in CS_2 soln as well as the NMR spectrum was identical with that of naturally derived 5β-cholestan-3-one, m.p. 57·5–58°.[85]

[85] H. Grasshof, *Z. Physiol. Chemie* **225**, 197 (1934).

dl-20-*Iso*-5β-*cholestan*-3-*one fraction*

A soln of 19 mg of the aforementioned oily mother liquor fraction rich in *dl*-20-iso-5β-cholestan-3-ol acetate in 2 ml MeOH containing 0·1 ml 10% KOH aq was treated as described above for saponification of **50** (R = Ac). The crude oily product (17 mg) was oxidized as described in the preceding experiment to give 17 mg oily product which was chromatographed on 1 g silica gel. Elution with 1% ether in hexane gave 14 mg clear colorless oil. The CS_2 soln IR spectrum of this material was identical in every detail with that of authentic 5β-cholestan-3-one. The PMR spectra of the two substances, however, were different, as described in the discussion.

dl-Δ^4-*Cholesten*-3-*one* (**52**)

Pyridine hydrobromide perbromide (36 mg) was added in small portions with stirring over a 10-min period to a soln of 36 mg of the aforementioned chromatographed semicrystalline *dl*-5β-cholestan-3-one in 2 ml AcOH. After a 2-min induction period, decoloration of the reagent was instantaneous as each portion was added. To the resulting colorless soln were added 0·102 g semicarbazide hydrochloride and 0·108 g anhyd AcONa, and the resulting suspension was heated at 80° under N for 4 hr with stirring. This mixture was cooled in order to add 0·5 ml 99% pyruvic acid, then heating was continued as before for an additional 3 hr. The mixture was cooled, poured into water and extracted with ether. The combined organic layers were washed with water, bicarbonate solution, sat. brine, and dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent at reduced press. was chromatographed on 2 g silica gel. The fraction eluted with 1% ether in hexane amounted to 5 mg material which, as shown by the IR spectrum and TLC, was mainly starting material. The fraction eluted with 2% ether in hexane amounted to 23 mg crystalline unsaturated ketone. Recrystallization from MeOH afforded long colorless needles, m.p. 120–121°, $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ε 15,900). (Found: C, 84·1; H, 12·0. $C_{27}H_{44}O$ requires: C, 84·31; H, 11·53%).

In another experiment the unsaturated ketone was obtained as colorless flat plates, m.p. 113–115°. When the melt from the needles described above was allowed to cool, it resolidified as plates and upon repeating the m.p. determination these plates melted at 113–115°.

All of the material and residues remaining from preparation of the analytical sample described above were combined and recrystallized from MeOH to give 15 mg unsaturated ketone, m.p. 115–120°. This material was used for the preparation of racemic cholesterol described below.

dl-*Cholesterol* (**32**)

A mixture of the aforementioned 15 mg *dl*-Δ^4-cholesten-3-one, m.p. 115–120°, 0·4 ml Ac_2O, and 0·5 ml AcCl was heated at gentle reflux under N for 1·7 hr. The excess AcCl was removed at 25° (water-pump press.), and the Ac_2O was removed by slow evaporation at 25° (0·1 mm). To the colorless semicrystalline residue were added 3 ml isopropyl alcohol and a soln of 46 mg $NaBH_4$ in 2 ml 80% aqueous isopropyl alcohol. The mixture was stirred at 0° for 12 hr; then an additional 23 mg NaH was added, and stirring was continued at 25° for 3 hr. Then 0·5 ml 5% NaOH aq was added, and the mixture was stirred at 25° for 10 hr, cooled to 0°, added slowly to cold 10% HCl aq and extracted with ether. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. amounted to 18 mg colorless semicrystalline solid, the IR spectrum of which showed no absorption in the carbonyl region. TLC showed two spots, R_f 0·37 and 0·45 (2:1 benzene–AcOEt), the former running coincidentally with that of natural cholesterol. The entire crude product was dissolved in 4 ml MeOH, 3 drops conc. HCl was added, and the mixture was heated at reflux under N for 1 hr in order to effect dehydration of any allylic alcohol. The MeOH was removed at 100° under a stream of N, and the final traces of water and HCl were eliminated by evacuation at 0·2 mm and 25° for 2 hr. The colorless residue was then chromatographed on 2 g silica gel. The early fractions eluted with 2% ether in hexane amounted to 3 mg crystalline material, presumably *dl*-3α-cholesterol, which was not examined further. The later fractions eluted with the same solvent system, having R_f 0·37 on TLC, amounted to 11 mg crude crystalline *dl*-cholesterol. Crystallization from acetonitrile afforded 9 mg, m.p. 147–148°. A recrystallization gave 8 mg colorless elongated prisms, m.p. 147–148°. The mass spectral fragmentation pattern, the PMR spectrum, and the IR spectrum were identical with the corresponding spectra of natural cholesterol. Material recovered from the spectral determinations was recrystallized from acetonitrile to give elongated prisms, m.p. 149–149·5°. (Found: C, 83·95; H, 11·8. $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%).

PART III

dl-1-*Acetyl*-8-*methyl*-Δ^1-trans-*hexahydroindene* (**62**)

Since this was a model study, no special effort was made to find optimum conditions for yields nor were the epimeric mixtures of intermediates separated or characterized.

The following procedure is similar to that already described in our report on the synthesis of aldosterone,[1] which should be consulted for details. A stirred suspension of 1·14 g of **59** (R = OH),[1] m.p. 104–129° (neut. equiv. 130, calc. 128), in 5 ml MeOH was titrated to neutrality (phenolphthalein indicator) with 45·5 ml 0·196N NaOH. The resulting soln was frozen in a Dry Ice–acetone bath and lyophilized under reduced press. The residue was dried at 0·05 mm and 100° for 2 hr and at 28° for 5 hr. A suspension of this salt in 50 ml anhyd. benzene containing 0·2 ml anhyd. pyridine was stirred with cooling (ice bath) while 13 ml oxalyl chloride was cautiously added in several portions. After the addition was complete, the mixture was stirred at 0° for 3 min and then for an additional 20 min after the ice bath was removed. The solvent and excess oxalyl chloride were removed by distillation under reduced press.; then 25 ml benzene was added and similarly distilled, and this process was repeated again to displace the last traces of oxalyl chloride. A hot soln of sodio dibenzyl malonate, prepared from 1·5 g NaH and 13·1 g dibenzyl malonate in 95 ml benzene, was decanted from the excess NaH into a soln of the acid chloride in 25 ml benzene. The resulting mixture containing suspended NaCl was heated at reflux for 2 hr under an atmosphere of N. After standing overnight at room temp., the mixture was cooled and stirred while a cold solution of 5·3 ml conc. HCl in 125 ml water was added. The aqueous phase was extracted with AcOEt, and the combined organic layers were washed with sat. brine, then dried over Na_2SO_4. The viscous oily residue obtained upon removal of the solvent under reduced press. was dissolved in 110 ml AcOEt and 54 ml abs. EtOH, and hydrogenated at 22° and atm. press. over 1·3 g 10% Pd-C. After 2·75 hr, 2 mole-equivs H had been absorbed, and the reaction had essentially stopped. The mixture was filtered, and the filtrate was heated at reflux for 3·5 hr in order to effect decarboxylation; then it was concentrated by distillation through a 4-in. Vigreux column. Some benzene was added, and the soln was further concentrated in order to remove EtOH. The malonic acid (2·65 g) which crystallized was separated by filtration. The filtrate was diluted with ether and washed thoroughly with cold 10% $KHCO_3$ aq, 4% KOH aq, water, sat. brine, and finally dried over Na_2SO_4. The solvent was removed by distillation under reduced press. through an 8-in. Vigreux column, leaving 0·873 g crude **59** (R = Me) as a pale yellow oil, λ_{max}^{film} 5·90 μ with a shoulder at 5·85. The bicarbonate and hydroxide washes yielded 0·62 and 0·11 g, respectively, of acidic oily material.

To a soln of 0·868 g of the aforementioned crude diketone in 190 ml CH_2Cl_2 was added 25 g anhyd. Na_2HPO_4. The suspension was cooled to 0°, and then a soln of 9·7 ml trifluoroacetic anhydride and 1·5 ml 90% H_2O_2 in 24 ml CH_2Cl_2 was added with stirring. After the addition was complete, the mixture was stirred for 5 min in the cold, for 30 min after the cooling bath was removed, and finally it was heated at reflux for 5 hr. The mixture was then cooled, diluted with water, and the aqueous phase was extracted with chf. The combined organic layers were washed with 10% $KHCO_3$ aq, water, sat. brine, and finally were dried over Na_2SO_4. The solvent was removed by distillation at reduced press. through an 8-in. Vigreux column, leaving 1·0 g crude **60** (R = Ac). A soln of this product in 22 ml MeOH containing 2·0 g 85% KOH aq was heated at reflux under an atm. of N for 5 hr. The soln was concentrated, water was added, and the mixture was then extracted thoroughly with chf. The combined organic layers were washed with sat. brine and dried over Na_2SO_4. The solvent was removed by distillation at reduced press. through an 8-in. Vigreux column, leaving 0·570 g crude **60** (R = H) as a viscous oil, λ_{max}^{film} 3·02 μ. A soln of 0·486 g of **60** in a mixture of 14·5 ml acetone, 4·9 ml t-butyl alcohol, and 2·4 ml water was cooled to 0°; then 0·66 g *N*-bromoacetamide, m.p. 105–107°, was added. The soln was allowed to stand for 6·5 hr at approx. 7°; then it was poured into 200 ml water containing 3 g Na_2SO_3, and extracted with chf. The combined organic layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The solvent was removed by distillation at reduced press. through an 8-in. Vigreux column, and the residue was dried for several hr under reduced press. at room temp. in order to remove a strong lachrymator (probably bromoacetone). The residual oil amounted to 0·464 g, λ_{max}^{film} 2·96–3·00 and 5·90 μ, and probably consisted of a mixture of starting diol and keto alcohol. A 35-mg portion of this oil was dissolved in 0·3 ml anhyd. pyridine and added to the complex from 63 mg anhyd. CrO_3 and 0·7 ml pyridine. An additional 0·4 ml pyridine was used for transferring the alcohol, and the mixture was allowed to stand under an atm. of N for 5 hr at room

temp.; then it was diluted with water and extracted with ether. The combined organic layers were filtered, washed with dil HCl aq, 10% $KHCO_3$ aq, sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent by distillation through an 8-in. Vigreux column amounted to 32 mg crude **61**, λ_{max}^{film} 3·70 μ (aldehyde C—H) and 5·85 (ketone C=O). There was only weak absorption in the OH region at 2·95 μ in the IR spectrum. Material thus prepared was immediately submitted to the cyclization as described below.

A specimen of the crude keto aldehyde prepared as described above from 55 mg crude oily *N*-bromosuccinimide oxidation product was dissolved in 3 ml t-butyl alcohol and added to 100 ml 2·5% KOH aq which had been rigorously degassed and placed under an atm. of N. The reaction mixture was heated at reflux under an atm. of N for 2 hr, then steam distilled. The distillate was saturated with NaCl and extracted with ether. The combined organic layers were dried over Na_2SO_4 and diluted to a known volume in order to determine the optical density of the UV absorption at 233 mμ. On the assumption that the extinction coefficient of the pure material was approximately 10,000,[86] the yield of pure **62** was calculated to be 23%. The 2,4-*dinitrophenylhydrazone* was prepared directly from the ether extracts from the steam-volatile material. It crystallized from benzene–pet. ether as deep-orange blades, m.p. 182–183°. (Found: C, 60·1; H, 6·0. $C_{18}H_{22}O_4N_4$ requires: C, 60·32; H, 6·19%).

The *semicarbazone* was obtained from aqueous EtOH as colorless blades, m.p. 210·5–211·8°, $\lambda_{max}^{95\%\ EtOH}$ 265·5 mμ (ϵ 26,300). (Found: C, 67·15; H, 9·0. $C_{13}H_{21}ON_3$ requires: C, 66·35; H, 9·00%).

Conversion of the unsaturated ketone **62** *into* dl-8-*methyl*-trans-*hydrindan*-1-*one* (**63**)[65]

To approx. 20 ml of an ethereal soln estimated by UV spectroscopy to contain 39 mg of **62**, prepared as described in the preceding experiment, were added 0·3 ml pyridine, 1·2 ml 95% EtOH, and 77 mg hydroxylamine hydrochloride. The ether was slowly removed by evaporation on a steam bath, and the residual soln was allowed to stand at room temp. for 19 hr. It was then warmed for 7 min on the steam bath, cooled, diluted with sat. brine, and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated at steam-bath temp. The residue was dissolved in 1·0 ml pyridine, cooled to 0°, and treated with 0·22 g *p*-toluenesulfonyl chloride. The soln was allowed to stand for 2·75 hr at 6° and for 4 hr at 28°. It was then acidified with a mixture of ice and 10 ml water containing 2 ml conc. H_2SO_4. After standing at 6° overnight, the two-phase mixture was extracted with ether. The combined organic layers were washed with sat. brine, 10% $KHCO_3$ aq, again with brine, and then stirred with 10 ml 2,4-dinitrophenylhydrazine solution[87] at room temp. while the ether was allowed to evaporate. After about 16 hr, sat. brine was added to the gummy ethanolic residue, and the mixture was extracted with chf. The combined organic layers were washed with 10% $KHCO_3$ aq, then with sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. was chromatographed on 4 g silicic acid. The first orange fraction eluted with chf amounted to 72 mg red oil which, on crystallization from MeOH–AcOEt, afforded 14 mg orange solid, m.p. 139–144°. Two recrystallizations from this solvent gave golden blades which melted at 145·7–146·7°, then partially resolidified in the form of square plates and remelted at 153·5–154·2° (reported[66] 146·5–147° and 153·5–154°). A mixture of this substance with an authentic sample[66] exhibited the same m.p. behavior. The solution IR spectra of the two specimens were identical.

dl-2-*Methyl*-3-(1-*carboxy*-2β-*carboxyethylcyclohexyl*)*propionitrile* (**64**, $R^1 = R^2 = H$)

Ozone was passed through a soln of 41·5 g of crude **56**[1] in 350 ml AcOEt at −70° until the soln turned blue; then 52 ml 30% H_2O_2 and 140 ml AcOH were added, and the soln was allowed to stand at room temp. for 20 hr. The soln was diluted with benzene and washed with water. The aqueous layer was washed with benzene, and the combined organic layers were washed with water, then extracted with 75 ml 5% KOH aq, followed by excess 10% $KHCO_3$ aq. The combined aqueous alkaline solns were acidified with conc. HCl and extracted with ether. The combined ether extracts were washed twice with sat. brine and twice with $FeSO_4$ aq, and then dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent was triturated with ether, and the resulting solid was washed with benzene, leaving 15·5 g colorless solid, m.p. 156–166°; neut. equiv. 133 (calc. 133·7); λ_{max}^{KBr} 4·45 μ (C≡N) and 5·89–5·93 (COOH). Evaporation of the triturates and washings yielded 17 g viscous oil. Both the

[86] Cf. L. Dorfman, *Chem. Rev.* **53**, 47 (1953).

[87] Reagent prepared as described by R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds* 3rd Ed., p. 171. Wiley, New York (1948).

solid and the oil were composed of mixtures of the two epimers as both afforded tribasic acid on hydrolysis.

In another run, the ether extract of the acidified aqueous alkaline solns was washed with acidified $FeSO_4$, water, sat. brine, and dried over Na_2SO_4. The residual oil obtained on evaporation of the solvent was triturated with benzene, and the product was washed with pet. ether to give a 68% yield of a solid, m.p. 134–156°, neut. equiv. 137 (calc. 133·7).

dl-2-*Methyl*-3-(1-*carbomethoxy*-2β-*carboxyethylcyclohexyl*)*propionitrile* (**64**, $R^1 = Me$, $R^2 = H$)

A 4·46-g specimen of crude **64** ($R^1 = R^2 = Me$), prepared by the action of excess ethereal diazomethane on the aforementioned cyano diacid fraction, m.p. 156–166°, was mixed with 12·3 ml 1·23N methanolic KOH and the soln was allowed to stand at room temp. for 4 days. The soln was then concentrated, diluted with water, and extracted with benzene. The organic layer was washed with sat. $NaHCO_3$ aq. All of the aqueous layers were combined, acidified with conc. HCl, and extracted with ether. The combined ether extracts were washed with sat. brine and dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent was triturated with ether, and the resulting solid was washed with 50% ether–pet. ether, leaving 1·82 g solid, m.p. 76–116°, neut. equiv. 278 (calc. 281), λ_{max}^{mull} 4·48 μ (C≡N), 5·83 (ester C=O) and 5·90 (COOH). A further 1·48 g colorless crystals, m.p. 78–83°, neut. equiv. 280, was obtained by evaporation of the combined mother liquors and retrituration as above. A third crop amounted to 0·29 g, m.p. 75–81°, neut. equiv. 279. The fraction, m.p. 78–83°, was analyzed. (Found: C, 64·1; H, 8·25; N, 5·2. $C_{15}H_{23}O_4N$ requires: C, 64·03; H, 8·24; N, 4·98%).

dl-2-*Methyl*-3-(1-*carboxy*-2β-*carboxyethylcyclohexyl*)*propionic acid* (**65**, $R^1 = R^2 = H$)

A soln of 60 g of the aforementioned cyano diacid, m.p. 156–166°, in 126 ml 10% KOH aq was heated at steam-bath temp. for 30 hr. Acidification of the cooled soln with 23 ml conc. HCl produced a colorless ppt which was filtered, washed with water and chf to leave 4·6 g, m.p. 192–195°. The combined filtrate and washings were extracted with AcOEt, and the organic layers were washed with water, sat. brine and dried over Na_2SO_4. Evaporation of the solvent left 1·63 g colorless solid, m.p. 172–190°. The analysis of the high-melting fraction was satisfactory considering that the material was not recrystallized. (Found: C, 58·1; H, 7·7. $C_{14}H_{22}O_6$ requires: C, 58·73; H, 7·75%).

Similar saponification of the 17-g oily cyano diacid fraction described above afforded 8·6 g solid tribasic acid, m.p. 177–183°, neut. equiv. 95·5 (calc. 95·3).

The cyano diacid, m.p. 134–156°, from the second run described above afforded a 57% yield of solid triacid, m.p. 175–196°, neut. equiv. 92·5, by direct crystallization. An additional 37% of material, m.p. 166–170°, neut. equiv. 98·2, was obtained by ether extraction and crystallization.

dl-2-*Methyl*-3-(1-*carbomethoxy*-2β-*carboxyethylcyclohexyl*)*propionic acid* (**65**, $R^1 = Me$, $R^2 = H$)

A 19·7-g sample of the aforementioned tribasic acid, m.p. 175–196°, was converted to **65** ($R^1 = R^2 = Me$). This transformation was actually effected in two stages, the first involving treatment by the method[88] which did not effect complete esterification. The product was therefore treated with excess ethereal diazomethane which gave 21·6 g neutral material after evaporative distillation at 160° (0·1–0·2 mm). This colorless, viscous oil was mixed with 126 ml 1·038N methanolic KOH, and the soln was allowed to stand at room temp. for 4 days. Since the soln was still alkaline (pH 11), it was heated at reflux for 16 hr. The MeOH was removed under a stream of air, water was added, and the mixture was extracted with benzene. The benzene layer was washed with sat. $NaHCO_3$ aq. The combined aqueous layers were acidified with conc. HCl and extracted with ether. The combined ether layers were washed with water, followed by sat. brine, and dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent, on treatment with a small volume of ether and seeding with some crystals obtained by chromatography, afforded 19·1 g of colorless solid, m.p. 105–119°, neut. equiv. 156 (calc. 150). (Found: C, 59·8; H, 8·2. $C_{15}H_{24}O_6$ requires: C, 59·98 H, 8·05%).

In another run when the tribasic acid specimen, m.p. 177–183°, was similarly esterified and saponified, an ester diacid specimen, m.p. 99–104°, neut. equiv. 151·5, was obtained. (Found: C, 59·9; H, 8·1. $C_{15}H_{24}O_6$ requires: C, 59·98; H, 8·05%).

Since other runs with other triacid specimens of different m.p.s gave rise to ester diacids also of different m.p.s, it is clear that there was not complete equilibration at the epimeric center. Thus the

[88] R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.* **70**, 3135 (1948).

triacid specimen, m.p. 192–195°, afforded ester diacid, m.p. 114–121°. (Found: C, 60·2; H, 8·3. $C_{15}H_{24}O_6$ requires: C, 59·98; H, 8·05%).

dl-1*β-Hydroxypropyl-2-formylmethylcyclohexanecarboxylic acid lactone* (**67**)

An 18·9-g sample of the aforementioned ester diacid, m.p. 105–119°, was converted to the disodium salt in aqueous alcoholic soln and then to the disilver salt by the usual technique. The gray solid was washed thoroughly with water, 95% EtOH, and ether, and was dried under reduced press. for 4 hr at 30°, and then for 7 hr at 60°. The yield was 31·3 g (97%).

A suspension of 10·7 g of the aforementioned disilver salt, dried at 70° (4 mm) over P_2O_5 for 9 hr, in 100 ml anhyd. CCl_4 was treated with 3·2 ml Br. The addition of the Br soln produced an exothermic reaction accompanied by evolution of CO_2. Gas evolution ceased after 15 min, and the mixture was heated at reflux for 30 min. The mixture was cooled, the solid material removed by filtration, and the combined filtrate and washings were washed with 5% $NaHSO_3$ aq, water, sat. $NaHCO_3$ aq, again with water, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. amounted to 3·69 g neutral oil. Evaporative distillation at reduced press. gave 2·06 g oil, λ_{max}^{film} 5·72 μ (γ-lactone) and 5·78. This material represented a very impure specimen of **66** since the Br analysis was only 18·3% (calc. 29·0%).

The following is an adaptation of the procedure of Lieberman.[70a] The potassium salt of 2-nitropropane was prepared by adding 22·9 ml 0·465N KOH in isopropyl alcohol to 1·0 ml 2-nitropropane. This soln was added over a 20-min period to a soln of 1·79 g of the aforementioned evaporatively distilled bromo lactone in 10 ml isopropyl alcohol. The mixture was then allowed to stand at room temp. overnight (N atm.) and then was heated at reflux for 2·25 hr. The mixture was cooled, filtered, and the filtrate concentrated under reduced press. Benzene was added and the concentration repeated to eliminate the isopropyl alcohol azeotropically. Ether was added to the residue and the soln was washed with water, 2% NaOH aq, again with water, and dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent under a stream of N amounted to 1·12 g. Treatment of this product with 2,4-dinitrophenylhydrazine reagent gave the *2,4-dinitrophenylhydrazone* which, after three recrystallizations from abs. EtOH, was obtained as golden elongated microprisms, m.p. 191·5–194°. (Found: C, 55·4; H, 5·7; N, 14·5. $C_{18}H_{22}O_6N_4$ requires: C, 55·38; H, 5·68; N, 14·35%).

dl-2-*Methyl*-3-(1-*carbomethoxy*-2*β-formylethylcyclohexyl*)*propionaldehyde* (**68**, R = H)

A 1·00-g specimen of an epimeric mixture of **68** (R = OH), m.p. 92–108°, neut. equiv. 156, was dissolved in 23 ml purified $SOCl_2$ and kept at 6–9° for 70 hr. The excess $SOCl_2$ was evaporated under reduced press. at room temp., and the last traces were removed by the successive addition and removal of three 20-ml portions of anhyd. benzene. The residue was used directly for the modified Rosenmund reduction;[1] 550 ml anhyd. benzene and 1 g 10% Pd-C were employed. After a total reaction period of 4 hr, 92% of the theoretical amount of HCl was evolved. The product was isolated as described[1] for the case with a methyl instead of carbomethoxyl group. The crude dialdehyde afforded a *bis*-2,4-*dinitrophenylhydrazone*, m.p. 160–184°, in 76% over-all yield from the ester diacid. One of the epimers was separated by three recrystallizations from AcOEt which gave a yellow microcrystalline powder, m.p. 218–220·5°. (Found: N, 17·9. $C_{27}H_{32}O_{10}N_8$ requires: N, 17·83%).

dl-3-*Methyl*-4-(1-*carbomethoxy*-2*β-acetylethylcyclohexyl*)*butan-2-one* (**68**, R = Me)

The diacid chloride prepared as described above from 0·500 g of **68** (R = OH), m.p. 105–119°, was treated in 10 ml anhyd. benzene with 6·58 mmoles sodio dibenzyl malonate in 12 ml benzene as described for the prep. of **59** (R = Me). The product, after chromatography on Florisil, amounted to 0·249 g colorless neutral oil which afforded a crystalline bis-semicarbazone (mixture of epimers), which because of its insolubility could not be recrystallized satisfactorily. (Found: C, 55·6; H, 8·3. $C_{19}H_{34}O_4N_6$ requires: C, 55·59; H, 8·35%).

The di-t-butyl malonate method[89] gave diketo ester in yields ranging from 68–91% on a small scale, but the yields dropped significantly when the reaction was carried out on a large scale. The dimethylcadmium method[90] gave the impure diketo ester in 48% yield, and the ketene acetal method[1,91] afforded the crude product in only 32% yield.

[89] G. S. Fonken and W. S. Johnson, *J. Amer. Chem. Soc.* **74**, 831 (1952).

[90] H. Gilman and J. F. Nelson, *Rec. Trav. Chim.* **55**, 518 (1936).

[91] G. R. McKay, Jr., private communication; S. M. McElvain and G. R. McKay, Jr., *J. Amer. Chem. Soc.* **78**, 6086 (1956).

Baeyer-Villiger oxidation of the diketo ester **68** (R = Me) *and some reactions of the product*

A 0·245-g specimen of the aforementioned diketo ester in 4 ml CH_2Cl_2 containing 2·4 g anhyd. Na_2HPO_4 was treated with 5·49 mmoles trifluoroacetic acid in 1 ml CH_2Cl_2 as described for the prep. of **60** (R = Ac). The crude product, amounting to 0·255 g, gave a negative test with 2,4-dinitrophenylhydrazine reagent. Chromatography on 13 g Florisil gave a total of 0·232 g material in various fractions, all of which had very similar IR spectra, λ_{max}^{chf} 5·83 μ. This product was dissolved in 10·5 ml 0·135N methanolic KOH aq. After 3 days at room temp., the soln was concentrated to approximately 2 ml under a stream of N without heating, diluted with water, and continuously extracted with ether. The ether extracts afforded 0·136 g viscous oil showing strong absorption at 5·76 μ (γ-lactone C=O) as well as absorption at 2·93 (OH) in the IR spectrum. This substance evidently was the lactone **70**.

An attempt to hydrolyze the acetyl groups without lactonization was made using an ester exchange with MeONa. Thus a soln of 0·588 g chromatographed Baeyer-Villiger oxidation product in 27 ml abs. MeOH was treated with 41 mg NaH. After heating at reflux for 21·5 hr, benzene was added and the soln concentrated in order to remove most of the MeOH. Ether was added and the soln was washed with water, 10% $KHCO_3$ aq, followed by brine, and dried over Na_2SO_4. The oily residue obtained on evaporation of the solvent amounted to 0·222 g. The IR spectrum was very similar to that of the material described directly above except that the absorption in the OH region was stronger and there was a shoulder at 5·79 μ suggestive of the presence of a small amount of the desired dihydroxy ester. The analysis for C (see below) of a sample evaporatively distilled at 95° (0·2 mm), however, was only slightly below that calculated for the hydroxy lactone **70**. Hence the percentage of dihydroxy ester was low. (Found: C, 67·0; H, 9·5. $C_{12}H_{20}O_3$ (hydroxy lactone) requires: C, 67·89; H, 9·50%. $C_{13}H_{24}O_4$ (dihydroxy ester) requires: C, 63·90; H, 9·90%).

A number of other methods of hydrolysis of **69**, like those described in detail for **73** ($R^1 = R^3 = Ac$, $R^2 = Me$), were tried, but it was not possible to avoid lactone formation.

The selective reduction of the hydroxy lactone with LAH was carried out according to a previously described procedure.[50] Thus a solution of 26·7 ml 0·101M (molarity based on active H evolution) LAH in THF was slowly added over an 18-min period to a cold (−70°) soln of 1·14 g of the aforementioned crude hydroxy lactone in 30 ml anhyd. ether. Water (0·55 ml) was added, and the ppt was removed by filtration and washed thoroughly with ether. The combined filtrate and washings were dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. amounted to 1·04 g oil which showed absorption in the IR spectrum for OH and γ-lactone. Chromatography of 0·90 g of this material on 40 g Florex afforded on elution with benzene and 2% ether in benzene 0·43 g colorless oil showing no absorption in the IR below 6·8 μ other than the C—H stretching bands. The analytical sample of **71** was evaporatively distilled at 150° (25 mm). (Found: C, 73·9 H, 10·9. $C_{12}H_{20}O_2$ requires: C, 73·43; H, 10·27%).

dl-17-*Furfurylidene*-3α-*hydroxy*-13α-(2-*cyanopropyl*)-D-*homo*-18-*noretiocholan*-17a-*one* (**54**, R = H)

This experiment was performed by John E. Pike. Methacrylonitrile (10 ml) was added to a soln of MeONa in MeOH (prepared from 0·28 g NaH and 15 ml MeOH) in 12 ml THF. The mixture was heated under reflux (N atm) for 10 min, cooled, and to it was added a soln of 9·50 g of **53**,[4b] m.p. 213–216°, in 10 ml THF. This mixture was then heated under reflux in an atm. of N for 15 hr. It was then cooled, and 3 ml glacial AcOH and 5 ml water were added. The solid which precipitated was collected by filtration and washed with 10% aqueous MeOH, water, MeOH and finally ether to give 8·9 g, m.p. 238–247°. Recrystallization from abs. EtOH gave 8·50 g *isomer* B, m.p. 248–251°. The purest specimen obtained from another run after chromatography and recrystallizations from methyl ethyl ketone was obtained as colorless irregular rhombs, m.p. 256·5–258°, $\lambda_{max}^{95\%\ EtOH}$ 328 mμ (ϵ 22,400). (Found: C, 77·3; H, 8·7. $C_{28}H_{37}O_3N$ requires: C, 77·20; H, 8·56%).

The filtrate and washings from the crude isomer B were combined, diluted with water and extracted with benzene. The combined organic layers were washed with 5% KOH aq, water, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was combined with the residue from the mother liquors from the recrystallization described above and chromatographed on 130 g Florisil. The fractions eluted with 10–20% ether in benzene amounted to 1·11 g crude crystalline *isomer* A. Recrystallization from MeOH gave 0·60 g, m.p. 204–207°. The purest specimen obtained from another run, after chromatography and recrystallizations from EtOH and from methyl ethyl ketone, was obtained as colorless irregular prisms, m.p. 208–209°, $\lambda_{max}^{95\%\ EtOH}$ 329 mμ (ϵ 20,900). (Found: C, 76·8; H, 8·6. $C_{28}H_{37}O_3N$ requires: C, 77·20; H, 8·56%).

The fractions from the aforementioned chromatography that were eluted with ether through 5% EtOH in ether amounted to 0·61 g crude isomer B. Recrystallization from abs. EtOH gave 0·270 g isomer B, m.p. 248–251°. The yield of isomer B was therefore 82% and of isomer A 10%.

Isomerization of **54** *isomer* A *to* **54** *isomer* B

This experiment was performed by John E. Pike. A soln of 0·30 g of the aforementioned isomer A, m.p. 205–207°, in ethanolic EtONa (prepared from 20 mg NaH and 25 ml abs. EtOH) was heated under reflux in an atm. of N for 24 hr. During this period, crystals were deposited from the initially homogeneous mixture. The cooled mixture was filtered to give 0·175 g product, m.p. 235–240°. Two recrystallizations from methyl ethyl ketone afforded material, m.p. 252–255°, undepressed on admixture with the specimen of isomer B described above.

dl-17-*Furfurylidene*-3α-*acetoxy*-13α-(2-*cyanopropyl*)-D-*homo*-18-*noretiocholan*-17a-*one* (**54**, R = Ac)

A fraction rich in isomer B of **54** (R = H) (6·95 g, m.p. 240–251°, and 1·45 g, m.p. 224–237°) was suspended in 60 ml pyridine containing 17 ml Ac_2O. The mixture was heated briefly at 100° to effect soln; then it was allowed to stand for 25 hr at room temp. Excess ice-cold 10% $KHCO_3$ aq was added, and the mixture was extracted with AcOEt. The combined organic layers were washed with water and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was treated with small portions of toluene which were distilled under reduced press. in order to remove the last traces of pyridine. This pyridine-free residue was crystallized from abs. EtOH to give 8·1 g, m.p. 173–178°, and 0·67 g (second crop), m.p. 143–158°. Repeated recrystallizations from abs. EtOH gave colorless shiny flakes, m.p. 188–189·5°. (Found: C, 75·8; H, 8·1. $C_{30}H_{39}O_4N$ requires: C, 75·44; H, 8·23%).

dl-4bβ-*Methyl*-1β-(2-*carbomethoxyethyl*)-2β-*carbomethoxy*-2α-(2-*carbomethoxypropyl*)-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**72**, R^1 = H, R^2 = Me, R^3 = OMe)

The ozonization and decomposition of the ozonide were accomplished as described above for the model series; the cyano diacid was not isolated but was hydrolyzed directly to the tribasic acid. Thus 8·10 g of the isomer B-rich **54** (R = Ac), m.p. 173–178°, in 500 ml AcOEt was treated with O_3, and then with 68 ml AcOH and 22 ml 30% H_2O_2. After standing for 2 days at room temp., the mixture was diluted with more AcOEt and washed thoroughly with $FeSO_4$ aq. The aqueous washes were extracted with AcOEt, and the combined organic layers were washed once with a soln consisting of equal parts of water and sat. brine. Ether was added, and the total organic soln was extracted with two 500-ml portions of 10% KOH aq. The aqueous alkaline extracts were combined, 50 g 85% KOH was added, and the soln was heated under reflux in an atm. of N for 36 hr. The mixture was cooled, acidified with conc. HCl, saturated with NaCl and extracted thoroughly with AcOEt. The combined organic layers were washed with sat. brine and dried over Na_2SO_4. As the soln was concentrated, a solid began to crystallize out of soln. This fraction amounted to 3·03 g, m.p. 244–248°. The filtrate and washings were concentrated to dryness under reduced press., and several portions of toluene were added and removed in order to eliminate acetic acid. Trituration with hot 2:1 AcOEt–acetone afforded 2·50 g solid, m.p. 221–224°. The triturate was concentrated to dryness, and the residue was triturated with a small volume of acetone to give 0·28 g, m.p. 220·5–225°. The total solid mixture of **72** ($R^1 = R^2$ = H, R^3 = OH) amounted to 5·81 g (80% yield).

The aforementioned triacid could be separated roughly into its epimeric forms by the crystallization technique described below. Thus the crude product from the oxidation of 2·16 g of **54** (R = Ac), m.p. 178–185°, was crystallized from AcOEt, giving 0·442 g (first crop), m.p. 238–241°; 0·209 g (second crop), m.p. 238–241°; and 0·040 g (third crop), m.p. 237–242°. These fractions were all rich in the higher-melting isomer B. Further crystallization of the residue obtained by evaporation of the mother liquor from the third crop of isomer B afforded material rich in isomer A: 0·453 g (fourth crop), m.p. 224–227°; 0·109 g (fifth crop), m.p. 218–221°.

A soln of 1·30 g isomer B-rich triacid, m.p. 236–239° (corresponding to second-crop material, as described above), in 100 ml anhyd. MeOH was treated with an ethereal soln of diazomethane until the reaction mixture became yellow. The crystalline residue obtained after filtration and concentration was chromatographed on 100 g silica gel. The fractions eluted with 25% ether in benzene amounted to 1·25 g colorless crystalline triester. Recrystallization from ether–hexane afforded 0·97 g *isomer* B, m.p. 89–92°. An additional recrystallization from ether–hexane gave colorless prisms, m.p. 90–92°. (Found: C, 66·8; H, 8·9. $C_{26}H_{42}O_7$ requires: C, 66·92; H, 9·07%).

Similarly a 2·18-g sample of isomer A-rich triacid, m.p. 220–230°, yielded, after chromatography and crystallization from ether, 1·73 g *isomer* A, m.p. 126–130°. Repeated recrystallizations from AcOEt–hexane gave colorless prisms, m.p. 131–132°. (Found: C, 66·9; H, 8·8. $C_{26}H_{42}O_7$ requires: C, 66·92; H, 9·07%).

dl-4bβ-*Methyl*-1β-(2-*carboxyethyl*)-2β-*carbomethoxy*-2α-(2-*carboxypropyl*)-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**72**, $R^1 = H$, $R^2 = Me$, $R^3 = OH$)

A soln of the total crude triester isomer B prepared as described above from 0·691 g isomer B-rich triacid, m.p. 238–241°, in 50 ml MeOH and 1·1 ml water containing 1·3 g 85% KOH aq was allowed to stand under an atm. of N at room temp. for 8 days. This soln was then concentrated under reduced press., acidified with HCl, and extracted thoroughly with AcOEt. The combined organic layers were washed thoroughly with sat. brine and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was crystallized from AcOEt, giving 0·563 g (79% yield from the triacid) of *isomer* B, m.p. 205–210°.

A comparable product from another run was repeatedly recrystallized from acetone–pet. ether, giving colorless irregular prisms, m.p. 215·2–218°. (Found: C, 65·8; H, 8·75. $C_{24}H_{38}O_7$ requires: C, 65·73; H, 8·73%).

Similarly the total crude triester isomer A from 1·00 g isomer A-rich triacid, m.p. 223–227°, yielded, after crystallization from AcOEt, 0·927 g *isomer* A, m.p. 118–122°. Repeated recrystallizations of comparable material from AcOEt gave colorless prisms, m.p. 120–120·5°. (Found: C, 65·4; H, 8·9; neut. equiv., 222. $C_{24}H_{38}O_7$ requires: C, 65·73; H, 8·73%; neut. equiv., 219).

dl-4bβ-*Methyl*-1β-(2-*carboxyethyl*)-2β-*carbomethoxy*-2α-(2-*carboxypropyl*)-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene acetate* (**72**, $R^1 = Ac$, $R^2 = Me$, $R^3 = OH$)

A soln of 0·103 g isomer B-rich **72** ($R^1 = H$, $R^2 = Me$, $R^3 = OH$), m.p. 204–208°, in 16 ml anhyd. AcOH was saturated with dry HCl and then allowed to stand at room temp. for 51 hr. The residue obtained on concentration to dryness under reduced press. was triturated thoroughly with ether, leaving 0·109 g crystalline material, m.p. 233–242° with softening at 227°. A single recrystallization from acetone–pet. ether gave material, m.p. 238–243°. Repeated recrystallizations from acetone–pet. ether gave *isomer* B as colorless microprisms, m.p. 245·3–246·3°. (Found: C, 64·7; H, 8·6. $C_{26}H_{40}O_8$ requires: C, 64·98; H, 8·39%).

In another run 0·563 g isomer B-rich diacid, m.p. 205–210°, afforded on crystallization from acetone–MeOH 0·272 g (first crop), m.p. 240–245°, and 0·287 g (second crop), m.p. 230–235°.

Similarly, acetylation of a 0·352-g sample of isomer A-rich diacid, m.p. 106–108°, afforded on crystallization from acetone–hexane 0·191 g (first crop), m.p. 171–174°; and 0·095 g (second crop), m.p. 170–172°. Material of this quality was converted directly to the diketone (see below) without further purification.

dl-4bβ-*Methyl*-1β-(2-*acetylethyl*)-2β-*carbomethoxy*-2α-(2-*acetylpropyl*)-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene acetate* (**72**, $R^1 = Ac$, $R^2 = R^3 = Me$)

A modification of the procedure described above for the preparation of **59** (R = Me) was employed. NaH (52 mg) was added to a soln of 0·332 g isomer B-rich diacid acetate, m.p. 240–245°, in 8·0 ml anhyd. THF, and the mixture was stirred at room temp. under an atm. of N for 4 hr. The mixture was cooled to 0°, then 0·07 ml anhyd. pyridine and 2·8 ml oxalyl chloride were added dropwise with stirring. After the addition was complete, the mixture was stirred with cooling for 5 min. The solvent was removed by distillation under reduced press. with no external heating; then several portions of benzene were added and similarly removed by distillation. To this acid chloride residue was added a warm soln of sodio dibenzyl malonate prepared from 0·48 g NaH and 2·6 g dibenzyl malonate in 10 ml benzene. The resulting mixture was heated at reflux for 4 hr, allowed to stand overnight at room temp., cooled to 0° and stirred while 50 ml cold 0·5M HCl was added. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with sat. brine and dried over Na_2SO_4. The oily residue was dissolved in 40 ml AcOEt and 25 ml abs. EtOH, and the soln was stirred under H at atm. press. in the presence of 0·30 g 10% Pd-C. The absorption of H ceased after about 2 hr. The mixture was filtered, the filtrate was heated at reflux for 4 hr and it was then concentrated to dryness under reduced press. The residue was dissolved in a small amount of AcOEt. This soln was chilled in an ice bath and washed thoroughly with ice-cold 10% $KHCO_3$ aq, ice-cold 2% KOH

aq, water, and then dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. was crystallized from ether-pet. ether (b.p. 30–60°) to give 0·206 g *isomer* B, m.p. 82–87°. A specimen of this isomer obtained from another run by chromatography on acid-washed alumina melted at 100–104°. Repeated recrystallizations from ether–pet. ether gave colorless elongated prisms, m.p. 102–104·3°. (Found: C, 70·2; H, 9·2. $C_{28}H_{44}O_6$ requires: C, 70·55; H, 9·31%).

Similarly from 0·780 g isomer A-rich diacid, m.p. 171–174°, there was obtained, by direct crystallization of the final crude product from ether, 0·310 g *isomer* A, m.p. 118–121°. A specimen of this isomer obtained from the aforementioned chromatographed run melted at 125–130°. It was repeatedly recrystallized from ether–pet. ether to give colorless irregular prisms, m.p. 132·2–133·2°. (Found: C, 70·5; H, 9·4. $C_{28}H_{44}O_6$ requires: C, 70·55; H, 9·31%).

The partial conversion of isomer B into isomer A was carried out under the conditions described[1] for a similar isomerization in the 11β-hydroxy (lactone) series. Thus from 97 mg isomer B, m.p. 101·2–104°, there was obtained, after heating for 2·5 hr with 0·8 g AcONa in 8·5 ml MeOH followed by reacetylation with Ac_2O in pyridine, 27 mg isomer A, m.p. 131·2–133·3°, undepressed on admixture with the analytical specimen described above.

dl-4bβ-*Methyl*-1β-(2-*acetoxyethyl*)-2β-*carbomethoxy*-2α-(2-*acetoxypropyl*)-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene acetate* (73, $R^1 = R^3 = Ac$, $R^2 = Me$)

The Baeyer-Villiger oxidation was carried out as described above for the preparation of **69**. Thus from 0·835 g of the aforementioned diketo acetate isomer A, m.p. 125–130°, in 95 ml CH_2Cl_2 and 12·4 g Na_2HPO_4, there was obtained on treatment with a mixture of 4·9 ml trifluoroacetic anhydride, 0·8 ml 90% H_2O_2, and 12 ml CH_2Cl_2, 0·906 g neutral oil. Chromatography on 44 g Florisil gave, in the fraction eluted with 2–20% ether in benzene, a total of 0·615 g oil which crystallized on trituration with a small amount of ether–pet. ether. A 0·436-g sample of material of this quality was crystallized from ether–pet. ether to give 0·354 g, m.p. 117·5–118·5°. Recrystallization from ether–pet. ether gave colorless prisms of *isomer* A, m.p. 117·7–118·7°. The m.p. was not altered by further recrystallization. (Found: C, 66·0; H, 8·7. $C_{28}H_{44}O_8$ requires: C, 66·11; H, 8·72%).

In another run there was obtained from 0·300 g diketo acetate, m.p. 118–121°, a total of 0·254 g crystalline isomer A triacetate by elution from Florisil with 5–10% ether in benzene. This material was satisfactory for use in subsequent transformations. Recrystallization from ether afforded 0·175 g m.p. 118–119·5°.

In the same way 0·757 g diketo acetate isomer B, m.p. 100–104°, afforded, after chromatography on 41 g Florisil and elution with 5–10% ether in benzene, a total of 0·527 g material which crystallized on trituration with pet. ether. A 0·203-g specimen of comparable material was crystallized from ether–pet. ether to give 0·164 g material, m.p. 119·3–120·6°. On admixture with the aforementioned isomer A, the m.p. was depressed to 103–115°. Three recrystallizations from ether–pet. ether gave *isomer* B as colorless elongated rectangular prisms, m.p. 121·4–122·7°. (Found: C, 66·1; H, 8·8. $C_{28}H_{44}O_8$ requires: C, 66·11; H, 8·72%).

It is to be noted that the residue from the filtrate from the first crystallization of the 0·527-g sample of chromatographed isomer B triacetate, when submitted to hydrolysis as described below, afforded an excellent yield of the lactone diol. Therefore crystallization of chromatographed material was unnecessary for further transformations.

dl-4bβ-*Methyl*-1β-(2-*hydroxyethyl*)-2α-(2-*hydroxypropyl*)-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene*-2β-*carboxylic acid lactone* (74)

A soln of 0·248 g of 73 ($R^1 = R^3 = Ac$, $R^2 = Me$), isomer A, m.p. 117·7–118·7°, in 12 ml MeOH containing 0·54 g 85% KOH aq was stirred at room temp. for 7 hr. The soln was concentrated to a small volume under reduced press., a little water was added to the concentrate, and the ppt was separated by filtration, then washed with water until neutral, and then with small volumes of 50% aqueous MeOH, AcOEt, and ether, leaving 0·144 g, m.p. 211–216°. Concentration of the 50% aqueous MeOH wash afforded an additional 10 mg material, m.p. 208–212°. The combined mother liquors and washes were extracted thoroughly with AcOEt, and the combined organic layers were washed with brine and then dried over Na_2SO_4. The residue obtained on evaporation of the solvent under reduced press. was combined with the 10-mg second-crop fraction described above and crystallized from MeOH–AcOEt to give 17 mg, m.p. 217–219°. The total yield of crystalline lactone diol *isomer* A was 0·151 g (88%). Four recrystallizations of the fraction melting at 211–216° gave colorless micro-

plates, m.p. 220–221°, with softening at 218°, λ_{max}^{KBr} 2·98 μ (OH) and 5·75 (γ-lactone C=O). (Found: C, 71·55; H, 9·8. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%).

When 0·615 g of the crude chromatographed (crystalline fractions) triacetate isomer A was treated as described above, there was obtained a total of 0·368 g (87% yield) crystalline lactone diol melting above 200°.

In another experiment a solution of 18 mg triacetate isomer A, m.p. 117·7–118·7°, in 2·0 ml 1N methanolic KOH was heated at reflux for 6 hr. The soln was concentrated to a volume of approx. 1 ml under reduced press. Dilution with water gave a clear soln (pH approx. 11) which was acidified in the cold with HCl, which resulted in the formation of a white ppt. This mixture was extracted with AcOEt and the combined organic layers were washed with 10% $KHCO_3$ aq (acidification yielded no acidic material), sat. brine, and dried over Na_2SO_4. The residue (15 mg) obtained on evaporation of the solvent under reduced press. was crystallized from AcOEt, affording 9 mg microcrystalline powder, m.p. 212–215°, undepressed on admixture with the analytical sample of the lactone diol isomer A described above. The IR spectra of the two materials were identical.

In another experiment a soln of 35 mg triacetate isomer A, m.p. 117·7–118·7°, in 10·4 ml abs. MeOH was treated with 0·5 ml conc. HCl, and the resulting soln was heated at reflux for 1·5 hr, concentrated to a small volume under reduced press., diluted with water, and extracted with AcOEt. The combined organic layers were washed with 10% $KHCO_3$ aq and sat. brine, and dried over Na_2SO_4. The residue obtained on evaporation of the solvent at reduced press. was crystallized from AcOEt, affording 17 mg lactone diol, m.p. 211–214°, undepressed on admixture with the analytical specimen described above. The IR spectra of the two specimens were identical.

As described above for isomer A, 23 mg triacetate isomer B, m.p. 119·5–120·8°, was treated with 1·0 ml 1N methanolic KOH at room temp. The product was isolated as described above, and crystallization from AcOEt gave 10·5 mg (first crop) solid, m.p. 214–216°, and 4 mg (second crop) crystals, m.p. 213–217°. Repeated recrystallizations of first-crop material (from another run) from MeOH–AcOEt afforded *isomer* B as colorless irregular microprisms, m.p. 216–218°, with sintering at 213°, λ_{max}^{KBr} 3·0 μ (OH) and 5·71 (γ-lactone C=O). (Found: C, 72·1; H, 9·7. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%).

By the same procedure, 0·527 g crude chromatographed (crystalline fractions) triacetate isomer B afforded a total of 0·309 g crystalline lactone diol isomer B, all but 22 mg (m.p. 185–205°) of which melted above 210°.

As in the A series, triacetate isomer B was converted, either by refluxing methanolic KOH or by methanolic HCl, essentially completely into the lactone diol isomer B.

dl-4bβ-*Methyl*-1β-(2-*ethylenedioxyethyl*)-2α-(2-*hydroxypropyl*)-7-*ethylenedioxy*-4aα,8aβ,10aβ-*perhydrophenanthrene*-2β-*carboxylic acid lactone* (76)

A soln of 0·118 g lactone diol isomer A, m.p. 217–218°, in 1·9 ml anhyd. pyridine was added to a slurry of the complex from 0·153 g CrO_3 in 1·7 ml pyridine.[48] After 5·2 hr at room temp. under N, the dark brown mixture was diluted with water and extracted thoroughly with AcOEt. The combined organic layers were washed with water, 10% $KHCO_3$ aq, again with water, sat. brine, and dried over Na_2SO_4. The residue obtained upon evaporation of the solvent under reduced press. was treated with portions of toluene followed by distillation in order to remove traces of pyridine. A soln of 1·0 ml ethylene glycol and 20 mg *p*-toluenesulfonic acid monohydrate in 16 ml benzene was added, and the soln was heated at reflux for 3 hr in a system equipped with a water separator containing Drierite. Excess 10% $KHCO_3$ aq was added and the aqueous layer extracted with benzene. The combined organic layers were washed with 10% $KHCO_3$ and dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was chromatographed on 3 g alkaline alumina affording, on elution with benzene, 85 mg oil which crystallized. Recrystallization from ether–pet. ether afforded 48 mg (first crop), m.p. 166·2–168°; 16 mg (second crop), m.p. 162–166°; and 8 mg (third crop), m.p. 154–162°. Two recrystallizations of the first-crop material from ether–pet. ether, followed by one recrystallization from benzene–pet. ether, gave the lactone acetal ketal *isomer* A as colorless plates, m.p. 167·2–168·6°, λ_{max}^{chf} 5·76 μ (γ-lactone C=O). (Found: C, 69·1; H, 9·0. $C_{25}H_{38}O_6$ requires: C, 69·09; H, 8·81%).

Further elution of the aforementioned chromatographic column with 5% ether in benzene to 10% MeOH in ether gave 31 mg non-crystalline material showing IR absorption in the 3μ region as well as at 5·76. This fraction evidently contained incompletely oxidized material.

Similarly 0·360 g lactone diol isomer B, m.p. above 210°, yielded a crude lactone acetal ketal, eluted from alkaline alumina with benzene, amounting to 0·258 g. Crystallization of a sample from pet. ether followed by two recrystallizations from acetone–pet. ether gave *isomer* B as colorless needles, m.p. 193·9–195·4°, λ_{max}^{chf} 5·75 μ (γ-lactone C=O) (Found: C, 69·4; H, 8·9. $C_{25}H_{38}O_6$ requires: C, 69·09; H, 8·81%).

The later eluates from the chromatogram afforded 71 mg incompletely oxidized material.

dl-4bβ-*Methyl*-1β-(2-*ethylenedioxyethyl*)-2β-*hydroxymethyl*-2α-(2-*hydroxypropyl*)-7-*ethylenedioxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (77, R = H)

A mixture of 54 mg lactone acetal ketal isomer A, m.p. 166–168°, and 77 mg LAH in 15 ml anhyd. ether was stirred for 2 hr room temp. It was then cooled to 0°, and excess AcOEt was added cautiously, followed by sat. Na_2SO_4 aq . The clear soln was decanted from the precipitated inorganic salts which were washed thoroughly with AcOEt. The combined organic solns were dried over Na_2SO_4 and concentrated under reduced press. Trituration of the residue with ether afforded 49 mg microcrystalline solid, m.p. 181–185°. Repeated recrystallizations from benzene–pet. ether gave acetal ketal diol *isomer* A as colorless clusters of elongated prisms, m.p. 185·3–186·4°, λ_{max}^{KBr} 2·86–2·92 μ. (Found: C, 68·4; H, 9·7. $C_{25}H_{42}O_6$ requires: C, 68·46 H, 9·65%).

The *diacetate* 77 (R = Ac), isomer A, prepared by the pyridine-Ac_2O method, was obtained from pet. ether as colorless elongated prisms, m.p. 116·8–118·2°. (Found: C, 66·6; H, 8·8. $C_{29}H_{46}O_8$ requires: C, 66·64; H, 8·87%).

The *ditosylate* 77 (R = Ts) was prepared by Armin Kreutzer who treated 89 mg acetal ketal diol isomer A, m.p. 184–186°, with 0·356 g *p*-toluenesulfonyl chloride in 4 ml anhyd. pyridine for 38 hr at room temp. The total crude product on trituration with AcOEt afforded 0·136 g, m.p. 136–137°. Repeated recrystallizations from ether–pet. ether afforded colorless crystals, m.p. 140–142°, $\lambda_{max}^{95\%\ EtOH}$ 225 mμ (ϵ 26,800). (Found: C, 62·5; H, 7·1. $C_{39}H_{54}O_{10}S_2$ requires: C, 62·72; H, 7·29%).

In another run performed by Armin Kreutzer in which the reduction was carried out on the total benzene eluate from the chromatographed lactone acetal ketal, there was obtained an 80% over-all yield of material, m.p. 179–182°.

Similarly, reduction of 0·225 g lactone acetal ketal isomer B (total benzene eluate from the chromatogram) afforded, on crystallization of the total crude product from ether, 0·197 g, m.p. 167–169°, λ_{max}^{chf} 3·0–3·04 μ. A second crop amounting to 15 mg, m.p. 163–167°, was obtained from the mother liquors, making the total yield 93%. Repeated recrystallizations of the first-crop material from benzene–pet. ether gave acetal ketal diol *isomer* B as clusters of microprisms, m.p. 170·9–171·4°. (Found: C, 68·1; H, 9·5. $C_{25}H_{42}O_6$ requires: C, 68·46; H, 9·65%).

The *diacetate* 77 (R = Ac), isomer B, was obtained from ether–pet. ether as colorless irregular prisms, m.p. 123–125·7°. (Found: C, 66·4; H, 8·9. $C_{29}H_{46}O_8$ requires: C, 66·64; H, 8·87%).

dl-4bβ-*Methyl*-1β-(2-*ethylenedioxyethyl*)-2β-*hydroxymethyl*-2α-*acetylmethyl*-7-*ethylenedioxy*-4aα,8aβ,10aβ-*perhydrophenanthrene lactol acetate* (79, R = Ac)

To a soln of 0·174 g of 77 (R = H), isomer B, m.p. 167–169°, in 4·3 ml anhyd. t-butyl alcohol and 0·2 ml anhyd. pyridine was added 0·111 g N-bromoacetamide. The mixture was stirred briefly until homogeneous and allowed to stand overnight at room temp. It was then diluted with AcOEt and ether, and the soln was washed with 75 ml water containing 0·62 g Na_2SO_3 followed by two portions of water. The combined aqueous layers were back-extracted with AcOEt and ether, and these extracts were washed with water. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced press. The foamy residue, which could not be induced to crystallize, was treated with 1·4 ml Ac_2O in 4 ml pyridine at room temp. for 25 hr. Excess cold 10% $KHCO_3$ aq was added, and the product, isolated by extraction with AcOEt, was chromatographed on 9 g Florisil. The fractions eluted with 2–5% ether in benzene amounted to 0·117 g crystallizable oil. Recrystallization from acetone–pet. ether afforded 68 mg, m.p. 166–175°. Repeated recrystallizations gave the lactol acetate as colorless rectangular prisms, m.p. 182·3–183·3°. (Found: C, 67·5; H, 8·7. $C_{27}H_{42}O_7$ requires: C, 67·75; H, 8·85%).

An attempt to convert 77 (R = H), isomer A, into the lactol acetate just as described above for the B series gave only non-crystallizable fractions on chromatography. The IR spectra of the fractions eluted with 2–5% ether in benzene, however, were almost identical with that of the lactol acetate derived from isomer B. It is to be noted that the A and B series converge stereochemically in the

product **78** of the *N*-bromoacetamide oxidation. Therefore the same lactol acetate should be produced from each epimer.

dl-3α-*Acetoxy*-5β-*cholestan*-24-*ol* (**82**, R = CH_2OH)

A soln of 1·26 g 3α-acetoxycholanic acid (prepared by direct esterification of lithocholic acid with AcOH and HCl as described for the prep. of **72** (R^1 = Ac, R^2 = Me, R^3 = OH)), m.p. 166–168°, in 5 ml anhyd. THF was stirred under N while 5·1 ml 0·32M soln of diborane in THF was added over a 30-min period at room temp. The soln was stirred for an additional hr, 0·05 ml water was added, and stirring was continued for 12 hr. The soln was diluted with water and extracted with ether. The combined organic layers were washed with dil. NH_4OH and with brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent was chromatographed on 25 g Florisil. The early fractions eluted with benzene amounted to 0·200 g oil, and the later fractions yielded 0·950 g crystalline alcohol. Recrystallization of the solid material from ether at −20° gave 0·460 g alcohol, m.p. 61–64°. Repeated recrystallizations afforded short colorless needles, m.p. 62–64°. (Found: C, 77·2; H, 10·8. $C_{26}H_{44}O_3$ requires: C, 77·17; H, 10·95%).

dl-3α-*Acetoxy*-5β-*cholestan*-24-*ol* p-*toluenesulfonate* (**82**, R = CH_2OTs)

A soln of 0·427 g recrystallized **82** (R = CH_2OH), m.p. 56–59° from a run comparable to that described above, and 0·228 g *p*-toluenesulfonyl chloride in 20 ml anhyd. pyridine was allowed to stand at 0° for 12 hr. The soln was added to excess 5% $NaHCO_3$ aq and extracted with ether. The combined organic layers were washed with 2% H_2SO_4 aq, water, 5% $NaHCO_3$ aq, sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent was crystallized from ether to give 0·380 g colorless needles, m.p. 112·5–116°. Two recrystallizations gave material melting very sharply at 117°. (Found: C, 70·9; H, 9·0; S, 5·75. $C_{33}H_{50}O_5S$ requires: C, 70·96; H, 8·96; S, 5·74%).

dl-3α-*Acetoxy*-5β-*cholestene*-23 (**83**)

A soln of 0·350 g of the aforementioned *p*-toluenesulfonate (total crude unrecrystallized product) in 2·0 ml anhyd. THF and 2·0 ml dimethylamine was chilled in a Carius tube at −70° which was sealed and then kept at room temp. for 24 hr. The tube was opened, the excess dimethylamine removed under a stream of N, excess 5% $NaHCO_3$ aq was added, and the mixture extracted with ether–benzene. The combined organic layers were washed with sat. brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was dried over P_2O_5 at 0·1 mm for 24 hr, leaving 0·259 g **82** (R = CH_2NMe_2) as an oil which failed to crystallize. In accordance with the procedure of Cope,[78] this probuct was cooled to −10° while 0·30 ml 44% peracetic acid was added. The mixture was maintained at −10° for 15 min and allowed to warm to room temp. over a 1-hr period. It was then diluted with 0·5 ml glacial AcOH and stirred at room temp. for 5 hr. The mixture was neutralized with solid $KHCO_3$ and extracted with chf. The combined organic layers were washed with water and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was evaporatively distilled at 160–190° (0·05 mm) to give 0·165 g crude olefin, λ_{max}^{film} 3·25 μ (=C—H), 5·78 (ester C=O), 6·11 (C=C), 11·05 and 11·28 (=CH_2). This material was chromatographed on 8 g Florisil. The fraction eluted with benzene amounted to 80 mg crystalline solid. A 62-mg portion was recrystallized from acetonitrile to give 52 mg, m.p. 110–112°. Recrystallization afforded colorless plates which melted very sharply at 112°. (Found: C, 80·4; H, 11·0. $C_{26}H_{42}O_2$ requires: C, 80·66; H, 10·95%).

dl-4bβ-*Methyl*-1β-(3-*hydroxypropyl*)-2β-*carbomethoxy*-2α-(2-*hydroxymethylpropyl*)-7α-*acetoxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**80**, R = OH)

A soln of **72** (R^1 = Ac, R^2 = Me, R^3 = OH), isomer B, m.p. 232–236°, in 2·5 ml anhyd. THF was stirred under N while 1·0 ml 0·32M soln of diborane in THF was added over a 10-min period. The soln was stirred for an additional 30 min, 0·080 ml water was added, and stirring was continued overnight. The soln was diluted with water and extracted with AcOEt. The combined organic layers were washed with 5% $NaHCO_3$ aq and with sat. brine, and were dried over Na_2SO_4. The residue obtained on evaporation of the solvent was chromatographed on 6 g Florisil. The fractions eluted with 1–2% MeOH in ether amounted to 70 mg crystalline product. Recrystallization from AcOEt–hexane afforded 40 mg colorless rods, m.p. 96–98°. A further recrystallization raised the m.p. to 98·5–100°. (Found: C, 69·2; H, 9·6. $C_{26}H_{44}O_6$ requires: C, 68·99; H, 9·80%).

In the early fractions from the aforementioned chromatogram, 28 mg crystalline product was eluted with 25% ether in benzene. Crystallization from AcOEt–hexane gave 15 mg square plates, m.p. 146–151°. This product may be the diol isomer A but it was not further investigated.

dl-4bβ-*Methyl*-1β-(3-*dimethylaminopropyl*)-2β-*carbomethoxy*-2α-(2-*dimethylaminomethylpropyl*)-7α-*acetoxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**80**, R = NMe_2)

A soln of 0·116 g of **80** (R = OH) (total chromatographed diol mixture recrystallized once from ether and once from acetone and consisting mainly of isomer A, m.p. 149–154°) and 0·100 g *p*-toluenesulfonyl chloride in 2·0 ml anhyd. pyridine was prepared at 0° and then kept at 10° for 24 hr. The product was isolated as described above for the prep. of **82** (R = CH_2OTs) and amounted to 0·155 g oil, $\lambda_{max}^{95\%\ EtOH}$ 225 mμ (ε 22,800). A 0·576-g specimen of ditosylate prepared in this manner was dissolved in 3·5 ml anhyd. THF and treated with 5·0 ml dimethylamine as described above for the preparation of **82** (R = CH_2NMe_2). The crude yellow oily product was crystallized from acetonitrile to give 0·266 g (70% yield) diamine, m.p. 95–97°. Recrystallization gave colorless needles, m.p. 96–97°. (Found: C, 71·1; H, 10·6; N, 5·3. $C_{30}H_{54}N_2O_4$ requires: C, 71·10; H, 10·74; N, 5·53%).

When the diamine was treated with peracetic acid and the product pyrolyzed as described above for the preparation of **83**, the product after distillation, obtained in only 10% yield, showed broad poorly defined peaks for the terminal olefinic bond in the IR spectrum. The residue was a brown resin showing no terminal olefinic bond absorption in the IR.

dl-4bβ-*Methyl*-1β-(3-*hydroxypropyl*)-2α-(2-*hydroxymethylpropyl*)-2β-*carboxy*-7α-*hydroxy*-4aα,8aβ,10aβ-*perhydrophenanthrene lactone* (**84**)

A soln of 0·150 g of **80** (R = OH) (mixture of isomers A and B, m.p. 115–116°) in 2·0 ml MeOH containing 0·02 ml water and 0·22 mg 85% KOH was allowed to stand at room temp. for 10 hr. The soln was diluted with water and extracted with AcOEt. The combined organic layers were washed with water and with sat. brine, and were dried over Na_2SO_4. The residue obtained on removal of the solvent at reduced press. was crystallized from AcOEt to give 48 mg (first crop), m.p. 205–215°; 67 mg (second crop), m.p. 168–172°; and 10 mg (third crop), m.p. 209–214°. Recrystallization of the first-crop material from AcOEt gave colorless cubical prisms, m.p. 213–216°, λ_{max} 3·0 μ (OH) and 5·83 (γ-lactone C=O). (Found: C, 73·1; H, 10·2. $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12%).

dl-4β-*Methyl*-1β-(2-*carbomethoxyethyl*)-2β-*carbomethoxy*-2α-(2-*carbomethoxypropyl*)-4aα,8aβ,10aβ-*perhydrophenanthren*-7-*one* (**85**)

A soln of 0·572 g of **72** (R^1 = H, R^2 = Me, R^3 = OMe), isomer A, m.p. 130·5–132°, in 25 ml acetone was cooled to 0°, and 0·35 ml 0·8N Jones reagent[23] was slowly added with stirring. The excess oxidant was decomposed with several drops of EtOH, and the green slurry was diluted with water and extracted with AcOEt. The combined organic layers were washed with sat. $NaHCO_3$ aq and with sat. brine, and were dried over Na_2SO_4. The residue obtained on evaporation of the solvent was crystallized from ether–hexane to give 0·469 g (first crop), m.p. 88–90°; and 36 mg (second crop), m.p. 83–86°. Repeated recrystallizations of the first-crop material gave pure *isomer* A as small colorless plates, m.p. 89·5–90·5°. (Found: C, 67·3; H, 8·55. $C_{26}H_{40}O_7$ requires: C, 67·21; H, 8·68%).

Similarly, oxidation of the crude hydroxy triester from 2·47 g of **72** (R^1 = R^2 = H, R^3 = OH), isomer B, m.p. 243–245°, yielded, upon evaporation of the extractant solvent, 2·40 g crude keto ester isomer B which could be induced to crystallize by trituration with ether–pet. ether. Material of this quality was used without further purification for the prep. of the ketal described below.

dl-4bβ-*Methyl*-1β-(2-*carbomethoxyethyl*)-2β-*carbomethoxy*-2α-(2-*carbomethoxypropyl*)-7-*ethylenedioxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**86**, R = Me)

A mixture of 0·389 g of the aforementioned keto triester isomer A, m.p, 88–90°, 20 ml benzene, 0·05 g ethylene glycol, and 5 mg *p*-toluenesulfonic acid monohydrate was heated at reflux (atm. of N) in a system containing a water separator. After 7 hr the soln was cooled, excess 5% $NaHCO_3$ aq was added, and the organic layer was washed with water, sat. brine and dried over $MgSO_4$. The residue obtained on evaporation of the solvent crystallized when seeded. Recrystallization from ether–pet.

ether gave 0·294 g (first crop), m.p. 133–135°; and 90 mg (second crop), m.p. 130–134°. Repeated recrystallizations of the first-crop material gave the ketal *isomer* A as colorless rhombic prisms, m.p. 138–139°. (Found: C, 66·1; H, 8·85. $C_{28}H_{44}O_8$ requires: C, 66·11; H, 8·72%).

Similarly a 1·68-g specimen of the aforementioned crude keto triester isomer B afforded 1·21 g (first crop), m.p. 85–87°; and 0·255 g (second crop), m.p. 81–84°. Recrystallizations of the first-crop material from ether–pet. ether gave ketal *isomer* B as colorless cubical prisms, m.p. 87–88°. (Found: C, 66·4; H, 8·6. $C_{28}H_{44}O_8$ requires: C, 66·11; H, 8·72%).

dl-4bβ-*Methyl*-1β-(*carboxyethyl*)-2β-*carbomethoxy*-2α-(2-*carboxypropyl*)-7-*ethylenedioxy*-4aα,8aβ,10aβ-*perhydrophenanthrene* (**86**, R = H)

A soln of 0·243 g of **86** (R = Me), isomer B, m.p. 85–87°, and 0·45 g 85% KOH aq in 40 ml MeOH and 3 ml water was heated at reflux with stirring under an atm. of N for 23 hr. The mixture was cooled and washed with ether. The alkaline aqueous phase was saturated with NaCl, cooled to −10° by the addition of ice, AcOEt was added, and the mixture was acidified by the addition, with stirring, of a mixture of ice and 10% HCl aq. The organic layer was washed thoroughly with water and then with sat. brine, and was dried over Na_2SO_4. The residue obtained on removal of the solvent was crystallized from ether to give 0·158 g (first crop), m.p. 125–127°; and 56 mg (second crop), m.p. 104–110°. Recrystallization of the first-crop material from ether afforded the diacid ketal isomer B as a dimorphic mixture of needles and prisms, m.p. 119–126°. (Found: C, 65·0; H, 8·2. $C_{26}H_{40}O_8$ requires: C, 64·98; H, 8·39%).

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