glycoside where a carboxyl group at the active site of the enzyme is participating in the reaction could, therefore, lead to significant catalysis.

Alkylation and Carbonation of Ketones by Trapping the Enolates from the Reduction of α,β-Unsaturated Ketones
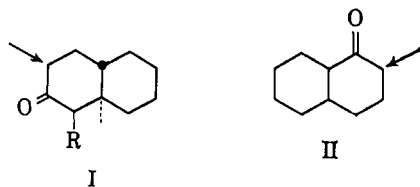
Gilbert Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji

Contribution from the Chandler Laboratories, Columbia University, New York 27, New York.   *Received August 31, 1964*

Evidence is given that during the course of the reduction of α,β-unsaturated ketones with lithium in liquid ammonia the β-carbon atom becomes nucleophilic and can be alkylated by a suitably placed electrophilic center. In the more usual case, the β-carbon becomes protonated by ammonia leading to an enolate ion. Full details are given of the method briefly reported in a preliminary communication,[1] by which trapping of that enolate ion with an alkyl halide or carbon dioxide leads to an alkylated or carboxylated saturated ketone in which the new group appears on the carbon which was the α-carbon of the original α,β-unsaturated system. The method has been used with six- as well as five-membered unsaturated ketones, with or without a hydrogen on the α-carbon. The free hydroxyl group of 4-methyltestosterone did not interfere with the reaction which led to 4,4-dimethyl-dihydrotestosterone.

Some progress in solving the problems involved in the alkylation of carbonyl compounds has been made by the introduction of the enamine alkylation method,[2] and later of the Schiff-base magnesium salt alkylation procedure.[3]

Situations not amenable to these solutions occur when an alkyl or carboxyl group must be introduced on that α-carbon atom which is not substituted by these methods. Two such situations are represented by the *trans*-2-decalone (I, R = H or alkyl) and the 1-decalone (II) systems where these methods—as well as direct base alkylation of the free ketone—lead to substitution at the position marked by an arrow.[4] There are a number of instances where it would be synthetically useful to introduce substituents on the other α-carbon, to produce III and IV.

I

II

III

IV

Various methods involving the use of blocking groups to prevent enolization in the unwanted direction are available,[5] but we were intrigued by the possibility that one of the most useful methods for the synthesis of a ketone such as I, *i.e.* the lithium–ammonia reduction of the corresponding α,β-unsaturated ketone V, should lead to an enolate ion VI which might be alkylated faster than it could isomerize.

V

Va

VI
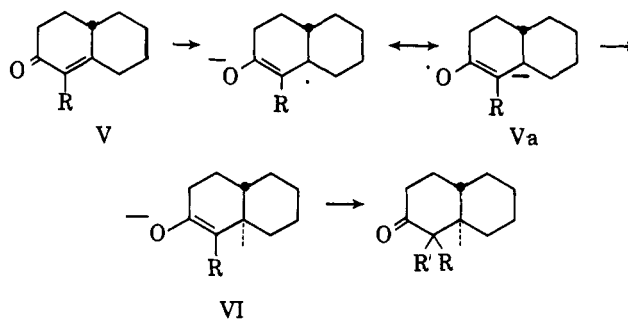
Previous work by Hauser[6] has shown that the metal-ammonia reduction of benzalacetophenone leads to a *dianion* VII which undergoes monoalkylation at the more nucleophilic position, β to the oxygenated carbon;

VII

but in unsaturated ketones of the type under consideration here, one would expect that a β-carbanion, not being stabilized by resonance with a benzene ring as in VII, should be sufficiently nucleophilic to abstract
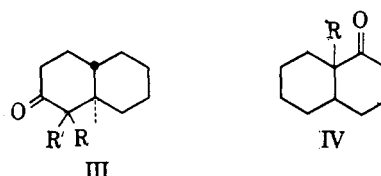
(1) G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).
(2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).
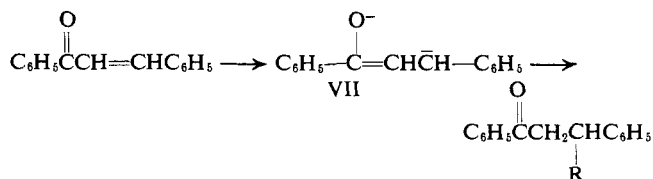(3) G. Stork and S. Dowd, *ibid.*, **85**, 2178 (1963).
(4) *Cf.* (a) A. R. Pinder and R. Robinson, *J. Chem. Soc.*, 1224 (1952); (b) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).

(5) *Cf.* W. S. Johnson, *ibid.*, **65**, 1317 (1943); A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944); W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947); R. B. Woodward and A. A. Patchett, *J. Chem. Soc.*, 1131 (1957); R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962); T. M. Harris and C. R. Hauser. *J. Am. Chem. Soc.*, **84**, 1750 (1962).
(6) P. J. Hamrick, Jr., and C. R. Hauser, *ibid.*, **81**, 493 (1959).

a proton from ammonia, thus leading to a *mono-enolate* (*cf.* VI). The product of the usual lithium–ammonia reduction of an α,β-unsaturated ketone does not throw light on the mono- or dienolate nature of the intermediate since either entity would give the same saturated ketone on protonation.

We will now turn to the examination of the course of the lithium–ammonia reduction of a $\Delta^{1,9}$-2-octalone (*cf.* V). We will first show that addition of lithium to an ammonia solution of derivatives of V does lead to an intermediate with nucleophilic character on the β-carbon atom (*cf.* Va). We then show that, in normal circumstances, this β-carbon becomes protonated by the *ammonia*, leading to enolate ions which have a structure corresponding to VI and can indeed be alkylated or carbonated to substances of type III.

I. Electrophilic Reaction at the β-Carbon Atom of an Enone, Following Electron Addition. As a suitable structure in which to demonstrate the nucleophilic character of the β-carbon atom we selected the tosylate of 10-hydroxymethyl-$\Delta^{1,9}$-2-octalone (IX) which was readily prepared from the ethylene ketal of 10-hydroxymethyl-$\Delta^{1,9}$-2-octalone[7] (VIII) by reaction with toluenesulfonyl chloride, followed by deketalization. Addition of the crystalline IX, m.p. 102–104°, to a lithium–

CH₂OH → CH₂OTs → CH₂OTs

VIII   IX
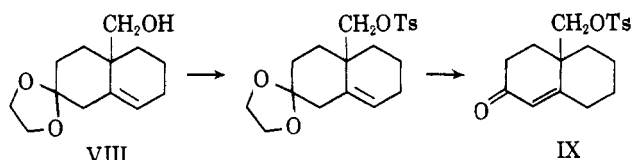
liquid ammonia solution readily gave a saturated ketone XI, $C_{11}H_{16}O$, characterized as its 2,4-dinitrophenylhydrazone, m.p. 153–154°. The fact that the ketone only had one oxygen shows that reduction did not involve the usual cleavage of a tosylate at the sulfur–oxygen bond to regenerate the hydroxymethyl group, but rather that a β-carbanionic intermediate was formed in which the negative charge was transferred to tosylate ion in a displacement reaction, as[8]

CH₂OTs   CH₂OTs   CH₂OTs

X   Xa

Xb   XI
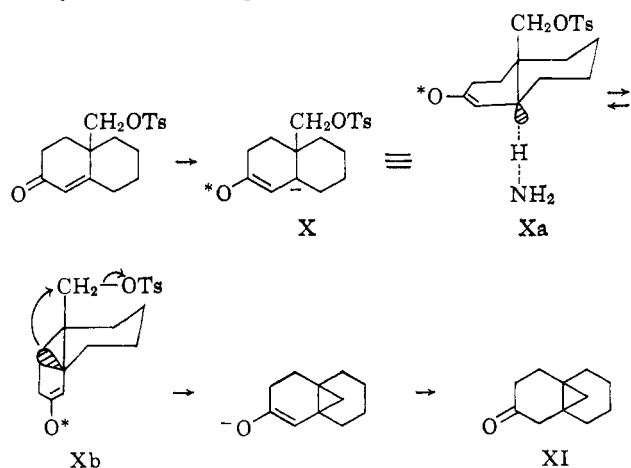
The structure of the saturated ketone XI was confirmed by its transformation on heating with acid into the known[9] 10-methyl-$\Delta^{1,9}$-2-octalone (XII), charac-

terized by comparison of its 2,4-dinitrophenylhydrazone with an authentic sample.

XII
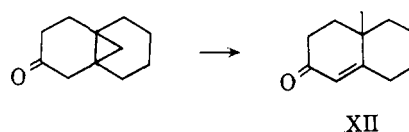
In an analogous manner, the reduction of the tosylate, m.p. 81–82°, of 10-hydroxymethyl-1-methyl-$\Delta^{1,9}$-2-octalone (XIII) gave the cyclopropane ketone XIV, characterized as its 2,4-dinitrophenylhydrazone, m.p. 125–127°, and transformed on heating with acid into 1,10-dimethyl-$\Delta^{1,9}$-2-octalone (XV), identified by comparison of its 2,4-dinitrophenylhydrazone, m.p. 200–202°, with an authentic sample.[10]

CH₂OH   CH₂OTs

XIII

XIV   XV
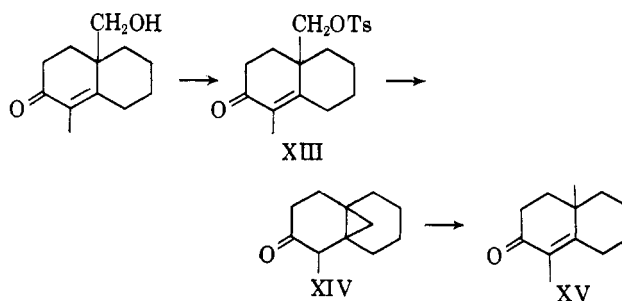
It is significant that, in these special cases, the decalones XI and XIV which are formed are necessarily *cis* fused. We have discussed in detail elsewhere[11] the stereochemistry of the lithium–ammonia reduction of α,β-unsaturated ketones. The transition state Xb is favored here over the normally preferred Xa because of the ease of formation of the three-membered ring and the efficient transfer of charge to form tosylate ion. In a less favorable case, for instance when the angular substituent is a 3-hydroxypropyl tosylate, the lower rate of formation of a five- compared to a three-membered ring leads to reductive loss of the tosylate group and to the usual protonation (from ammonia, see below) on the β-carbon atom *via* transition state Xa.[12]

The β-carbon alkylations that have just been described would be compatible with the formation of a stable dicarbanion such as that (VII) obtained from benzalacetophenone. It can easily be shown, however, that with the type of ketone under consideration here the nucleophilic character of the β-carbon of the enone undergoing reduction is such that abstraction of a proton from ammonia does take place, when more efficient alternatives are not available. Addition of $\Delta^{1,9}$-2-octalone to lithium in anhydrous liquid ammonia, followed by replacement of the solvent by benzene and addition of deuterium oxide, leads to deuteration on the α-carbon only, since all deuterium can be removed from the *trans*-2-decalone produced by washing with dilute aqueous base. Had a β-carbanion not previously been protonated by ammonia, the β-carbon would have acquired a nonexchangeable deuterium.[13]

(7) W. G. Dauben and J. B. Rogan, *J. Am. Chem. Soc.*, **79**, 5002 (1957).

(8) For a preliminary report on this cyclopropane formation, *cf.* G. Stork and J. Tsuji, *ibid.*, **83**, 2783 (1961).

(9) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); M. Yanagita, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 841 (1958).

(10) F. D. Gunstone and R. M. Heggie, *ibid.*, 1437 (1952).

(11) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).

(12) M. Rosenberger, unpublished observation in this laboratory.

(13) It has more recently been shown that similar reductions in *deuterated* liquid ammonia introduce a *deuterium* atom on the β-carbon atom: D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963).
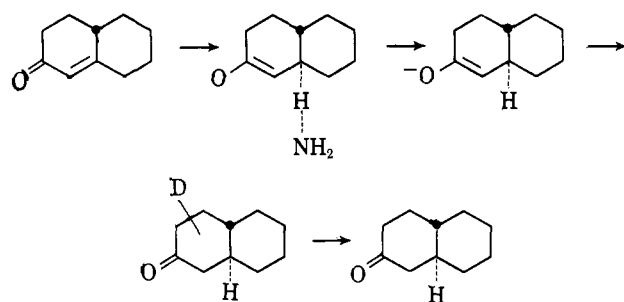
We conclude that enolate ions of type VI are formed in the lithium–ammonia reduction of enones. Their alkylation or carbonation should lead to the introduction of a substituent on a specific α-carbon atom (the α-carbon of the precursor α,β-unsaturated ketone). Such a reaction would be of considerable utility when the α-position at which reaction is thus made to proceed is not the same as that at which it would take place in the corresponding saturated ketone. Obviously in such a case, reaction of the initially formed enolate will have to occur faster than its equilibration.

II. Electrophilic Reactions at the α-Carbon Atom of an α,β-Unsaturated Ketone Following Electron Addition.[14] Reduction of $\Delta^{1,9}$-2-octalone with lithium in liquid ammonia, followed by addition of methyl iodide instead of the usual proton source, led to *ca.* 50% yield of methyldecalone which was shown by v.p.c. to be very largely (>80%) *trans*-1-methyl-2-decalone (XVI) by comparison of its 2,4-dinitrophenylhydrazone with an authentic sample. The melting point of the derivative of the isomeric *trans*-3-methyl-2-decalone (XVII) which would have resulted from enolate equilibration prior to methylation was almost identical, but was strongly depressed on admixture with the 2,4-dinitrophenylhydrazone in question.

Authentic 1-methyl-[15] and 3-methyl-*trans*-2-decalones were prepared by the reduction of 1-methyl-$\Delta^{1,9}$-2-octalone[2] and of 3-methyl-$\Delta^{1,9}$-2-octalone[2] with lithium in liquid ammonia.

Similar enolate trapping with butyl iodide gave *trans*-1-butyl-2-decalone (XVIII) in 43% yield. The butyl compound was essentially free of its isomer as shown by v.p.c. Here again, direct comparison of derivatives was carried out. 1-Butyl-$\Delta^{1,9}$-2-octalone (XX) was made by the Grignard reaction of amylmagnesium bromide with the enol lactone[16] of 2-cyclohexanone-

(14) It has come to our attention during the preparation of this manuscript that the trapping of enolates arising from α,β-unsaturated ketones was attempted several years ago (J. Schreiber, Ph.D. Dissertation, Zürich, 1953). Reduction of 2-methyl-Δ^2-cyclohexenone (a) with lithium and ammonia, followed by addition of 1,3-dichloro-2-butene or of methyl vinyl ketone, led to moderate yields of 2-methyl-2-alkyl-cyclohexanones (b).
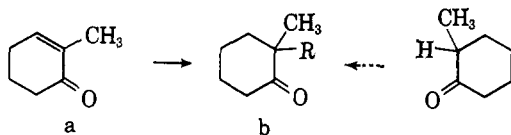
The choice of 2-methyl-Δ^2-cyclohexenone was unfortunate. It is not possible to tell from this example whether enolate trapping did indeed occur or whether simple reduction, followed by normal base-catalyzed alkylation, took place. The base-catalyzed alkylation of 2-methylcyclohexanone is well known to introduce the alkyl group in the same position (*cf.* D. Caine, *J. Org. Chem.*, 29, 1868 (1964); H. M. E. Cardwell, *J. Chem. Soc.*, 2442 (1951)). Our own early work (with A. W. Burgstahler, 1953) was also inconclusive.

(15) D. K. Banerjee, S. Chatterjee, and S. P. Bhattacharya, *J. Am. Chem. Soc.*, 77, 408 (1955).
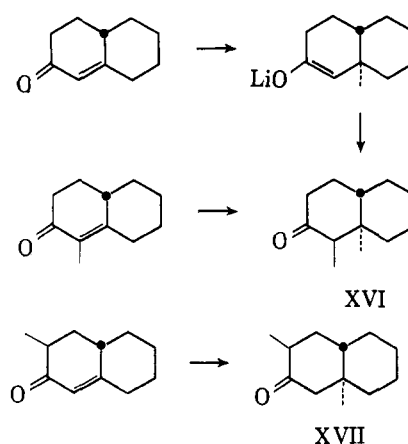
propionic acid[2] (XIX) and was reduced to authentic 1-butyl-*trans*-2-decalone (XVIII), characterized as its 2,4-dinitrophenylhydrazone, m.p. 125–126.5°. The isomeric 3-butyl compound XXII was produced by alkylation of 3-hydroxymethylene-*trans*-2-decalone[4a] (XXI) with butyl iodide followed by cleavage of the formyl group with base. The 2,4-dinitrophenylhydrazone of XXII melted at 173–174.5°.
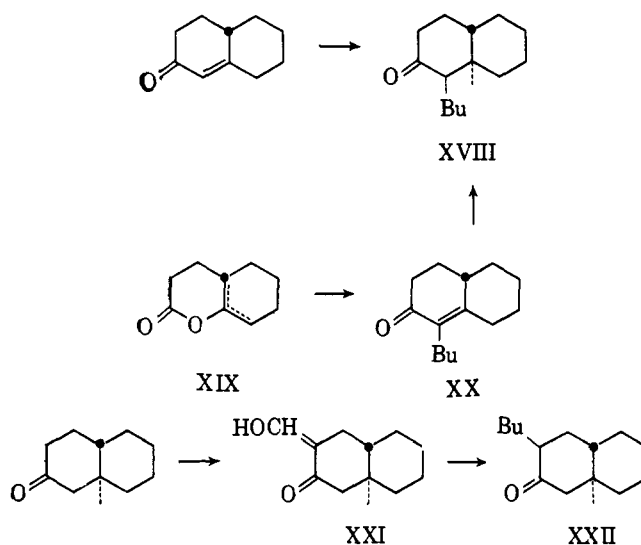
The implicit assumption in the use of lithium for the generation of enolate ions *via* reduction of α,β-unsaturated ketones was that, in contrast to the sodium or potassium enolates, it could be expected to undergo *slow* equilibration *via* exchange with alkylated ketone.[17] In fact, under the conditions which gave 83% monomethyl compound with lithium, either sodium or potassium led to much polyalkylated material (*ca.* 80%). Rapid equilibration of even the lithium enolate could be expected in a dissociating solvent like dimethyl sulfoxide: When alkylation of the lithium enolate was conducted with butyl iodide as usual, except that the ammonia was replaced by dimethyl sulfoxide before addition of the alkylating agent, the butyldecalone formed proved to be 3-butyl-*trans*-2-decalone (XXII). This is the product to be expected from equilibration to the more stable enolate prior to alkylation.

Trapping of the enolate ion from lithium addition to α,β-unsaturated ketones can also be done with carbon

(16) N. P. Shusherina, R. Ya Levina, and M. Yu Lure, *Zh. Obsch. Khim.*, 26, 750 (1956).

(17) *Cf.* D. Caine, *J. Org. Chem.*, 29, 1868 (1964).

dioxide. Addition of lithium in ammonia to 10-methyl-$\Delta^{1,9}$-2-octalone (XXIII), followed by replacement of the ammonia by anhydrous ether and addition of solid carbon dioxide, gave a β-keto acid which was isolated as the β-keto ester after treatment with diazomethane. The structure of the β-keto ester, characterized as its 2,4-dinitrophenylhydrazone, m.p. 184–185°, was established as XXIV by methylation followed by acid hydrolysis which produced 1,10-dimethyl-*trans*-2-decalone (XXV), identical with an authentic sample[18,19] formed by the reduction of 1,10-dimethyl-$\Delta^{1,9}$-2-octalone (XXVI) with lithium and ammonia.


XXIII   XXIV

XXV   XXVI
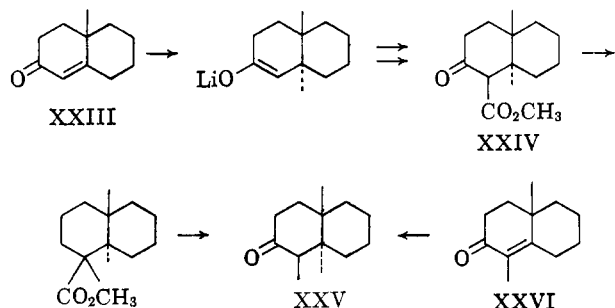
Application of the trapping procedure to the construction of hydrophenanthrene systems is illustrated by the sequence starting with 10-methyl-$\Delta^{1,9}$-2-octalone, using 1,3-dichloro-2-butene as the alkylating agent to give the crude alkylated product XXVII (2,4-dinitrophenylhydrazone, m.p. 147–148.5°) which was cyclized with concentrated sulfuric acid to the phenanthrone XXVIII, m.p. 125–127°, undepressed

XXIII   XXVII   XXVIII

XXIX   XXX   XXXI
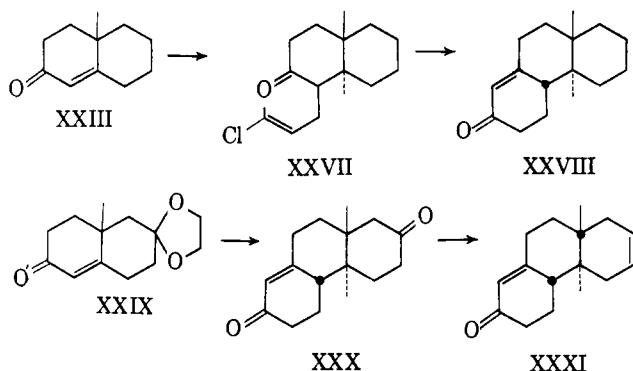
on admixture with an authentic sample.[20]

The same sequence, starting with the substituted octalone XXIX, led to the dione XXX, the structure of which was proved by degradation (*via* pyrolysis of the benzoate of the hydroxy unsaturated ketone) to the known[21] XXXI. The yield in the synthesis of XXX

(18) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).
(19) (a) S. L. Mukherjee and P. C. Dutta, *J. Chem. Soc.*, **67** (1960); (b) B. Gaspert, T. G. Halsall, and D. Willis, *ibid.*, 624 (1958).
(20) Prepared by Dr. P. C. Mukharji, in this laboratory, by Pd-C hydrogenation of i (R. B. Woodward, F. Sondheimer, D. Taub, K.

i
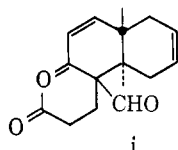
Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952)), followed by cyclization with potassium hydroxide in aqueous dioxane; m.p. 123–124° (from ether–petroleum ether). *Anal.* Calcd. for $C_{15}H_{22}O$: C, 82.56; H, 10.09. Found: C, 82.75; H, 10.24.

was, however, very low, possibly because of the losses involved in the concentrated sulfuric acid treatment.

Trapping of the reduction enolate in the hydrindenone series was also examined. The reduction of 5,6,7,8-tetrahydroindan-5-one[2] (XXXII) with lithium and ammonia is known to give predominantly the *trans* isomer.[22] Addition of methyl iodide after the lithium reduction was complete led, in 40% yield, to a ~4:1 mixture of products which proved identical with the mixture obtained on lithium–ammonia reduction of XXXIV. The major product (XXXIII) from that reaction was readily isolated as its 2,4-dinitrophenylhydrazone, m.p. 144–145°. The fact that the same ratio of products was obtained by trapping the enolate from XXXII and by the lithium–ammonia reduction of XXXIV incidentally shows that the presence of a 1-alkyl group has little effect on the *cis*:*trans* ratio of the reduction products.

XXXII   XXXIII   +

XXXIV
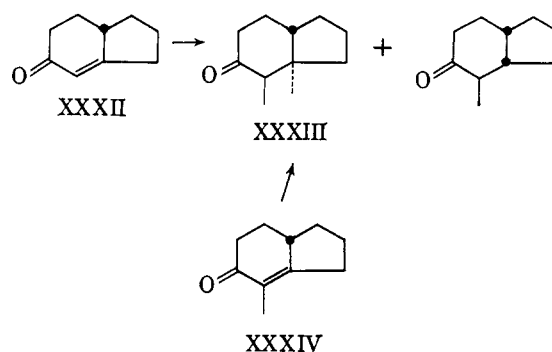
So far, the various alkylations which we have reported in this paper involve the introduction of a substituent at a position which does not already carry an alkyl group. As the sequel will demonstrate, the reaction is equally useful in the creation of a quaternary center.

For instance, reduction of XXXIV with lithium in ammonia, followed by trapping with methyl iodide, gave 1,1-dimethyl-*trans*-2-hydrindanone (XXXV), characterized as its 2,4-dinitrophenylhydrazone, m.p. 150–152°. In addition to this product a considerable amount of the product of simple reduction, the 1-methyl ketone XXXIII, was formed.

XXXV
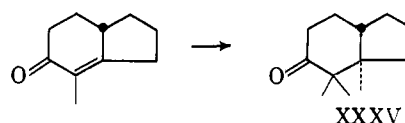
Formation of the simple reduction product without alkylation proved to be an even more serious matter in the case of 1,10-dimethyl-$\Delta^{1,9}$-2-octalone[18] (XV) which, under the usual alkylation conditions (addition of alkyl halide to the liquid ammonia solution of the enolate), gave almost entirely the unalkylated dihydro product. The formation of insoluble lithium enolates was suspected to be responsible for failure in this and similar cases, and we devised an alternative procedure which involved replacement of the liquid ammonia, prior to alkylation, by tetrahydrofuran. Under these conditions, alkylation of the reduction enolate of XV

(21) Prepared by Dr. P. C. Mukharji, in this laboratory: *cf.* British Patent 746,620 (1956); *Chem. Abstr.*, **51**, 1282 (1957).
(22) Lithium–ammonia reduction of XXXII gives a *trans*:*cis* ratio of 85:15: W. G. Dauben, private communication.

gave an 85% yield of saturated ketones, consisting of *ca.* 70% of the desired 1,1,10-trimethyl-*trans*-2-decalone (XXXVI), in addition to about 30% of XXV, the product of reduction without alkylation.

XXXVII ← XV → XXXVI

$C_6H_5CH_2$
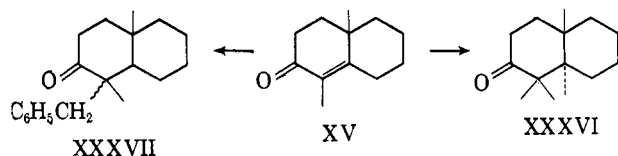
The 2,4-dinitrophenylhydrazone of XXXVI melted at 184–186°. This is almost identical with the melting point of the derivative of XXV, but a mixture of the two substances gave a strong melting point depression. The structure of XXXVII was further established by the presence of absorption peaks at τ 9, 9.1, and 9.15 (singlets, 3H each) in the n.m.r. spectrum.
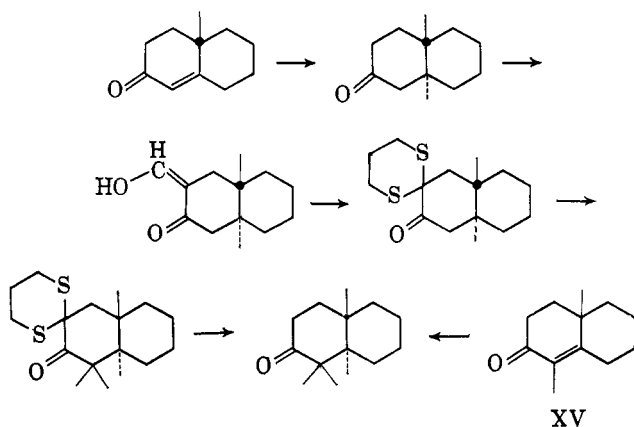
It is an interesting illustration of the usefulness of the enolate trapping method which we are describing here that 1,1,10-trimethyl-*trans*-decalone-2 is available in one step and in ~60% yield from the octalone XV. The classical synthesis of the same compound gives a 25% over-all yield from 9-methyl-$\Delta^{1,9}$-octalone and requires five steps.[19b]


XV

In a similar manner, alkylation of the reduction enolate from XV with benzyl chloride gave the anticipated 1-benzyl-1-methyl-*trans*-2-decalone (XXXVII) while from 1-methyl-$\Delta^{1,9}$-2-octalone, a very good yield of 1,1-dimethyl-*trans*-2-decalone (XXXVIII) (2,4-dinitrophenylhydrazone, m.p. 145–146°) was formed in addition to some polyalkylated material.


XXXVIII
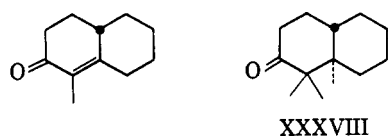
A particularly interesting case was that of $\Delta^{9,10}$-1-octalone[23] (XXXIX) which under the tetrahydrofuran conditions led to a mixture of *cis*- and *trans*-9-methyl-1-decalones in 62% yield, in addition to 23% of material which had been methylated at the 2-position. The mixture of *cis*- and *trans*-9-methyl-1-decalones was shown to consist predominantly of the *cis* isomer. It was isolated by preparative gas chromatography and characterized as its 2,4-dinitrophenylhydrazone, m.p.

(23) H. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

162–163°.[24] The ratio of the *cis* and *trans* isomers was approximately 3:1.

XXXIX
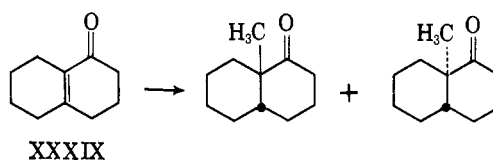
It is worth noting that in many cases the use of the tetrahydrofuran method is not necessary. For example, the reduction of 4-methyltestosterone[25] (XL) with lithium in ammonia, followed by addition of methyl iodide, gave, in about 60% yield, 4,4-dimethylandrostan-3-on-17-ol[25] (XLI). This is a particularly interesting case since, under these conditions, there was no deleterious effect from the presence of the free secondary hydroxyl group.[26]

XL → XLI
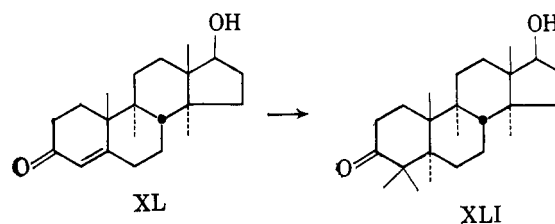
Experimental

Deuteration of the Anion from the Lithium–Ammonia Reduction of $\Delta^{1,9}$-2-Octalone. A mixture of 5 g. of $\Delta^{1,9}$-2-octalone[2] and 125 ml. of dry liquid ammonia (distilled from lithium) was kept under dry nitrogen and treated with lithium in small pieces until persistence of a blue color. After stirring for 1 hr. the excess lithium was destroyed by careful addition of methyl iodide until disappearance of the blue color. The ammonia was removed under nitrogen, finally under vacuum, and 100 ml. of anhydrous benzene and 10 ml. of deuterium oxide were then added. After standing overnight, the organic layer was separated, washed twice with water, dried over magnesium sulfate, and distilled to give 3.4 g., b.p. 124–128° (20 mm.). The material still contained *ca.* 8% of α,β-unsaturated ketone on the basis of its ultraviolet absorption and showed the expected strong carbon–deuterium absorption in the infrared. The deuterium absorption bands completely disappeared after letting the ketone stand in a 0.2% methanolic potassium hydroxide for 3 days at room temperature, followed by working up and repeating the washing for another 20 hr. The ketone thus recovered showed no excess deuterium on deuterium analysis.[27]

10-Hydroxymethyl-$\Delta^{1,9}$-2-octalone Tosylate (IX). The ketal alcohol VIII[7] (4.2 g.) was dissolved in 40 ml. of pyridine and 3.1 g. of toluenesulfonyl chloride was

(24) *Cf.* W. S. Johnson, ref. 5; also, J. M. Conia and F. Rouessac, *Tetrahedron*, **16**, 45 (1961).

(25) G. Rosenkranz and H. Ringold, *J. Org. Chem.*, **22**, 602 (1957).

(26) The use of enolate trapping has been reported, following our initial description of this synthetic method, in a number of steroid cases: R. E. Schaub and M. J. Weiss, *Chem. Ind.* (London), 2003 (1961); R. Deghenghi and R. Gaudry, *Tetrahedron Letters*, No. 11, 489 (1962); M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. J. Coscia, *Chem. Ind.* (London), 118 (1963); R. Deghenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963); M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(27) Analysis performed by Mr. J. Nemeth, Urbana, Ill.

added slowly with cooling. The mixture was stirred for 6 hr. at room temperature and then poured into an ice–hydrochloric acid mixture. The tosylate was extracted with ether and then the ether was removed. The oily residue was dissolved in a mixture of 50 ml. of methanol and 10 ml. of hydrochloric acid and the solution was refluxed for 15 min. on a steam bath. The tosylate was extracted with ether and the ethereal solution was washed with sodium bicarbonate solution. On evaporating the solvent, the residue solidified, yield 4.7 g. It crystallized from hexane–ethyl acetate mixture, m.p. 102–104°.

Anal. Calcd. for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63. Found: C, 64.67; H, 6.80.

9,10-Methylene-cis-2-decalone (XI). Liquid ammonia was poured into a three-necked flask and a small amount of lithium was added. Then the ammonia was slowly distilled into a second flask and about 300 ml. of dry ammonia was collected. The tosylate IX (6.2 g.) was dissolved in 30 ml. of dry tetrahydrofuran and the solution was poured into ammonia. Lithium (0.55 g.) was added in small portions. The lithium reacted instantaneously and no blue color was observed during the reaction. At the end, the milky solution became partly blue. After 15 min., 2 g. of ammonium chloride was added and the ammonia was allowed to evaporate. The residue was extracted with ether and the ethereal solution was washed with water. After evaporating the solvent, the residue was distilled from an oil-jacketed flask. The first fraction (1.3 g.) distilled at 70° (0.4 mm.), and the second (0.9 g.) at 100–110° (0.4 mm.). The low boiling fraction was redistilled and a colorless liquid was obtained, b.p. 75–78° (0.4 mm.) The 2,4-dinitrophenylhydrazone was prepared under mild conditions (0°) and orange crystals were obtained, m.p. 153–154°, $\lambda_{max}^{CHCl_3}$ 366 mμ (ϵ 20,400). If the hydrazone is prepared under the usual hot acid conditions, a mixture of orange and red hydrazones is obtained.

Anal. Calcd. for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.37; H, 5.57; N, 16.41.

Rearrangement of XI to 10-Methyl-$\Delta^{1,9}$-2-octalone (XII). Refluxing XI in benzene solution with toluenesulfonic acid for 8 hr. gave a mixture of unsaturated product XII and starting material.

A solution of XI in a 1:2:2 sulfuric acid–acetic acid water mixture was refluxed for 6 hr. After the usual work-up, the infrared spectrum of the product showed the complete conversion of XI into XII. The product was isolated as its 2,4-dinitrophenylhydrazone. The deep red hydrazone melted at 168–169° (reported[9] m.p. of 10-methyl-$\Delta^{1,9}$-2-octalone 2,4-dinitrophenylhydrazone, 169°); the identity was confirmed by a mixture melting point determination.

1-Methyl-10-carbethoxy-$\Delta^{1,9}$-2-octalone. (This experiment was done by William H. Brown.) To a well-chilled solution of 29.0 g. (1.28 g.-atoms) of clean sodium in 1500 ml. of ethanol was added 208 g. (1.22 moles) of 2-carbethoxycyclohexanone.[28] The sodium salt soon precipitated as a white cake. To this was added over 0.5 hr. 336 g. (1.22 moles) of crude 1-dimethylamino-3-pentanone methiodide,[29] and the

(28) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 531.

whole stirred 1 hr. at 0°, 3 hr. at room temperature, and 3 hr. at reflux. The major portion of the solvent was removed by distillation at reduced pressure and the residue was taken up in ether, washed, dried, and concentrated. Distillation gave 224.4 g. (74.5%) of the octalone, b.p. 105–118° (0.5–0.7 mm.), $n^{25}D$ 1.5092, λ_{max}^{EtOH} 247 mμ (ϵ 12,400).

The *semicarbazone*, crude m.p. 167–168°, was recrystallized twice from ethanol–water with no change in melting point.

Anal. Calcd. for $C_{15}H_{23}N_3O_3$: C, 61.40; H, 7.90. Found: C, 61.30; H, 7.72.

1-Methyl-2-hydroxy-10-hydroxymethyl-$\Delta^{1,9}$-octalin. Lithium aluminum hydride (8 g.) was added to 1 l. of ether, and then 1-methyl-10-carbethoxy-$\Delta^{1,9}$-2-octalone (see above, 30 g.), dissolved in a small amount of ether, was added slowly. The mixture was stirred overnight at room temperature. Excess lithium aluminum hydride was destroyed with ethyl acetate, saturated sodium sulfate solution was added, and the ethereal layer was decanted. The sodium sulfate was washed with ether, and the ethereal solution was dried and evaporated. The oily residue was distilled by using an oil-jacketed flask; b.p. 130–140° (0.1 mm.). It solidified on standing and was recrystallized from hexane–ethyl acetate mixture; m.p. 113–116°, yield 21 g. (84.7%).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.51; H, 10.19.

1-Methyl-10-hydroxymethyl-$\Delta^{1,9}$-2-octalone. Manganese dioxide was prepared by adding a saturated potassium permanganate solution to a hot solution of manganese sulfate with stirring until no more permanganate was consumed. During the reaction the temperature was kept between 80 and 90°. The manganese dioxide was filtered off and washed with water until the washing water became neutral. It was then washed with methanol and dried overnight at 100°. Since the allylic alcohol is sensitive to acidic conditions, incomplete washing tends to give lower yield of unsaturated ketone.

The dialcohol (22 g.) was dissolved in chloroform (2 l.) and oxidized with the above manganese dioxide (170 g.) for 24 hr. at room temperature. The manganese dioxide was filtered off, and the chloroform was evaporated. The oxidized product was distilled by using an oil-jacketed flask at 135–140° (0.07 mm.); yield 16 g. (76%), λ_{max}^{EtOH} 251 mμ, (ϵ 19,300). This material was used directly in the next step.

10-Hydroxymethyl-1-methyl-$\Delta^{1,9}$-2-octalone Tosylate (XIII). A solution of 3 g. of the above allylic alcohol in 50 ml. of pyridine was thoroughly cooled, and 4.5 g. of toluenesulfonyl chloride was added in small portions. The mixture was stirred for 5 hr. with cooling. After the usual work-up, the oily residue was passed through a column of alumina. The fraction eluted with benzene–hexane mixture (1:1) solidified and was recrystallized from hexane–ethyl acetate mixture; yield 3 g., m.p. 81–82°.

Anal. Calcd. for $C_{19}H_{24}O_4S$: C, 65.50; H, 6.94. Found: C, 65.33; H, 6.88.

The deep red *2,4-dinitrophenylhydrazone* had m.p. 150–151°.

(29) P. S. Adamson, F. C. McQuillin, R. Robinson, and J. L. Simonsen, *J. Chem. Soc.*, 1576 (1937).

Anal. Calcd. for $C_{25}H_{30}N_4O_7S$: C, 56.81; H, 5.34; N, 10.60. Found: C, 56.77; H, 5.55; N, 10.64.

9,10-Methylene-1-methyl-cis-2-decalone *(XIV).* The same procedure was followed as with IX (5.6 g. of XIII, 20 ml. of tetrahydrofuran, and 0.38 g. of lithium) and 1.4 g. of XIV was obtained, b.p. 75–77° (0.4 mm.). The 2,4-dinitrophenylhydrazone was prepared under mild conditions, and orange crystals were obtained, m.p. 125–127°; $\lambda_{max}^{CHCl_3}$ 363 mμ (ϵ 23,100).

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.70; H, 6.37; N, 15.58.

Isomerization of XIV to 1,10-Dimethyl-$\Delta^{1,9}$-2-octalone. The same procedure used for XI was followed. The cyclopropane (0.4 g.) was heated in 15 ml. of acetic acid–sulfuric acid mixture for 5 hr., and the product was isolated as its 2,4-dinitrophenylhydrazone; yield 0.6 g., m.p. 200–202° (lit.[10] m.p. 199–200°). The melting point of the mixture with an authentic sample was undepressed.

General Procedure for the Methylation in Liquid Ammonia of the Enolate Intermediate Formed during the Metal–Ammonia Reduction of $\Delta^{1,9}$-2-Octalone. A 500-ml., three-necked flask fitted with a stirrer, Hirshberg dropping funnel, and Dry Ice condenser was heated for 15 min. with a free flame. Dry nitrogen gas was swept through the system while heating, and for several additional minutes. The system was then evacuated and filled with nitrogen. After 150 ml. of ammonia was distilled into the reaction flask from an ammonia–sodium solution, 4 g. (0.0266 mole) of $\Delta^{1,9}$-2-octalone was introduced and stirring begun. Two equivalents of the reducing metal was then added and the resulting blue solution allowed to stir for 1 hr. Methyl iodide (16 g., 0.11 mole) was then added dropwise and the medium soon turned white. After a further 30 min., the Dry Ice condenser was replaced by a water condenser and the ammonia was allowed to evaporate overnight. The remaining salts were dissolved in 100 ml. of water, and the mixture was made acid by the addition of 10% hydrochloric acid. The organic material was taken up in ether, the ether was washed with water, dried, and concentrated. By gas chromatography of the distilled material through a silicone column and by comparison with an authentic mixture, it was possible to determine the approximate composition of the material obtained.

(a) *Lithium.* From 4 g. (0.027 mole) of $\Delta^{1,9}$-2-octalone,[2] 150 ml. of ammonia, and 0.38 g. (0.053 g.-atom) of lithium was obtained 2.6 g. of a colorless liquid, b.p. 60–63° (0.1mm.). By gas chromatography, using an 11-ft. silicone column at a temperature of 175°, it was determined that the mixture consisted of 17% of *trans*-2-decalone and 83% of 1-methyl-*trans*-2-decalone (XVI). The *2,4-dinitrophenylhydrazone*, recrystallized twice from ethyl acetate, had m.p. 182–183°; mixture melting point with authentic (*vide infra*) 1-methyl-*trans*-2-decalone, 182–183°.

(b) *Sodium.* From 4 g. (0.027 mole) of $\Delta^{1,9}$-2-octalone, 150 ml. of ammonia, and 1.22 g. (0.053 g.-atom) of sodium was obtained 2.25 g. of colorless liquid, b.p. 64–67° (0.02 mm.). By gas chromatography the mixture was shown to contain 77% of polyalkylated *trans*-2-decalone.

(c) *Potassium.* From 4 g. (0.029 mole) of $\Delta^{1,9}$-2-octalone, 150 ml. of ammonia, and 2.08 g. (0.0532 g.-atom) of potassium was obtained 2.97 g. of a colorless liquid, b.p. 64–66° (0.015 mm.). By gas chromatography the mixture was shown to be approximately of the same composition as in the sodium case.

1-Methyl-2-trans-decalone *(XVI).* A 1-l., three-necked flask equipped with stirrer, dropping funnel, and Dry Ice condenser was heated with a free flame for 15 min. while dry nitrogen gas was being swept through the system, over a 45-min. period. A solution of 5 g. (0.034 mole) of 1-methyl-$\Delta^{1,9}$-2-octalone in 600 ml. of ether was then added to a solution of 2.8 g. (0.40 g.-atom) of lithium in 500 ml. of liquid ammonia. The solution was stirred for 30 min. and then dry ethanol added until the blue color was discharged. After removal of the ammonia, 200 ml. of water was added and the mixture extracted with ether, washed with dilute hydrochloric acid, dried, and concentrated. The yellow residue was then taken up in 50 ml. of acetone, and oxidation of the decalol was effected by the careful addition of an 8 N chromic acid solution containing 5 ml. of concentrated sulfuric acid. The oxidizing solution was added until an orange color persisted for 2 min. The acetone was then removed under vacuum and the green residue treated with water and solid bicarbonate to pH 7–8. After extraction with ether and subsequent washing of the ether extracts with water and saturated salt solution, the decalone was isolated and purified by vacuum distillation of the concentrated ether extract to give 3.5 g. (63%) of XVI, b.p 66–67° (0.07 mm.), lit.[15] b.p. 170–175° (60 mm.). The *2,4-dinitrophenylhydrazone*, recrystallized twice from ethyl acetate, had m.p. 180–182°, lit.[15] m.p. 179–180°.

3-Methyl-trans-2-decalone *(XVII).* The reduction of 3-methyl-$\Delta^{1,9}$-octalone was carried out exactly as described above for 1-methyl-$\Delta^{1,9}$-2-octalone. From 3.92 g. (0.0239 mole) of 3-methyl-$\Delta^{1,9}$-2-octalone [b.p. 68–70° (0.15 mm.), λ_{max}^{EtOH} 238 mμ (log ϵ 4.08); lit.[2] b.p. 100–105° (0.5 mm.)], 3 g. (0.43 g.-atom) of lithium, 400 ml. of dry ether, and 500 ml. of ammonia was obtained 2.5 g. (62.5%) of 3-methyl-*trans*-2-decalone, b.p. 71° (0.1 mm.).

The *2,4-dinitrophenylhydrazone*, recrystallized twice from ethyl acetate, had m.p. 180–182° and depressed the m.p. of the derivative of the isomeric XVI.

Anal. Calcd. for $C_{11}H_{18}O$: C, 58.94; H, 6.40. Found: C, 58.79; H, 6.59.

Butylation of the Enolate Intermediate Formed During the Lithium–Ammonia Reduction of $\Delta^{1,9}$-Octalone-2. The procedure was very similar to that used for the successful methylation of the enolate intermediate derived from the lithium–ammonia reduction of $\Delta^{1,9}$-octalone-2, but differed in that the octalone was added to a solution of excess lithium in ammonia, as compared to the previous method of adding an equivalent of the metal to a solution of the ketone in liquid ammonia. From 5.05 g. (0.337 mole) of V, R = H, 250 ml. of dry ammonia, 0.6982 g. (0.101 g.-atom) of lithium, and 37 g. (0.2 mole) of butyl iodide there was obtained 3 g. (43%) of 1-butyl-*trans*-2-decalone (XVIII), b.p. 90–91° (0.05 mm.). Gas chromatography indicated 99% purity. The 2,4-dinitrophenylhydrazone

showed m.p. 125–126.5°, which was undepressed when mixed with an authentic sample (*vide infra*).

A higher boiling fraction (0.8 g.) of polyalkylated material was also obtained, b.p. 115–120° (0.05 mm.).

Attempted Alkylation with n-Butyl Bromide. The procedure was that used for the methylation reactions previously described. From 4 g. (0.0266 mole) of $\Delta^{1,9}$-2-octalone, 150 ml. of ammonia, 0.6 g. (0.087 g.-atom) of lithium, and 16 g. of *n*-butyl bromide was obtained 2 g. of *trans*-2-decalone, b.p. 55–60° (0.01 mm.). No alkylation product could be detected.

$\Delta^{9,10}$-*Hexahydrocoumarin* (*XIX*). 2-Ketocyclo-hexanepropionic acid[2] (30 g., 0.18 mole) was refluxed 16 hr. with 140 ml. of acetic anhydride and 10 g. of anhydrous sodium acetate. The solvent was removed at atmospheric pressure and the residue was dissolved in 400 ml. of ether, the ether solution was washed with 5% sodium bicarbonate followed by water, and was then dried and concentrated. Distillation gave 19 g. (70.3%), b.p. 75–78° (0.02 mm.); lit.[16] b.p. 117–118° (5 mm.).

1-Butyl-$\Delta^{1,9}$-*2-octalone* (*XX*). To a solution of 19 g. (0.125 mole) of $\Delta^{9,10}$-hexahydrocoumarin in 400 ml. of ether was added an ether solution of Grignard reagent prepared from 21 g. (0.139 mole) of *n*-amyl bromide and 3.4 g. (0.14 g.-atom) of magnesium. The amylmagnesium bromide was made in a jacketed Grignard flask, and was added dropwise over a period of 1.5 hr. while the lactone solution was kept at −20° in a nitrogen atmosphere. The mixture was then allowed to stir a further 2 hr., the temperature rising to −15°. It was then decomposed with 5% hydrochloric acid and a further 200 ml. of water was added. The organic layer was separated and washed with 5% sodium bicarbonate, water, and was then dried and evaporated. The residue was refluxed with potassium hydroxide (14 g.) in methanol (200 ml.) for 9 hr., and the product was isolated with ether in the usual way. Distillation gave 8.9 g. (34.6%) of XX, b.p. 105–108° (0.15 mm.). This was used directly in the next step.

1-Butyl-trans-2-decalone (*XVIII*). To a solution of 8.9 g. (0.04 mole) of 1-butyl-$\Delta^{1,9}$-2-octalone, 150 ml. of ether, and 300 ml. of anhydrous liquid ammonia was added 0.62 g. (0.087 g.-atom) of lithium metal cut in small pieces. The resulting blue solution was stirred for 1 hr. Then, ammonium chloride (10 g.) was added and the ammonia was removed at room temperature. The remaining salts were dissolved with 200 ml. of water and the mixture was acidified with 20% hydrochloric acid. The organic material was extracted with ether, the ether solution was washed to neutrality, dried, and the ether was removed. Distillation afforded the desired decalone, b.p. 90–91° (0.05 mm.), which was characterized as its *2,4-dinitrophenylhydrazone*. After three recrystallizations from ethyl acetate this gave an analytical sample, m.p. 125–126.5°.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27. Found: C, 62.16; H, 7.34.

General Procedure for the Alkylation of the Reduction Intermediate in Dimethyl Sulfoxide. The reduction was carried out in a manner similar to that described previously. To a solution of 4 g. (0.0266 mole) of $\Delta^{1,9}$-2-octalone in 150 ml. of distilled ammonia was added a calculated amount of the reducing metal. The

resulting blue solution was allowed to stir for 1 hr. By the gradual addition of dimethyl sulfoxide, the total volume was maintained at 100 ml. during the evaporation of the ammonia. After all the dimethyl sulfoxide (100 ml.) had been added, the system was warmed to 30° and placed under vacuum for 15 min. *n*-Butyl iodide was then added dropwise, and the solution was stirred overnight. The solvent was then dissolved in 400 ml. of water and the mixture was extracted twice with 400 ml. of ether. The ethereal extracts were washed with water, dried, and concentrated. Analysis of the various samples was carried out by means of gas chromatography.

Lithium. Distillation of the product obtained from 4 g. (0.0266 mole) of $\Delta^{1,9}$-2-octalone, 0.4 g. (0.058 g.-atom) of lithium, and 10 g. (0.0532 mole) of *n*-butyl iodide afforded two fractions: (a) 1.1 g., b.p. 95–105° (0.08 mm.); (b) 2.75 g., b.p. 110–120° (0.08 mm.). Both fractions were submitted separately to gas chromatography. Fraction a contained approximately 18% of *trans*-2-decalone, 75% of monoalkylated-*trans*-2-decalone, and 7% polyalkylated *trans*-decalone. A 2,4-dinitrophenylhydrazone was purified by chromatography according to the method of Elvidge.[30] Recrystallization from ethyl acetate afforded a bright yellow material, m.p. 173–174°. Mixture melting point with the 2,4-dinitrophenylhydrazone from authentic 3-butyl-*trans*-2-decalone (XXII) was not depressed; m.p. 172–173°. Fraction b consisted of approximately equal amounts of *trans*-2-decalone, monoalkylated decalone, and polyalkylated decalone.

Sodium. Distillation of the product from 4 g. (0.0266 mole) of $\Delta^{1,9}$-2-octalone, 1.2 g. (0.0532 g.-atom) of sodium, and 6 g. (0.033 mole) of *n*-butyl iodide afforded three fractions: (a) 1 g. of *trans*-2-decalone, b.p. 55–60° (0.06 mm.); (b) 1 g., b.p. 85–98° (0.05 mm.); (c) 1.7 g., b.p. 99–105° (0.05 mm.). Fractions b and c were separately submitted to gas chromatography. Fraction b was approximately 30% *trans*-2-decalone, 64% monoalkylated decalone, and 6% polyalkylated decalone. A 2,4-dinitrophenylhydrazone of the monoalkylated fraction was purified by chromatography.[30] Recrystallization from ethyl acetate gave a bright yellow compound, m.p. 172–173°, which did not depress the melting point of authentic 3-butyl-*trans*-2-decalone. Fraction c contained only polyalkylated material.

Potassium. Distillation of the product from 4 g. (0.0266 mole) of $\Delta^{1,9}$-2-octalone, 2.08 g. (0.0532 g.-atom) of potassium, and 10 g. (0.0532 mole) of *n*-butyl iodide gave two fractions: (a) 0.6 g., b.p. 80–84° (0.03 mm.); (b) 2.2 g., b.p. 96–107° (0.03 mm.). These were separately submitted to gas chromatography. Fraction a contained approximately 37% of *trans*-2-decalone, 60% of monoalkylated decalone, and 3% of polyalkylated compound. A 2,4-dinitrophenylhydrazone from the monoalkylated fraction was purified by chromatography[30] and recrystallized from ethyl acetate; m.p. 172–173°. Mixture melting point with an authentic sample of 3-butyl-*trans*-2-decalone gave no depression. Fraction b contained only polyalkylated material.

(30) L. A. Elvidge and M. Whalley, *Chem. Ind.* (London), 589 (1955).

trans-2-Decalone (*I*, *R* = *H*). The apparatus was flame-dried as previously described. To a blue solution of 0.14 g. (0.06 g.-atom) of lithium in 200 ml. of dry ammonia was added dropwise over a period of 0.5 hr. a solution of 4.5 g. (0.03 mole) of $\Delta^{1,9}$-2-octalone, 2.2 g. (0.03 mole) of *t*-butyl alcohol, and 50 ml. of dry ether. After the blue color was discharged, 10 g. of ammonium chloride was added. The ammonia was removed and the mixture was acidified by the addition of 250 ml. of 10% hydrochloric acid. The reduced octalone was extracted with 400 ml. of ether and the ether solution was washed and dried. Distillation gave 3.4 g. (76%) of the desired decalone, b.p. 122–124° (20 mm.), reported b.p.[15] 162–164° (60 mm.). By ultraviolet analysis [λ_{max}^{EtOH} 239 mμ (ϵ 170)] the material was found to contain 1–1.5% of the unreduced ketone.

3-Butyl-trans-2-decalone (*XXII*). To a mixture of 1.05 g. of sodium hydride (54.5%) in 50 ml. of dry ether was added 4 g. (0.022 mole) of 3-hydroxymethylene-*trans*-2-decalone.[4a] The sodium salt precipitated as a white cake (several hours). To this was added 16.5 g. (0.09 mole) of *n*-butyl iodide in 50 ml. of ether and the resulting mixture was refluxed until it was no longer basic (2 days). The excess butyl iodide was removed by distillation at reduced pressure and the residue was refluxed 5 hr. with a 10% potassium hydroxide solution. The organic material was taken up in ether and the ether solution was washed with water, dried, and concentrated. Distillation of the straw-yellow residue gave 2.5 g. (55%) of 3-butyl-2-*trans*-decalone as a water-white liquid.

The *2,4-dinitrophenylhydrazone*, recrystallized twice from ethyl acetate, had m.p. 173–174.5°.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27. Found: C, 61.97; H, 7.32.

Carbonation of the Enolate Intermediate from the Lithium–Ammonia Reduction of 10-Methyl-$\Delta^{1,9}$-2-octalone (*XXIII*). To a solution of 1.93 g. (0.28 g.-atom) of lithium in 400 ml. of dry ammonia was added dropwise a solution of 11.48 g. (0.07 mole) of 10-methyl-$\Delta^{1,9}$-2-octalone[9] dissolved in 100 ml. of dry ether. After 0.5 hr. a few crystals of anhydrous ferric chloride were added and the mixture was stirred until the excess lithium was converted to lithium amide (approximately 4 hr.). The ammonia was evaporated and replaced by ether and a 20-fold excess of Dry Ice was then added. The mixture was acidified, extracted with ether, and the ether solution was then treated with diazomethane. Fractionation of the crude product gave 3.55 g. of 10-methyl-*trans*-2-decalone, b.p. 76–84° (0.2 mm.), and 5.2 g. of 10-methyl-1-carbomethoxy-*trans*-2-decalone (XXIV), b.p. 108–111° (0.1 mm.).

The *2,4-dinitrophenylhydrazone*, recrystallized from ethyl acetate, had m.p. 184–185°.

Anal. Calcd. for $C_{19}H_{26}N_4O_6$: C, 56.43; H, 5.98. Found: C, 56.15; H, 5.96.

Identification of the β-Keto Ester XXIV by Conversion to 1,10-Dimethyl-trans-2-decalone (*XXV*). To a suspension of 0.617 g. of 54.5% sodium hydride dispersion in paraffin oil in 10 ml. of dry benzene was added 3.13 g. (0.014 mole) of the β-keto ester XXIV in 10 ml. of benzene. A bright yellow solution of the sodium salt of the β-keto ester was observed to form after stirring overnight. A twofold excess of methyl iodide was

then added and the solution allowed to stir an additional 24 hr. The precipitated sodium iodide was filtered off and the solvent was removed *in vacuo*. Distillation of the residue gave 2.3 g. (70%) of 1,10-dimethyl-1-carbomethoxy-*trans*-2-decalone, b.p. 115° (0.1 mm.). The crude keto ester (2 g., 0.0084 mole) in 5 ml. of concentrated hydrochloric acid and 15 ml. of glacial acetic acid was refluxed for 7 hr. Water (20 ml.) was then added and the mixture was neutralized by the addition of solid sodium bicarbonate. The organic material was extracted with ether; the ether solution was washed with water, dried, and concentrated. Distillation afforded 1.0 g. (66%) of 1,10-dimethyl-*trans*-2-decalone (XXV), b.p. 75–78° (0.2 mm.) [lit.[18] b.p. 99° (3 mm.)].

The *2,4-dinitrophenylhydrazone*, recrystallized from ethyl acetate, had m.p. 185–186°. The mixture melting point with an authentic sample (*vide infra*) gave no depression.

Authentic 1,10-Dimethyl-2-trans-decalone (*XXV*). The metal–ammonia reduction described above for 1-methyl-$\Delta^{1,9}$-2-octalone was carried out with a solution of 5 g. (0.028 mole) of 1,10-dimethyl-$\Delta^{1,9}$-2-octalone,[18] 600 ml. of dry ether, 500 ml. of ammonia, and 2.8 g. (0.40 g.-atom) of lithium. This gave 3 g. (59.5%) of 1,10-dimethyl-*trans*-2-decalone, b.p. 75° (0.2 mm.), lit.[18] b.p. 99° (3 mm.).

The *2,4-dinitrophenylhydrazone*, recrystallized twice from ethyl acetate, had m.p. 184–185°, lit.[18] m.p. 186°.

1-(3'-Chlorocrotyl)-10-methyl-trans-2-decalone (*XXVII*) *from 10-Methyl-$\Delta^{1,9}$-octalone-2*. The procedure here employed was exactly that used for the butylation of the enolate intermediate derived from the lithium–ammonia reduction of $\Delta^{1,9}$-octalone-2. From 6.25 g. (0.0381 mole) of XXIII,[9] 200 ml. of distilled ammonia, 0.802 g. (0.116 g.-atom) of lithium, and 25 g. (0.2 mole) of 1,3-dichlorobutene-2, there was obtained 3.8 g. (40%) of 1-(3'-chlorocrotyl)-10-methyl-*trans*-2-decalone (XXVII), b.p. 116–124° (0.025 mm.).

The *2,4-dinitrophenylhydrazone*, recrystallized from ethyl acetate, had m.p. 147–148.5°.

Anal. Calcd. for $C_{21}H_{27}ClN_4O_4$: C, 57.99; H, 6.26. Found: C, 58.27; H, 6.32.

2-Keto-14-methyl-$\Delta^{1,11}$-dodecahydrophenanthrene (*XXVIII*). To 2 g. (0.0078 mole) of XXVII was added 4 ml. of concentrated sulfuric acid Thorough mixing was effected by passing a stream of nitrogen through the dark mixture. After 20 hr. the viscous mass was poured onto a mixture of 20 g. of ice in 20 ml. of water and the acid neutralized with solid sodium carbonate. The organic material was extracted with ether and the ethereal solution dried and concentrated. The residue was dissolved in 5 ml. of benzene and chromatographed with acid-washed alumina. By eluting with a 10% ether–benzene solution, there was obtained 0.5 g. (31%) of XXVIII, m.p. 125–127°. The mixture melting point with an authentic sample[20] was not depressed.

2-Methyl-4-ethylenedioxycyclohexanone. A solution of 600 g. (2.5 moles) of dimethyl γ-ethylenedioxy-pimelate[31] in 1 l. of dry benzene was added with stirring to a suspension of 117 g. (4.8 moles) of sodium hydride

(31) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, 74, 1401 (1952).

(213 g. of sodium hydride dispersion) in 1 l. of benzene. The evolution of hydrogen which began 1 hr. after the addition was complete became so vigorous as to require cooling of the reaction mixture. After 24 hr., methyl iodide (825 g., 6.0 moles) was added to the heavy yellow suspension and the mixture was stirred for an additional 24 hr. The mixture was then filtered and the residue was thoroughly extracted with ether. The combined organic layers were washed with water, dried, and concentrated. There was obtained 185 g. of crude 2-carbomethoxy-2-methyl-4-ethylenedioxycyclohexanone.

The above β-keto ester (185 g.) was refluxed with 1500 ml. of a 5% potassium hydroxide solution for 36 hr. The mixture was then saturated with potassium carbonate and extracted with ether. The ethereal solution was washed with saturated sodium chloride solution, dried, and concentrated. Distillation of the residue afforded 100 g. of 2-methyl-4-ethylenedioxycyclohexanone, b.p. 70–72° (0.2 mm.). Redistillation afforded an analytical sample, b.p. 70–71° (0.2 mm.).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.96; H, 8.41.

10-Methyl-6-ethylenedioxy-Δ^{1,9}-2-octalone (XXIX). Sodium metal (0.2 g.) was added to a stirred solution of 155 g. (0.911 mole) of 2-methyl-4-ethylenedioxycyclohexanone which had previously been degassed and placed under an atmosphere of nitrogen. After the sodium had dissolved (1 hr. at 50°), 56 g. (0.412 mole) of 1-diethylaminobutanone-3 was added and the mixture slowly heated to 125° (oil bath temperature). Soon the separated diethylamine began to reflux. The temperature was maintained for 3 hr. The reaction mixture was then cooled and acidified with 28 ml. of glacial acetic acid followed by 75 ml. of ice–water. The mixture was quickly extracted with ether, and the ethereal solution was washed with 10% sodium bicarbonate solution, saturated sodium chloride, dried, and concentrated. Distillation of the residue gave 95 g. of 2-methyl-4-ethylenedioxycyclohexanone, b.p. 72–75° (0.2 mm.), and 55.4 g. (75% based on unrecovered ketone) of XXIX, b.p. 135–140° (0.3 mm.), m.p. 92–94°. An analytical sample was recrystallized from petroleum ether (b.p. 60–90°).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.43; H, 8.21.

2,7-Diketo-14-methyl-Δ^{1,11}-dodecahydrophenanthrene (XXX). The alkylation of XXIX with 1,3-dichlorobutene-2 was achieved in the usual manner. From 10.152 g. (0.051 mole) of XXIX, 400 ml. of distilled ammonia, 1.035 g. (0.15 g.-atom) of lithium, and 25 g. (0.2 mole) of 1,3-dichlorobutene-2, there was obtained 6.2 g. (50%) of dark viscous oil which was distilled through an oil-jacketed flask (bath temperature: 210°, 0.2 mm.). The compound was assumed to be the desired 7-keto-4-(3′-chlorocrotyl)-9-methyl-*trans*-decalone. Cyclization with concentrated sulfuric acid and subsequent purification was carried out as described previously. From 1.0205 g. (0.0038 mole) of the alkylation product and 2 ml. of concentrated sulfuric acid there was obtained 0.1 g. (13%) of XXX, m.p. 147–148.5°.

Conversion of XXX to 2-Keto-14-methyl-Δ$^{1(11),6}$-decahydrophenanthrene (XXXI). A solution of 50 mg. of XXX (0.00021 mole) in methanol (10 ml.) was treated with 12 mg. (0.00035 mole) of sodium boro-

hydride for 1 hr. at 0°. A few drops of acetic acid was then added and the solution was brought to dryness *in vacuo.*

The residual ketoalcohol was dissolved in 1 ml. of dry pyridine to which was added 35 mg. (0.00025 mole) of benzoyl chloride. The mixture was allowed to stand at room temperature for 18 hr. Water (2 ml.) was then added and the organic material was extracted with ether. The ethereal solution was dried and concentrated. The residue had λ 5.88, 6.0 μ.

The elimination of benzoic acid was accomplished by heating the benzoate ester, gently at first, and then more vigorously, with a free flame. The procedure was repeated three times. The residue was then dissolved in a mixture of sodium carbonate (0.5 g.), 2 ml. of water, and methanol (3 ml.), and allowed to stand overnight. Most of the solvent was then removed *in vacuo* and the organic material was extracted with ether. The ethereal solution was then dried and concentrated. The solid was dissolved in 2 ml. of benzene and chromatographed on 10 g. of acid-washed alumina. Elution with benzene afforded 6.3 mg. of material which gave on admixture with authentic XXXI[21] an undepressed m.p. 90–91°. The infrared spectrum was identical with that of an authentic sample.

5,6,7,8-Tetrahydroindanone-5 (XXXII) was prepared, by the procedure previously described,[2] from the pyrrolidine enamine of cyclopentanone and methyl vinyl ketone. The unsaturated bicyclic ketone was obtained in 40% yield, b.p. 73–75° (0.3 mm.), lit.[2] b.p. 80–81° (0.4 mm.).

Alkylation of the Reduction Enolate from XXXII. Methylation of the enolate from the reduction of XXXII with lithium in ammonia was carried out by the general procedure outlined above. The recovered material (42%) had b.p. 51–54° (0.15 mm.) and was shown to consist of *ca.* 80% *trans*-4-methyl-4,5,6,7,8,9-hexahydroindanone-5 and 20% of the corresponding *cis* isomer as determined by v.p.c. on a 5-ft. silicone column at 150°. The structure and stereochemistry of the isomeric 4-methyl compounds follow from the ratio of *cis:trans* isomers from the reduction of the parent unsaturated ketone[22] (see below) and from the identity of the peaks in the v.p.c. with the isomers formed by reduction of the 4-methyl unsaturated ketone XXXIV (see below).

Lithium–Ammonia Reduction of 5,6,7,8-Tetrahydroindanone-5. A solution of the ketone (3 g.) in ether (50 ml.) was added over 5 min. to a solution of 1 g. of lithium in 150 ml. of anhydrous liquid ammonia. After stirring for 1 hr., the blue color was discharged by addition of ammonium chloride and the mixture was worked up as usual after evaporation of the ammonia. The resulting ketones were saturated (infrared) and had b.p. 50–54° (0.2 mm.). They were shown to be a mixture of two components in ~4:1 ratio by v.p.c. (Craig polyester, 10-ft. column at 210°). Previous work[22] has shown the major component to be the *trans* isomer.

4-Methyl-5,6,7,8-tetrahydroindanone-5 (XXXIV) was prepared by a slight modification of the general method previously described, in which 1-chloropentanone-3 was used instead of the corresponding α,β-unsaturated ketone. To a solution of the pyrrolidine

enamine of cyclopentanone (0.2 mole) in 200 ml. of dry dioxane containing 20.2 g. (0.2 mole) of triethylamine was added 24 g. (0.2 mole) of 1-chloropentanone-3. After standing for 24 hr. at room temperature, the triethylamine hydrochloride which had precipitated was filtered off (23.5 g., 86%) and the filtrate was worked up in the usual manner to give 17 g. of material, b.p. 111–112° (0.8 mm.), largely uncyclized diketone, which was cyclized by keeping at room temperature for 3 hr. with a solution of 33.6 g. of potassium hydroxide in 1 l. of methanol. Work-up as usual gave 12.7 g. (42% over-all) of the desired bicyclic enone, b.p. 74–78° (0.25 mm.). The substance was homogeneous by v.p.c. and showed the expected absorption in the ultraviolet: λ_{max}^{EtOH} 245 mμ (ϵ 14,900).

Lithium–Ammonia Reduction of 4-Methyl-5,6,7,8-tetrahydroindanone-5 (XXXIV). Reduction with lithium–ammonia in the usual way gave 3.7 g. (74%) of material, b.p. 52–55° (0.2 mm.), which consisted of two components, identical with the products from the reductive methylation of XXXII. Since the ratio (3:1) was also similar, it can be concluded that the *trans* compound was the predominant one and that the presence of a 4-methyl group did not greatly alter the ratio of reduction products of the unsaturated ketone system. A 2,4-dinitrophenylhydrazone, m.p. 144–145° after crystallization from ethanol–ethyl acetate, was prepared in very good yield from the mixture, and must therefore be derived from *trans*-4-methyl-4,5,6,7,8,9-hexahydroindanone-5 (XXXIII).

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.82; H, 6.07. Found: C, 57.97; H, 6.13.

Reduction–Carbonation of 4-Methyl-5,6,7,8-tetrahydroindanone-5 (XXXIV). A solution of the unsaturated ketone XXXIV (7.8 g.) in 50 ml. of anhydrous ether was added over 5 min. to a solution of 0.78 g. of lithium in liquid ammonia (150 ml.). After 30 min., a trace of anhydrous ferric chloride was added and the solution was then stirred until disappearance of the blue color. The ammonia was then replaced by ether (200 ml.) and the mixture was heated under reflux for 15 min. to remove as much ammonia as possible. It was then cooled and poured onto a large excess of solid carbon dioxide in ether previously saturated with carbon dioxide. After it had warmed to room temperature, the mixture was neutralized by the addition of the calculated quantity of anhydrous hydrogen chloride in ether. Removal of the precipitated salts and treatment with excess diazomethane gave a solution containing the desired β-keto esters. Removal of solvent and distillation gave about 3.0 g., b.p. 84–88° (0.2 mm.). Examination of the product by v.p.c. showed three components in the approximate ratio 2:1:1. Since it is already known that the ratio of *trans* to *cis* bicyclic ketone on reduction without carbonation (see above) is largely in favor of the *trans* compound,[22] it follows that the product consisted of the two possible epimers of the *trans* series in a ratio of 3:1 to *cis*-β-keto ester.

Reduction–Methylation of 4-Methyl-5,6,7,8-tetrahydroindanone-5 (XXXIV). By the general procedure used for the reduction–alkylation of $\Delta^{1,9}$-2-octalone with lithium, a mixture of dihydro compound and methylated dihydro compound was obtained. This was separated by preparative v.p.c., and the first fraction was identified by its 2,4-dinitrophenylhydrazone,

m.p. 144–145° from ethyl acetate, as *trans*-4-methyl-4,5,6,7,8,9-hexahydroindanone-5 (XXXIII, see above). The second fraction was (largely) the anticipated *trans*-4,4-dimethyl-4,5,6,7,8,9-hexahydroindanone-5 (X-XXV); (the stereochemistry follows from the stereochemistry of the reduction process). It was isolated as its 2,4-dinitrophenylhydrazone, m.p. 150–152° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.92; H, 6.40. Found: C, 58.87; H, 6.29.

Alkylation of the Enolates from Lithium–Ammonia Reduction in Tetrahydrofuran Solution. The low yields obtained in a number of cases with the general procedure involving alkylation in the ammonia solution suggested that solubility problems might be responsible. A modified procedure was evolved which led to better yields in a number of cases. It is illustrated below for the reduction–alkylation of 1-methyl-$\Delta^{1,9}$-2-octalone.

Reduction–Methylation of 1-Methyl-$\Delta^{1,9}$-2-octalone (V, R = CH$_3$). A solution of 0.02 mole of the α,β-unsaturated ketone[2] in 50 ml. of dry tetrahydrofuran was added dropwise to a solution of 0.34 g. of lithium in 150 ml. of liquid ammonia which had been distilled from lithium. The blue solution was stirred for 10 min. after addition was complete, and the ammonia was then replaced by 150 ml. of dry tetrahydrofuran. Removal of ammonia was completed by heating under reflux and, after allowing the mixture to cool (inert atmosphere), 30 g. of methyl iodide was added and the mixture was refluxed for 1 hr. After standing at room temperature overnight, the mixture was poured into water and extracted with three 100-ml. portions of ether. The ethereal solution was washed with saturated salt solution and dried over magnesium sulfate. Distillation gave a mixture of alkylated ketones in ~80% yield, b.p. 72–77° (0.2 mm.). Analysis by v.p.c. showed that the mixture consisted of 80% of the expected 1,1-dimethyl-*trans*-decalone-2 (XXXVIII), in addition to 20% of material from further alkylation. Collection of the former by preparative v.p.c. gave material from which the 2,4-dinitrophenylhydrazone, m.p. 145–146° from ethyl acetate–ethanol, was prepared.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71. Found: C, 60.08; H, 6.61.

Reduction–Alkylation of 1,10-Dimethyl-$\Delta^{1,9}$-2-octalone (XV) with Methyl Iodide. Initial attempts to effect alkylation by direct introduction of methyl iodide in the liquid ammonia solution of the enolate from lithium reduction gave mostly the product of reduction without alkylation, 1,10-dimethyl-*trans*-decalone-2 (X-XV). Methylation by the tetrahydrofuran procedure described above for 1-methyl-$\Delta^{1,9}$-octalone-2 gave a mixture of saturated ketones, b.p. 78–84° (0.15 mm.), in ~85% yield. The mixture was shown by v.p.c. to consist of 30% of the product of reduction without alkylation, 1,10-dimethyl-*trans*-2-decalone, and 70% of the desired 1,1,10-trimethyl-*trans*-2-decalone (XX-XVI). The latter, after separation by preparative v.p.c., showed the expected three singlet methyl peaks in the n.m.r. (τ 9.0, 9.1, 9.15) and was characterized as its 2,4-dinitrophenylhydrazone, orange needles, m.p. 184–186° from ethyl acetate–ethanol (lit.[19a] m.p. 185.5–186.5°). The melting point was depressed on

admixture with the 2,4-dinitrophenylhydrazone, m.p. 184–185°, of 1,10-dimethyl-*trans*-2-decalone (*XXV*).

Reduction–Alkylation with Benzyl Chloride. Reduction and replacement of the liquid ammonia by tetrahydrofuran were carried out as described for the reduction of V, R = CH₃, using 0.7 g. of lithium for 4 g. (0.023 mole) of 1,10-dimethyl-$\Delta^{1,9}$-octalone. Alkylation with a large excess (25.3 g.) of benzyl chloride, followed by the usual work-up, gave an oil which was passed through alumina, eluted with benzene, and then submitted to v.p.c. which showed the presence of two overlapping benzylation products (presumably C-1 stereoisomers) in the ratio of 80:20. Distillation of the crude material from an oil-jacketed flask gave, after removal of lower boiling dihydro unalkylated ketone, a final fraction at ∼125° (0.15 mm.). This mixture of epimeric 1-benzyl-1,10-dimethyl-*trans*-2-decalones (*XXXVII*) had the expected n.m.r. spectrum (aromatic protons at τ 2.8 and two unsplit methyl peaks at 8.95 and 9.0. A 2,4-dinitrophenylhydrazone of the major component was prepared. It had m.p. 158–159° (from ethanol–ethyl acetate).

Anal. Calcd. for C₂₅H₃₀N₄O₄: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.70; H, 6.88; N, 12.17.

Reduction–Methylation of $\Delta^{9,10}$*-1-Octalone (XXXIX).* Reduction and replacement of the liquid ammonia by tetrahydrofuran was carried out as with V, R = CH₃, using 0.7 g. of lithium for 4 g. of ketone,[23] the other quantities, etc., being identical. Work-up as usual gave 3.4 g. of material (80–85%), b.p. 67–72° (0.25 mm.). This had a strong camphoraceous odor and was shown (infrared, v.p.c.) to contain only traces of unalkylated material. The major peak was the one first eluted after a trace of α-decalone. This was collected and showed an unsplit methyl peak at τ 8.8, thus establishing its structure as a 9-methyl-1-decalone. The 2,4-dinitrophenylhydrazone, prepared in 90% yield, established that the substance was 9-methyl-*cis*-1-decalone. It had m.p. 162–163° (after crystallization from ethyl acetate–ethanol). The reported[24] melting point of the derivative of authentic 9-methyl-*cis*-1-decalone is 164°. The melting point of the derivative of 9-methyl-*trans*-1-decalone[24] (168–169°) was strongly depressed on admixture with our 2,4-dinitrophenylhydrazone. The next fraction eluted from the v.p.c. contained both some *trans*-9-methyldecalone and some

2-methylated compound, the next peak being dimethylated material. Condensation of the total mixture with ethyl formate led to the recovery of *ca.* 28% of ketone which must therefore have had a 2-methyl group, while the ketone recovered from the hydroxymethylene derivative after heating with dilute sodium hydroxide showed a 3:1 ratio of 9-methyl-*cis*-1-decalone to the *trans* isomer. The yields thus obtained in this reduction–alkylation were 46% 9-methyl-*cis*-1-decalone, 16% 9-methyl-*trans*-1-decalone, and 23% of material having a methyl group at C-2, with and without a C-9 methyl.

Reduction–Methylation of 4-Methyltestosterone (XL). A solution of 500 mg. of 4-methyltestosterone[25] in 50 ml. of ether was added over 3 min. to a solution of 0.2 g. of lithium in 150 ml. of anhydrous liquid ammonia. The blue solution was stirred for another 2 min. before the addition of a solution of 10 g. of methyl iodide in 30 ml. of ether. The solution was stirred under reflux for 2 hr. and the ammonia was allowed to evaporate. The resulting solids were dissolved in water (150 ml.) and the mixture was acidified with 10% hydrochloric acid. The solution was extracted with benzene (three 100-ml. portions). The combined extracts were washed with dilute sodium thiosulfate and with water, and were then dried and evaporated, leaving 445 mg. of crude solid material. This was dissolved in the minimum quantity of benzene and chromatographed on 30 g. of Merck alumina (1.5 × 15 cm.). Elution with hexane, hexane–benzene, benzene, and benzene containing up to 10% ether removed 72 mg. of material and this was followed by ∼300 mg., eluted with benzene–25% ether to benzene–ether 1:1, in various fractions which melted in the range 136–142°. These showed only one spot on t.l.c., different from starting material. Recrystallization from acetone gave apparently pure 4,4-dimethyl-5α-androstan-3-one, m.p. 142–144° (lit.[25] m.p. 145–147°). The structure was confirmed by the n.m.r. spectrum (in pyridine) which showed singlets at 70 (3H) and 63 c.p.s. (3H), in addition to a singlet at 57 c.p.s. (6H). The parent 4-methyltestosterone showed 3 singlets at 57, 63, and 112 c.p.s., the last being due to the 4-methyl group.