Ring expansion of cyclic ketones: The reliable determination of migration ratios for 3-keto steroids by ^{13}C nuclear magnetic resonance and the general implications thereof[1,2]

VINOD DAVE, J. B. STOTHERS, AND E. W. WARNHOFF

Department of Chemistry, University of Western Ontario, London, Ont., Canada N6A 5B7

Received November 27, 1978

VINOD DAVE, J. B. STOTHERS, and E. W. WARNHOFF. Can. J. Chem. 57, 1557 (1979).

Several ring-expansion reactions (diazomethane, diazoacetic ester, Tiffeneau–Demjanov, Baeyer–Villiger, and Schmidt) of 3-keto steroids have been reexamined to determine the true migration ratios for C-2 and C-4 in these unsymmetrical cyclohexanones. Migration ratios were measured to $\pm 3\%$ accuracy by integration of baseline-separated signals in the proton-decoupled ^{13}Cmr spectra of total reaction products. This underexploited method provides for the first time a way to get accurate migration ratios without loss of components during separation and without interference from excess starting material under conditions minimizing side reactions. In contrast to numerous literature reports, all but one of the 16 reactions studied were found to give nearly the same amount of both possible *A*-homo products. (The single exception was the only reaction in which the *A*-homo product reacts markedly faster than the starting material.) This simple, consistent $\sim 1:1$ pattern is that expected if migration is governed mainly by the electronic effect of the α- and α′-carbon atoms and not by any conformational or near-by-to-remote substituent effect.

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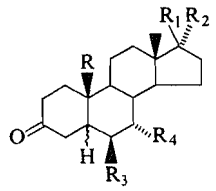
On a réétudié plusieurs réactions d'extension de cycles (diazométhane, esterdiazoacétique, Tiffeneau–Demjanov, Baeyer–Villiger et Schmidt) de céto-3 stéroïdes afin de déterminer les rapports réels de migration de C-2 et de C-4 dans ces cyclohexanones qui ne sont pas symétriques. On a mesuré ces rapports d'aptitudes à la migration avec une exactitude de $\pm 3\%$ en intégrant les signaux séparés à la base, des spectres rmn du ^{13}C découplés pour le proton, des produits totaux de réaction. Cette méthode sous-exploitée fournit pour la première fois une façon d'obtenir des rapports précis d'aptitudes à la migration sans perte de composants au cours de la séparation et sans interférence de la part du produit qui n'a pas réagi dans des conditions minimisant les réactions secondaires. Par opposition à de nombreux rapports publiés dans la littérature, on a trouvé, dans tous les 16 cas étudiés, à l'exception d'un, qu'il se forme des quantités égales des deux produits *A*-homo possibles. (La seule exception est notée dans la seule réaction dans laquelle le produit *A*-homo réagit beaucoup plus rapidement que le produit de départ). Ce résultat, $\sim 1:1$, obtenu d'une façon systématique est celui que l'on peut prévoir si la migration n'est gouvernée que par l'effet électronique des atomes de carbone α et α′ et non pas par un effet conformationnel ou d'un substituant proche ou éloigné.

[Traduit par le journal]

The ring expansion of cyclic ketones is a useful synthetic reaction, but it is frequently complicated by the problem of similar α- and α′-migratory aptitudes leading to two isomeric ring-expanded products which can be difficult to separate or analyze. This problem has been of most concern with unsymmetrical cyclohexanones, and a conspicuous example is the ring homologation of 3-keto steroids **1**. The conflicting reports (2–15) of varying product composition from this series of compounds has led to the postulation of remarkable differential migratory aptitudes and their equally remarkable rationalizations (4, 7, 13, 16). It has now become apparent, through the work of Jones and Price (15) and Levisalles *et al.* (10) on the homologation reactions, that most of the complexities are the result of analytical techniques inadequate for the task.

For example, initial reports of the formation of a majority (≥ 50–60%) of *A*-homo-4-ketone **4***a* (Scheme 1) from ring expansion of 5α-cholestan-3-one (**2***a*) by either diazomethane (CH_2N_2) (3) or by the Tif-



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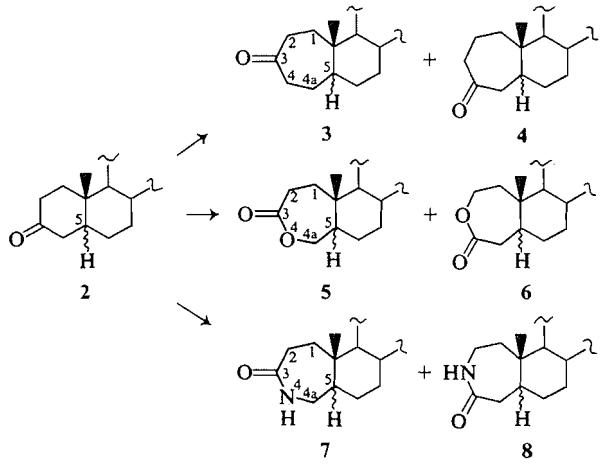
R = CH_3 or H
R_1 = OH, OAc, H, or 2-isooctyl
R_2 = OH, CH_3, or H
R_3 = OAc, H, or *p*-π
R_4 = OBz, H, or *p*-π

[1]This paper is dedicated to the memory of R. H. F. Manske.
[2]Part 86 of ^{13}C nuclear magnetic resonance studies of one of us (J.B.S.). For Part 85, see ref. 1.

0008-4042/79/131557-12$01.00/0

feneau–Demjanov method (amino alcohol diazotization) (2, 3) were based on analysis by alumina chromatography and infrared spectroscopy. Later, the additional use of ord was introduced by Jones and co-workers (4, 7) to determine the ratio of *A*-homo ketones in product mixtures from 3-keto steroids by comparison with the ord curves for the pure products. With the nearly inseparable products from 5α-cholestan-3-one, the ratio of 3-ketone **3***a* to 4-ketone **4***a* determined by this method was 21:79 ±3% (7). However, further investigation revealed that one or both of the reference samples **3***a* or **4***a* was apparently contaminated. Thus, Levisalles *et al.* (10) prepared these two ketones by methods leading unambiguously to pure specimens, and both they and Jones and Price (15) used these samples to recheck the ring-expansion ratio for **2***a* + CH_2N_2. Both groups found a new **3***a*:**4***a* ratio of 57:43 ±5% (10) ≈ 58.5:41.5 ±3% (15) in good agreement with ratios for other 3-keto steroids whose homologation products were more readily separated (see entries from ref. 7 in Table 1). The Tiffeneau–Demjanov expansion of 5α-cholestan-3-one was also checked by Levisalles *et al.* (10) who found the **3***a*:**4***a* product ratio to be 50:50 (Table 1, entry 7) comparable to the value found for CH_2N_2. In complete disagreement, Sykes and co-workers (13) reported concurrently that the 4-ketone **4***a* was the only *A*-homo ketone formed from either epimer of the amino alcohol **9**; the absence of *A*-homo-3-ketone **3***a* was judged by glpc comparison with authentic specimens of **3***a* and **4***a*. In a more recent repetition of the reaction, Jones and Price (15) have reaffirmed that both *A*-homo ketones are formed in slightly different proportions from each epimer of the amino alcohol **9** (Table 1, entries 8 and 9). It was desirable to have an independent check both on these conflicting accounts of the Tiffeneau–Demjanov reaction and on the CH_2N_2 reaction.

As can be appreciated from the foregoing, the analytical methods employed had inherent shortcomings. The use of ord requires both optical activity and the availability of both ring-expansion products in pure form; it also requires that *only* the two compounds of interest be present in the mixture to be analyzed. However, CH_2N_2 ring expansion usually produces small amounts of epoxides and polyhomologation products difficult to separate from the homo ketones. With CH_2N_2 another drawback of the chromatography–ord method of analysis is that the 3-keto starting material should be completely used up to simplify the product separation. In this way is introduced the additional complication of possible differential ring expansion of the initial *A*-homo ketones. Should the 3- and 4-ketones react



a 5α-Cholestane skeleton
b 5β-Cholestane skeleton
c 17β-Hydroxy-5α-androstane skeleton
d 6β-Acetoxy-5α-cholestane skeleton

SCHEME 1

at different rates, the final **3**:**4** ratio would not reflect the true migration ratio for the reaction of **2**. On the other hand, the use of glpc requires sufficiently different retention times for the two expansion products, a requirement not easily met for such closely similar high molecular weight compounds (15). Although the application of ^{1}Hmr spectra to the analysis of these product mixtures should be more successful, it depends on there being well-separated signals for the two isomers, and for 3-keto steroids very high magnetic fields may be needed to achieve separation (17).

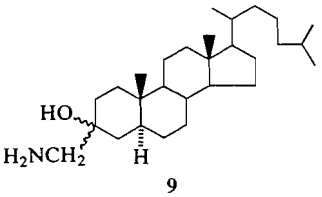
A convenient, more recently available analytical method which does overcome all of the aforementioned difficulties is integration of appropriate peaks in the proton-decoupled ^{13}Cmr spectra of product mixtures. Although for smaller molecules peak areas are not necessarily proportional to numbers of nuclei, Wehrli (18, 19) has shown that for molecules as large and rigid as **2***a*, under non-saturating conditions the nuclear Overhauser effect in proton-decoupled spectra is complete and equal for all skeletal carbon atoms (including quaternary), and therefore signal integration can be used for quantitative analysis. Moreover, unlike the ord or glpc methods, the nature of ^{13}Cmr spectra reflects the structural identity of a mixture's components. We have found, in the course of examining the ^{13}Cmr spectra of some *A*-homo steroids (1, 20), that several of the lower-field signals in the 40–60 ppm region were well separated in isomeric *A*-homo compounds and their precursor. Fortunately, integration of these separated peaks in mixtures was not only reproducible in duplicate reactions, but with test mixtures

it was found to give reliable isomer ratios accurate to $\pm 3\%$.[3] Hence, there were no complications from potentially unequal Overhauser effects (21). The absence of interfering absorptions from starting material meant that it was now possible to perform the CH_2N_2 ring expansions with a large excess of starting material remaining in order to minimize the likelihood of further reaction of initially formed *A*-homo ketones, a bothersome problem in some instances. Furthermore, if any side products such as epoxides and bishomo ketones should be formed to any significant ($\geq 5\%$) extent, they would be readily detected by extra peaks in the low-field end (40–70 ppm) of the ^{13}Cmr spectrum, but they would not cause any difficulties with integration of carefully selected signals. The extent of mono- and polyhomologation could be estimated from the mass spectrum of the reaction product.[4] The advantages of the method were well demonstrated in examining the reactions of 3-keto steroids.

The first compound studied was 5α-cholestan-3-one (**2***a*) whose ^{13}Cmr spectrum has a region devoid of signals between 46 and 54 ppm (22). Authentic samples of **4***a* and **3***a* prepared by known methods (10, 23) (see Experimental) were used for ^{13}C peak assignments (1). Each of the *A*-homo ketones absorbed in the region free of **2***a* absorption, **3***a* at 50.6 (C-5) and 53.3 ppm (C-9), and **4***a* at 47.9 (C-4a) and 54.1 ppm (C-9). The accuracy of integration of these peaks was verified with three known mixtures of **3***a* and **4***a* (see Experimental). Limited ring expansion of the 3-ketone **2***a* with CH_2N_2 by both the *in situ* and *ex situ* procedures (see Experimental) gave a product containing 20–28% of *A*-homo ketones. Integration of the ^{13}C signal at 53.3 ppm relative to that at 54.1 ppm and of the peak at 47.9 ppm relative to that at 50.6 ppm gave the same **3***a*:**4***a* ratio of 58:42 $\pm 3\%$ (Table 1, entries 1, 2, and 5) in excellent agreement with the ord derived value of Levisalles *et al.* (10) and Jones and Price (15) (Table 1, entries 3 and 4), which therefore did represent the true kinetic migration ratio in spite of consumption of most of the starting ketone **2***a* in their reactions.

To test whether the initial *A*-homo ketones would show selectivity in the event of their reaction, a synthetic 50:50 mixture of **3***a* + **4***a* was treated to the extent of 15% reaction with CH_2N_2 generated *in situ*. ^{13}Cmr examination of the remaining *A*-homo ketones gave an altered **3***a*:**4***a* ratio of 57:43 $\pm 3\%$, and consequently the 4-ketone is more reactive. The probable reason that this selectivity was not reflected in Levisalles's and Jones's ratios is that the reaction of CH_2N_2 with both **3***a* and **4***a* is slower than with **2***a*, and any excess CH_2N_2 may have been used up in polymerization.[5]

As independent confirmation that the Tiffeneau–Demjanov expansion of 5α-cholestan-3-one does indeed give both *A*-homo ketones, this reaction too was reexamined. Diazotization of a 30% α – 70% β mixture of hydroxyl epimers of amino alcohol **9** gave a product whose ^{13}Cmr spectrum revealed the presence of both **3***a* and **4***a* in the ratio of 43:57 (Table 1, entry 6) in reasonable agreement with the ord-derived values of Levisalles *et al.* (10) and Jones and Price (15) (Table 1, entries 7, 8, and 9). Apparently, as pointed out by Jones and Price (15), the very close glpc retention times for **3***a* and **4***a* used by Sykes and co-workers (13) did not permit resolution of mixtures of the two isomers.



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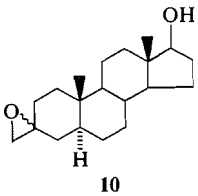

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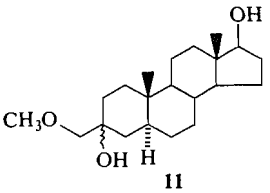

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The next migration ratio determined was for a reported (7, 9, 15) ring expansion giving products more easily separated by chromatography, and for which the migration ratio determined by a combination of separation and ord should therefore be accurate provided that no by-products contaminated the ord samples. Ring expansion of an excess of 17β-hydroxy-5α-androstan-3-one (**2***c*) afforded a product containing 35–43% of *A*-homo ketones. The ^{13}C peaks were assigned (1) with the aid of authentic specimens of both products (7) separated by chromatography from a reaction in which all starting material had been consumed. In the spectrum of the mixture, the best separated peaks for integration were the signals at δ 27.8 in homo ketone **3***c* and at δ 18.9 in **4***c*. Values of the **3***c*:**4***c* ratio of 56:44 and

[3]The accuracy is probably better than that (± 3–5%) estimated for the ord method (7, 10). Note also that integration of two or more peaks for each component provides an internal check.

[4]The extra CH_2 group or two would have a negligible effect on the vapour pressure of these large molecules.

[5]Note that the selectivity found (**4***a* reacts faster than **3***a*) is in the wrong sense to account for the originally reported **3***a*:**4***a* ratio of 21:79 (7) by further preferential reaction of initial *A*-homo products.

TABLE 1. Migration ratios for ring expansions of 3-keto steroids

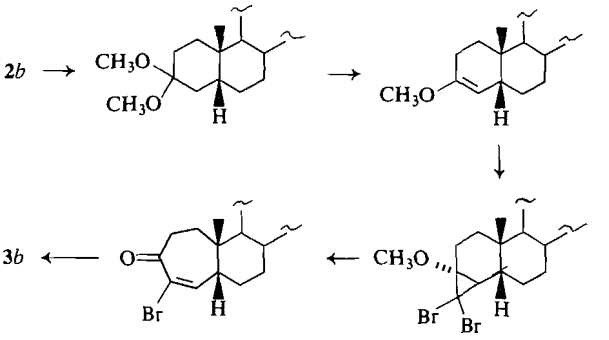
Entry	Starting material	Reaction	3 C=O : 4 C=O ratio[a]	Analytical method	Ref.
1	5α-Cholestan-3-one (*2a*)	CH_2N_2 NMU[b] *in situ*	**58:42**	^{13}Cmr	[a]
2	5α-Cholestan-3-one (*2a*)	CH_2N_2 NMU[b] *ex situ*	**59:41**	^{13}Cmr	[a]
3	5α-Cholestan-3-one (*2a*)	CH_2N_2 NMU[b] *in situ*	57:43	ord	10
4	5α-Cholestan-3-one (*2a*)	CH_2N_2 NMU[b] *in situ*	58.5:41.5	ord	15
5	5α-Cholestan-3-one (*2a*)	CH_2N_2 Diazald[c] *in situ*	**58:42**	^{13}Cmr	[a]
6	5α-Cholestan-3-one (*2a*)	Tiffeneau–Demjanov 30%α-OH, 70%β-OH	**43:57**	^{13}Cmr	[a]
7	5α-Cholestan-3-one (*2a*)	Tiffeneau–Demjanov	50:50	ord	10
8	5α-Cholestan-3-one (*2a*)	Tiffeneau–Demjanov β-OH, α-CH_2NH_2	48:52	ord	15
9	5α-Cholestan-3-one (*2a*)	Tiffeneau–Demjanov α-OH, β-CH_2NH_2	63:37	ord	15
10	5α-Cholestan-3-one (*2a*)	DAE[f] and —COOEt	**46:54**	^{13}Cmr	[a]
11	5α-Cholestan-3-one (*2a*)	*m*-CPBA[d] Baeyer–Villiger	**55:45**	^{13}Cmr	[a]
12	5α-Cholestan-3-one (*2a*)	CF_3CO_3H Baeyer–Villiger	**58:42**	^{13}Cmr	[a]
13	5α-Cholestan-3-one (*2a*)	PPA[e] Schmidt	**50:50**	^{13}Cmr	[a]
14	17β-Hydroxy-5α-androstan-3-one (*2c*)	CH_2N_2 NMU[b] *in situ*	**56:44**	^{13}Cmr	[a]
15	17β-Hydroxy-5α-androstan-3-one (*2c*)	CH_2N_2 NMU[b] *in situ*	59:41	ord	7, 15
16	17β-Hydroxy-5α-androstan-3-one (*2c*)	Tiffeneau–Demjanov 3β-OH, 3α-CH_2NH_2	49.5:50.5	ord	15
17	17β-Hydroxy-5α-androstan-3-one (*2c*)	Tiffeneau–Demjanov 3α-OH, 3β-CH_2NH_2	61.5:38.5	ord	15
18	17β-Hydroxy-5α-androstan-3-one (*2c*)	*m*-CPBA[d] Baeyer–Villiger	**58:42**	^{13}Cmr	[a]
19	5β-Cholestan-3-one (*2b*)	CH_2N_2 NMU[b] *in situ*	**52:48**	^{13}Cmr	[a]
20	5β-Cholestan-3-one (*2b*)	DAE[f] and —COOEt	**47:53**	^{13}Cmr	[a]
21	5β-Cholestan-3-one (*2b*)	*m*-CPBA[d] Baeyer–Villiger	**58:42**	^{13}Cmr	[a]
22	5β-Cholestan-3-one (*2b*)	PPA[e] Schmidt	**51:49**	^{13}Cmr	[a]
23	17α-Hydroxy-5α-androstan-3-one	CH_2N_2 NMU[b] *in situ*	55:45	ord	7
24	5α-Androstan-3-one	CH_2N_2 NMU[b] *in situ*	58:42	ord	7
25	17β-Acetoxy-5α-androstan-3-one	CH_2N_2 NMU[b] *in situ*	55:45	ord	7
26	17β-Hydroxy-17α-methyl-5α-androstan-3-one	CH_2N_2 NMU[b] *in situ*	62:38	ord	7
27	17β-Hydroxy-5α-estran-3-one	CH_2N_2 NMU[b] *in situ*	60:40	ord	7
28	17β-Acetoxy-5α-estran-3-one	CH_2N_2 NMU[b] *in situ*	55:45	ord	7
29	17β-Hydroxy-5β-androstan-3-one	CH_2N_2 NMU[b] *in situ*	50:50	ord	7
30	17β-Hydroxy-5β-estran-3-one	CH_2N_2 NMU[b] *in situ*	61:39	ord	7
31	7α-Benzoyloxy-5α-cholestan-3-one	CH_2N_2 Diazald[c] *in situ*	60:40	ord	14
32	5α-Cholest-6-en-3-one	CH_2N_2 NMT[i] *ex situ*	60:40	^{1}Hmr	17
33	6β-Acetoxy-5α-cholestan-3-one	CH_2N_2 NMU[b] *ex situ*	**50:50**	^{13}Cmr	[a]
34	*B*-Nor-5β-cholestan-3-one	CH_2N_2 NMU[b] *in situ*	(*70:30*)[h]	^{13}Cmr	[a]
35	*B*-Nor-5β-cholestan-3-one	DAE[f] and —COOEt	**42:58**	^{13}Cmr	20
36	*trans*-2-Decalone	CH_2N_2 NMU[b] *in situ*	56:44	glpc	24
37	*trans*-2-Decalone	Tiffeneau–Demjanov 3β-OH, 3α-CH_2NH_2	50:50	glpc	24
38	*trans*-2-Decalone	Tiffeneau–Demjanov 3α-OH, 3β-CH_2NH_2	61:39	glpc	24

[a]Present work.
[b]*N*-Nitroso-*N*-methylurea.
[c]*N*-Nitroso-*N*-methyl-*p*-toluenesulfonamide.
[d]*m*-Chloroperbenzoic acid.
[e]Polyphosphoric acid.
[f]Ethyl diazoacetate.
[g]Numbers in boldface are from present work. For the ratios determined by ^{13}Cmr and ord the error limits are ±3%. See also footnote 3 and the ^{13}Cmr part of the Experimental.
[h]Not reliable because one or both products reacts faster than starting material.
[i]*N*-Nitroso-*N*-methylterephthalamide.

57:43 were obtained in this way from two reactions. Four lower-field signals at δ 47.8, 50.5, 53.4, and 54.2 were not sufficiently separated from starting material peaks for confident integration unless most of the **2***c* had been consumed. Therefore, a homologation carried to >90% consumption of **2***c* was chromatographed to separate the *A*-homo ketone mixture which was integrated over all six peaks to give a **3***c*:**4***c* ratio of 55:45, identical with the two-peak integration ratio within experimental error. The validity of the integrations was also checked with a known mixture. The **3***c*:**4***c* migration ratio of 56:44 (Table 1, entry 14) obtained by averaging the above results agrees within experimental error with the earlier reported value of 59:41 (7, 15).

For 5β-cholestan-3-one, the only reported (7) value of 78:22 (ord derived) for the **3***b*:**4***b* ring-expansion ratio was suspect because the almost 4:1 preference for C-4 migration deviated from the negligible preference now established for other 3-keto steroids. Accordingly, the reaction was re-examined. The ^{13}C absorption-free region was slightly shifted to 44–56 ppm for **2***b* (22). Limited ring expansion by the *in situ* method gave a product with 39–53% of starting material remaining.[6] Its ^{13}C signals were assigned by comparison with those of starting ketone **2***b* and of an authentic specimen of *A*-homo-5β-cholestan-3-one (**3***b*) prepared as shown in Scheme 2 (also see Experimental). The true **3***b*:**4***b* product ratio found by integration of baseline separated peaks at 46.6 ppm (C-5 of **3***b*) and 45.9 ppm (C-5 of **4***b*) was 52:48 in good agreement with the values of other 3-ketones.

There are two other reports in the literature which are at variance with the present findings. In ref. 6, only the *A*-homo 4-ketone[7] was isolated from the reaction of *B*-nor-5β-cholestan-3-one with CH_2N_2. Actually, both *A*-homo ketones were undoubtedly formed since the Tiffeneau–Demjanov expansion of the same *B*-nor ketone gave both *A*-homo-3- and -4-ketones (14), and since diazoacetic ester expansion gave a 42:58 ratio of *A*-homo-3- to -4-ketone after decarbethoxylation (20). Repetition of the reaction with CH_2N_2 to a limited extent gave a product containing 83.4% of unreacted *B*-nor ketone, 11.2% of *A*-homo ketone mixture, and surprisingly 5.3% of



SCHEME 2

bis-*A*-homo ketones. Therefore, one or both of the *A*-homo ketones reacts considerably faster with CH_2N_2 than does the starting material. Consequently, the *A*-homo-3- to -4-ketone ratio found of ~70:30[7] probably does not represent the true migration ratio which should be closer to the 42:58 figure from the diazoacetic ester reaction (Table 1, entry 35).

The second anomalous case is that of 6β-acetoxy-5α-cholestan-3-one (**2***d*) from whose reaction with a large excess of CH_2N_2 + $AlCl_3$ only bis- and tris-homo products were isolated (12). However, from reaction with a limited amount of CH_2N_2 such that 69% of starting material remained, we find that both *A*-homo ketones are formed in a ratio not experimentally different from 50:50 by comparison of the integral of the ^{13}C signal at δ 75.3, which contains the absorption from C-6 of both *A*-homo ketones, with peaks at δ 30.0, 30.5, 51.9, and 53.0, each of which arises from only one of the *A*-homo ketones.

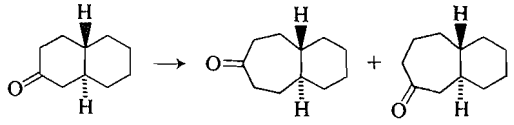
Therefore, for all of the 15 steroids whose ring homologation has been studied with care (see Table 1) there is either no preference or else a negligible preference for migration of C-4 over C-2, and the **3**:**4** ratio does not exceed 6:4 (or *vice versa*) in any case.[8] This is as would be expected in consideration of both C-2 and C-4 being secondary and there being no conformational migratory preference discernible from Dreiding models. It should also be noted that the C-19 methyl group and the steroid C- and substituted D-ring do not play a detectable role in determining the migration ratio since CH_2N_2 ring expansion of *trans*-2-decalone (**12**), a bicyclic model for 5α-3-keto steroids, also gave the same value of 56:44 for the **13**:**14** ratio (24). Likewise, the Tiffeneau–Demjanov rearrangement of each of the

[6]If ring expansion of the 5β-ketone **2***b* is carried to near completion, a much more complex mixture of products is apparent from the ^{13}Cmr spectrum than is the case with the 5α-ketone **2***a* under similar conditions.

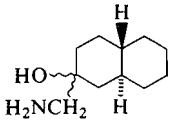
[7]It is not clear which ketone isomer is meant in ref. 6; the structural formula is that of the *A*-homo-3-ketone but the name given in the Experimental is for the *A*-homo-4-ketone. Since excess CH_2N_2 was used and since the $[\alpha]_D$ was +21°, the product was probably the *A*-homo-3-ketone (20) in view of the present findings, even though its melting point was low.

[8]Strictly speaking, the homologations of the compounds listed in entries 23–31 of Table 1 should also be reexamined by the ^{13}Cmr method but the 1:1 pattern from all five different reactions examined by this technique in the present work now leaves no real doubt that the earlier ord results for these compounds (7) are substantially correct.

epimeric bicyclic amino alcohols **15** gave the same ratios as did the Tiffeneau-Demjanov rearrangement of the corresponding amino alcohols from 5α-cholestan-3-one and 17β-hydroxy-5α-androstan-3-one (compare entries 8, 9, 16, and 17 with 37 and 38 in Table 1).



12 **13** **14**

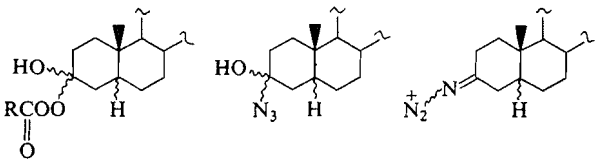


15

The consistency of the results emerging from these experiments prompted the scrutiny of related ring expansion reactions to see how widely the generalization held.

Homologation of ketones with diazoacetic ester (DAE) has become a useful alternative to the use of CH_2N_2 (25, 26). When both 5α- and 5β-cholestan-3-one were partially homologated with DAE–$Et_3O^+BF_4^-$ and decarbethoxylated,[9] the ratios of *A*-homo products were the same for both (Table 1, entries 10 and 20) and were changed slightly in favor of more 4-ketone relative to the CH_2N_2 reactions, but for all practical purposes the change is negligible.

The ring expansion of ketones to lactones by migration to oxygen in the Baeyer–Villiger reaction involves an intermediate **16** that is of the same type as in the diazoalkane reaction, and the simplest view would lead one to expect the same migration ratio for both reactions. Unfortunately, the Baeyer–Villiger cleavage of 3-keto steroids has been beset by the same difficulties found with the CH_2N_2 reactions. Most investigators report only the isolation of the 3-oxolactone **5** in yields as high as 76% (27–35) from peracid oxidation, but on reinvestigation some of these reactions have been shown to produce both lactones **5** and **6** (36). In other cases both lactones were found initially (37, 38). However, no accurate values for product ratios have been reported. Therefore, we have carried out the cleavage by *m*-chloroperbenzoic acid – $CHCl_3$ of 5α- and 5β-cholestan-3-one as well as 17β-hydroxy-5α-androstan-3-one. In each case both lactones were formed in a nearly 1:1 ratio. The different location of the introduced oxygen atom in the two lactones made unambiguous the assignment by chemical shift of the lowest-field sp^3-^{13}C signals in the ^{13}Cmr spectrum without the necessity of authentic samples of the lactones. For example, the lowest field sp^3-^{13}C peak in the spectrum of the 5α-cholestan-3-one product at 70.0 ppm can only be C-4a (O—CH_2—CH) of lactone **5***a*, while the next lowest sp^3-^{13}C peak at 64.7 ppm must be C-2 (O—CH_2—CH_2) of lactone **6***a* (39). These assignments were confirmed for the **2***a* reaction by preparation of pure lactone **5***a* (40) as described in the Experimental. Integration of the spectrum of the lactone mixture gave a **5***a*:**6***a* migration ratio of 55:45 (Table 1, entry 11), very nearly the same as the CH_2N_2 migration ratio with this ketone (Table 1, entries 1–5). The product ratios for the lactones from **2***b* and **2***c* (Table 1, entries 18 and 21) were likewise as easily determined[10] and were close to those for the corresponding CH_2N_2 reactions.



16 **17** **18**

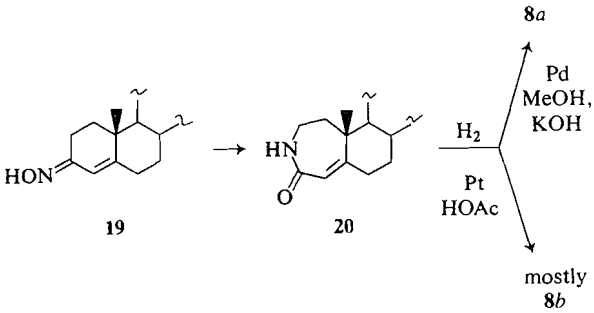
Because different peracid oxidation conditions have been known to influence the proportion of cleavage products from some ketones, the oxidation of **2***a* was also done with CF_3CO_3H–$CHCl_3$, a much stronger peracid. Contrary to a previous report for this reagent (34), the migration ratio (Table 1, entry 12) was found to be essentially the same as for the *m*-chloroperbenzoic acid – $CHCl_3$ cleavage.

Finally, ring expansion to nitrogen was examined by means of the Schmidt reaction. The mechanistic evidence (41, 42) allows for the reaction to proceed to amide through either the tetrahedral intermediate **17**, analogous to those of the already mentioned ring expansion reactions, or else through *anti* rearrangement of the geometrical isomers of the diazoimonium ion **18**. Since the proportion of *syn* and *anti* isomers is determined by steric factors, and since the steric situation is the same for both isomers with these 3-keto steroids, either mechanism would be expected to lead to an approximately 1:1 ratio of products **7** and **8**. However, the Schmidt reaction with both 5α- and 5β-cholestan-3-one has been

[9]The crude β-keto esters were decarbethoxylated with water in sealed tubes at 150°C (26). Under these conditions the ketonic components underwent condensation reactions to some extent. Possibly these side reactions were acid catalyzed (by traces of boron compounds remaining?) because they were minimized by the addition of a small amount of $NaHCO_3$ to the water (see Experimental).

[10]With the 17β-hydroxy compound **2***c* care had to be taken to avoid an excess of peracid which oxidized the 17β-OH to a carbonyl group.

reported by Doorenbos and Wu (43) to yield only isomer **8**. Repetition of the reaction of the 5α- and 5β-ketones **2***a* and **2***b* according to their procedure gave products each of whose ^{13}Cmr spectra clearly showed the presence of both lactams **7** and **8** in similar amount. The assignment of ^{13}C peaks in each lactam mixture was made with the aid of spectra of pure **8***a* and **8***b* prepared as described below.



Beckmann rearrangement of the mixture of cholest-4-en-3-one oximes **19** at room temperature with $SOCl_2$ in dioxane results only in migration of the sp^3 C-2 to produce the unsaturated lactam **20** (44, 45). Hydrogenation over Pd/C in methanol–KOH gave the 5α-lactam **8***a* (44) whose *trans* A/B fusion was verified by its ^{13}C-19 methyl signal at 12.0 ppm (46). Hydrogenation of **20** over Pt in HOAc gave mostly the 5β-lactam **8***b* which was purified by thick-layer chromatography; the *cis* A/B fusion was confirmed by its ^{13}C-19 methyl peak at 23.3 ppm (46). With the ^{13}C signals identified in the Schmidt reaction mixtures, the 1:1 ratios given in entries 13 and 22 of Table 1 were calculated.[11]

In conclusion, we see that the supposedly widely differing results of various 3-keto steroid ring-expansion reactions actually fit a consistent pattern. Thus, for 16 of these similar unsymmetrical cyclohexanones (including 2-decalone) and five different reactions, ring expansion to C, N, and O gives a migration ratio of ~1:1. This simple outcome is to be expected if migration in all of these reactions is governed *mainly* by the electronic effect of the α- and α′-methylene groups and not by any conformational or long range effects. As a corollary, in each of the many cases in which the lactones and lactams from Baeyer–Villiger or Schmidt or even Beckmann reactions on 3-keto steroids have been prepared or used (on the assumption that pure compounds were involved) in structure assignments to other compounds or as starting materials for synthesis (*inter alia* 32, 34, 40, 47, 48), the conclusion or purity of product is dubious, and this implication of the present work will be considered in a subsequent paper.

[11]Although the ratios turned out to be exactly 50:50, assignment of signals to individual lactams gave assurance that the integrated peaks were not all from a single lactam.

Experimental

General

Reagents, instruments, and procedures are the same as in ref. 20 except for the following. Camag DSF-O silica gel was used for some tlc plates. Some ir spectra were recorded on a Perkin Elmer model 621 instrument. The samples of **2***a*, **2***b*, **2***c*, and **2***d* used were shown to be pure by ^{13}Cmr spectroscopy. Complete ^{13}Cmr assignments for the steroids in this work are given in ref. 1. The mass spectra for quantitative analysis of product mixtures were run at 25 eV to minimize fragmentation and maximize molecular ions. The figures in parentheses after the ion masses are the percentages of starting material and homo and bishomo products calculated from the ion intensities and estimated to be accurate to ±3%.

^{13}C Nuclear Magnetic Resonance Spectra

Spectra were obtained at 25.2 MHz with a Varian XL-100-15 system operating in the Fourier transform mode with square-wave modulated proton decoupling. Solutions were usually ~0.25 *M* in $CDCl_3$ and in no case exceeded 1.25 *M*; TMS was used as an internal reference. Wehrli has shown (18) that all carbons of the steroid ring system exhibit maximum and equal nOe's under appropriate operating conditions. With 2 or 2.5 kHz sweep widths, flip angles ≤45°, and pulse acquisition times of 0.8–1.0 s, our conditions insured that the protonated skeletal carbons gave full nOe's although the quaternary carbons were probably partially saturated. To achieve suitable signal-to-noise levels the number of scans varied from 10–50 K and 8 K transforms were used. Integrations were done both by the usual electronic means and by comparing the products of peak height × peak width at half-height for the best-separated signals in expanded traces of the region of interest. If peak separation permitted, two or more signals per component were integrated, and the results were averaged to obtain the reported composition data. Integrals were found to be reproducible to ±2% and, from control experiments, the composition of known mixtures of **3***a* and **4***a* was found to a precision of ±2%; in these controls the following signal areas were measured: **3***a*, 50.6 (C-5) and 53.3 ppm (C-9); **4***a*, 47.9 (C-4a) and 54.1 ppm (C-9). This led to the following results.

Mixture (mg)		3a		
3a	4a	By weight %	By integration	Average
12.0	36.0	25	26, 25, 27, 26	26
24.0	24.0	50	49, 49, 50, 49	49
36.0	12.0	75	76, 74, 76, 75, 74	75

On this basis, the compositions of the product mixtures are judged by the 4d rule to have precisions of 3%. Whenever possible, the crude mixtures of ring expansion products were not chromatographed before ^{13}Cmr spectroscopy to avoid any possibly unequal irreversible adsorption. Each CH_2N_2 and DAE ring expansion was done at least in duplicate, but only one experiment per ring expansion is described in the sequel.

General Procedure for In Situ *CH_2N_2 Reactions*

To a stirred (magnetic bar) solution of 100 mg of steroid, 30 mg of powdered KOH, 1 mL of MeOH, and 2 mL of ether at 0–5°C was added a known amount of CH_2N_2 precursor. When less than 100 mg was used, the amounts of MeOH and ether were reduced proportionately. Throughout the reaction

solid was present, initially the partially soluble CH_2N_2 precursor and later presumably potassium salts. After the two-phase mixture had been stirred at 5–8°C for 6 h, the solvents were evaporated in a stream of N_2. Water and 10% aqueous HCl were added, and the product was extracted with ether. The organic layer was washed with water, dried, and evaporated to leave the crude product which was examined by ^{13}Cmr and mass spectroscopy. The amount of CH_2N_2 precursor required to achieve partial homologation varied because of the limited solubility of the CH_2N_2 precursor and the competing polymerization side reaction of CH_2N_2. For the same reasons, a given level of homologation was difficult to reproduce in duplicate reactions.

(a) 5α-Cholestan-3-one + N-Methyl-N-nitrosourea (NMU)

From 100 mg (0.26 mmol) of **2***a* and 15 mg (0.15 mmol) of NMU was obtained 92 mg of colorless solid product, *m/e* 386 (72% of **2***a*) and 400 (28% of **2***a* + CH_2) with no detectable bis homologation at 414. ^{13}C peaks integrated: δ 47.9 (C-4a of **4***a*), 50.6 (C-5 of **3***a*), 53.3 (C-9 of **3***a*), and 54.1 ppm (C-9 of **4***a*) (Table 1, entry 1).

(b) 5α-Cholestan-3-one + Diazald

From 100 mg (0.26 mmol) of **2***a* and 94 mg (0.44 mmol) of Diazald was obtained 88 mg of colorless solid, *m/e* 386 (20.5% of **2***a*), 400 (78.7% of **2***a* + CH_2), and 414 (0.7% of **2***a* + 2 CH_2). ^{13}C peaks integrated: same as in (*a*) (Table 1, entry 5).

(c) A-Homo-5α-cholestan-3- and -4-ones (1:1) + NMU

From 20 mg (0.05 mmol) of **3***a* plus 20 mg (0.05 mmol) of **4***a* and 21 mg (0.20 mmol) of NMU was obtained 40 mg of colorless solid, *m/e* 400 (84% of **3***a* + **4***a*) and 414 (16% of **3***a* and **4***a* + CH_2) with no detectable amount of bis homologation product. ^{13}C peaks integrated: same as in (*a*); **3***a*:**4***a* ratio, 57:43 ± 3%.

(d) 5β-Cholestan-3-one + NMU

From 50 mg (0.13 mmol) of **2***b* and 15 mg (0.15 mmol) of NMU was obtained 47 mg of colorless solid, *m/e* 386 (53% of **2***b*), 382 and 400 (47% of **2***b* + CH_2 and its $M^+ - 18$ ion) with less than 0.5% of bis homologation. ^{13}C peaks integrated: δ 45.9 (C-5 of **4***b*) and 46.6 ppm (C-5 of **3***b*) (Table 1, entry 19).

(e) 17β-Hydroxy-5α-androstan-3-one + NMU

From 50 mg (0.17 mmol) of **2***c* and 12 mg (0.12 mmol) of NMU was obtained 44 mg of colorless solid, *m/e* 290 (65% of **2***c*) and 304 (35% of **2***c* + CH_2) with no more than 0.2% of bis homologation. ^{13}C peaks integrated (see Discussion): δ 18.9 (C-2 of **4***c*), 27.8 (C-4a of **3***c*), 47.8 (C-4a of **4***c*), 50.5 (C-5 of **3***c*), 53.4 (C-9 of **3***c*), and 54.2 ppm (C-9 of **4***c*). Duplicate reactions gave **3***c*:**4***c* ratios of 56:44 and 55:45 (Table 1, entry 14).

A synthetic mixture of 17.0 mg of **3***c* and 13.0 mg of **4***c* (ratio 56.6:43.4) was analyzed by integration of the same set of signals, and it gave a **3***c*:**4***c* ratio of 56:44.

(f) B-Nor-5β-cholestan-3-one + NMU

From 48 mg (0.13 mmol) of *B*-nor-5β-cholestan-3-one and 13 mg (0.13 mmol) of NMU was obtained 48 mg of colorless noncrystalline product, *m/e* 372 (83.4% starting material), 386 (11.2% of monohomo product), and 400 (5.3% of bishomo product). ^{13}C peaksi ntegrated: δ 47.8 (C-4a of the *A*-homo-4-ketone) and 50.0 ppm (C-5 of the *A*-homo-3-ketone) (Table 1, entry 34).

Ex Situ *Diazomethane Reactions*

(a) 5α-Cholestan-3-one

A solution of 100 mg of **2***a* in 1.5 mL of ether, 1.5 mL of MeOH, and 0.1 mL of water was treated with excess distilled ethereal CH_2N_2 at 5–8°C for 2 days. After evaporation of solvent, the residue was dissolved in ether, washed with water, dried, and concentrated to give 90 mg of colorless solid, *m/e* 400 (93% of **2***a* + CH_2) and 414 (7% of **2***a* + 2 CH_2) with no **2***a* remaining. ^{13}C peaks integrated: same as in (*a*) of the *in situ* reactions (Table 1, entry 2).

(b) 6β-Acetoxy-5α-cholestan-3-one

To a solution of 44 mg (0.10 mmol) of 6β-acetoxy-5α-cholestan-3-one in 0.75 mL of ether plus 0.75 mL of MeOH was added 0.3 mL of 0.33 *N* CH_2N_2 in ether and 1 drop of water. After 2 days at 5–8°C, solvent was evaporated to leave 44 mg of solid which gave two tlc spots. Since the ^{13}Cmr spectrum of the crude product was not suitable for integration, it was chromatographed on a 10-g preparative plate developed (2×) in benzene–ether (90:10). Extraction of the band at R_f 0.54 gave 32 mg of the major, more polar material, *m/e* 444 (79% of starting material) and 458 (21% of starting material + CH_2) with no detectable amount of bis homologation product. ^{13}C peaks integrated [relative peak area] δ: 30.0[177], 30.5[177], 51.9[163], 53.0[165], and 75.3 ppm [350] (Table 1, entry 33).

Preparative Reaction with 17β-Hydroxy-5α-androstan-3-one (2c)

To a stirred (magnetic bar) solution of 200 mg of **2***c* (Sigma Chemical Co.), 980 mg of powdered KOH, 3 mL of ether, and 3 mL of MeOH at 0–5°C was added 750 mg of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide during 10 min; the two-phase mixture was then stirred at 5°C for 6 h. After evaporation of most of the solvent in a stream of nitrogen, the residue was dissolved in ether, washed with water, dried, and concentrated to leave 186 mg of oily solid which was chromatographed on four preparative plates developed (3×) with benzene–ether (50:50).

Extraction of the band at R_f 0.76 gave 12 mg of a colorless oily mixture of oxides, probably **10**, ir: no C=O absorption. M^+ calcd. for $C_{20}H_{32}O_2$: 304.2402; found: 304.2405.

Extraction of the band at R_f 0.73 gave 25 mg of colorless solid. Recrystallization (2×) from EtOAc gave 8 mg of 17β-hydroxy-*A*-homo-5α-androstan-4-one (**4***c*), mp 196–199°C (lit. (7) mp 193.5–194.5°C); ^{1}Hmr ($CDCl_3$) δ: 0.74 (3H, s, CH_3), 0.88 (3H, s, CH_3), 2.41 (2H, m, band w = 16 Hz, ketone α-CH_2), 2.82 (1H, dd, J_{AX+BX} = 25 Hz, ketone α-H), and 3.64 ppm (1H, bt, J_{AX+BX} = 18 Hz, C*H*OH).

Extraction of the band at R_f 0.67 gave 44 mg of colorless solid. Recrystallization from MeOH (1×) and from EtOAc (1×) gave 13 mg of colorless plates of 17β-hydroxy-*A*-homo-5α-androstan-3-one (**3***c*), mp 207–210°C (lit. (4) mp 212–213°C). M^+ calcd. for $C_{20}H_{32}O_2$: 304.2402; found: 304.2404.

Extraction of the most polar band at R_f 0.52 gave 17 mg of colorless solid, *m/e* 336 (M^+) and 291 ($M - CH_3OCH_2$); ir ($CHCl_3$): 3700–3300 cm^{-1} (broad OH) and no C=O absorption; ^{1}Hmr ($CDCl_3$) δ: 0.73 (3H, s, CH_3), 0.76 (3H, s, CH_3), 3.18 (2H, s, —OCH_2—), 3.39 (3H, s, OCH_3), and 3.64 ppm (1H, bt, J_{AX+BX} = 18 Hz, C*H*OH). M^+ calcd. for $C_{21}H_{36}O_3$: 336.2664; found: 336.2665. The ^{13}Cmr spectrum was in agreement with structure **11**. The compound did not react with $NaIO_4$ or $Pb(OAc)_4$.

Tiffeneau–Demjanov Expansion of 5α-Cholestan-3-one

A mixture of epimeric amino alcohols **9** was made from **2***a* by the method of ref. 13 without purification of intermediates. Integration of the —CH_2N protons at δ 2.75 for the 3β-OH epimer and δ 2.55 for the 3α-OH epimer gave 70% β-OH and 30% α-OH. To a stirred (magnetic bar) solution of 110 mg (0.26 mmol) of the amino alcohol mixture in 2 mL of HOAc and 2 mL of ether at 0–5°C was added a solution of 400 mg (5.8 mmol) of $NaNO_2$ in 1 mL of water during 10 min. The reaction mixture was stirred at ~8°C for 1 h and at room temperature for 17 h. After dilution with water and extraction with ether, the organic layer was washed with water and 5%

aqueous $NaHCO_3$. Evaporation of the dried organic solution left 90 mg (86%) of oily solid, ir ($CHCl_3$): 1695 cm^{-1} (C=O); *m/e* 400 (M^+). ^{13}C peaks integrated: same as in (*a*) of the *in situ* CH_2N_2 reactions (Table 1, entry 6).

Diazoacetic Ester Reactions

*(a) 5α-Cholestan-3-one (***2a***)*

To a stirred (magnetic bar) solution of 100 mg (0.26 mmol) of **2***a* and 99 mg (0.52 mmol) of $Et_3O^+BF_4^-$ in 1 mL of CH_2Cl_2 at 0–5°C was added a solution of 59 mg (0.52 mmol) of DAE in 0.5 mL of CH_2Cl_2. The cooling bath was allowed to warm to room temperature, and the reaction mixture which slowly darkened was stirred for 7 h. After addition of 5% aqueous $NaHCO_3$, stirring was continued for 15 min. Evaporation of CH_2Cl_2 and partition of the residue between ether and water yielded a dark brown oil which was heated in a sealed glass tube at 150°C with 1 mL of water and 5 mg of $NaHCO_3$ for 1 h.[9] There was obtained 83 mg (83%) of amber oily ketone mixture, ir ($CHCl_3$): 1695 and 1705 cm^{-1} (C=O); *m/e* 386 (46% of **2***a*), 400 (51% of **2***a* + CH_2), 414 (1% of **2***a* + 2 CH_2), and 416 (2% of **2***a* + ?) (Table 1, entry 10).

*(b) 5β-Cholestan-3-one (***2b***)*

A reaction was carried out as in (a) on 50 mg of **2***b* and half quantities of the other reagents. There was obtained 46 mg (92%) of amber oily ketone mixture after decarbethoxylation, *m/e* 386 (31% of **2***b*), 382 and 400 (69% of **2***b* + CH_2 and its $M^+ - 18$ fragmentation ion). ^{13}C peaks integrated: same as (*d*) of the *in situ* reaction (Table 1, entry 20).

Synthesis of Authentic A*-Homo-5α-cholestan-4-one (***4a***)*

(a) 3,3-Dimethoxy-5α-cholestane

This dimethyl ketal was prepared by the method of Levisalles *et al.* (10). From 500 mg of **2***a* was obtained after recrystallization (4×) from ether–MeOH 228 mg (40%) of colorless granules, mp 77–79°C, $[\alpha]_D^{19}$ +35° (*c* 1.06, $CHCl_3$) (lit. (10) mp 78–80°C, $[\alpha]_D$ +24°); ir, no C=O absorption; ^{1}Hmr ($CDCl_3$) δ: 3.15 (3H, s, OCH_3) and 3.20 ppm (3H, s, OCH_3); *m/e* 432.4 (M^+).

(b) 3-Methoxy-5α-cholest-2-ene

The procedure of Levisalles *et al.* (10) was modified. The dimethyl ketal (125 mg) from (*a*) was evaporatively distilled in a tube at 200°C/1 Torr over a period of ~7 h. The solidified distillate was recrystallized (4×) from ether–methanol to give 35 mg (30%) of colorless plates of the enol ether, mp 98–100°C, $[\alpha]_D^{19}$ +69° (*c* 1.04, $CHCl_3$) (lit. (10) mp 100–101°C, $[\alpha]_D$ +61°); ir ($CHCl_3$): 1680 cm^{-1} (C=C of enol ether); ^{1}Hmr ($CDCl_3$) δ: 3.50 (3H, s, OCH_3) and 4.50 ppm (1H, bd, C=CH) M^+ calcd. for $C_{28}H_{48}O$: 400.3705; found: 400.3708.

On a larger scale (500 mg) the reaction was conducted by heating the ketal in a sealed tube at 200°C for 10–20 h.

(c) 2α,3α-Dibromomethylene-3β-methoxy-5α-cholestane

The procedure of Levisalles *et al.* (10) was used. The reaction of 92 mg of enol ether from (*b*) with dibromocarbene gave 50 mg (38%) of adduct, mp 128–130°C, $[\alpha]_D^{19}$ +51.5° (*c* 1.10, $CHCl_3$) (lit. (10) mp 137–138°C, $[\alpha]_D$ +44°); ir, no C=C absorption; ^{1}Hmr ($CDCl_3$) δ: 3.51 ppm (3H, s, OCH_3). M^+ calcd. for $C_{29}H_{48}Br_2O$: 572.2051; found: 572.2037.

*(d) 3-Bromo-*A*-homo-5α-cholest-2-en-4-one*

The AgOAc-catalyzed solvolysis of the dibromocarbene adduct (50 mg) from (*c*) was carried out according to the published procedure (10) to yield 20 mg (47%) of bromo enone, mp 108–110°C (lit. (10) mp 112–112.5°C); ir ($CHCl_3$): 1680 cm^{-1} (conjugated C=O); ^{1}Hmr ($CDCl_3$) δ: 4.79 ppm (1H, t, $|J_{AX} + J_{BX}| = 15$ Hz, C=CH). M^+ calcd. for $C_{28}H_{45}BrO$: 478.2633; found: 478.2639.

(e) A*-Homo-5α-cholestan-4-one (***4a***)*

The bromo enone (200 mg) from (*d*) and a larger scale run was hydrogenated in benzene over 10% Pd/C and Na_2CO_3 according to ref. 10 to yield 166 mg (99%) of colorless plates of **4***a* after recrystallization from MeOH, mp 96–99°C, $[\alpha]_D^{20}$ +107° (*c* 1.02, $CHCl_3$) (lit. (10) mp 96–97.5°C, $[\alpha]_D$ +103°); ir ($CHCl_3$): 1695 cm^{-1} (7-ring C=O). M^+ calcd. for $C_{28}H_{48}O$: 400.3705; found: 400.3701.

Synthesis of Authentic A*-Homo-5α-cholestan-3-one (***3a***)*

*(a) 4-Chloro-*A*-homocholesta-4,5-dien-3-one*

This compound was prepared in 13% yield from 1.0 g of cholest-4-en-3-one without purification of the pyrrolidine dienamine or dichlorocarbene adduct according to the procedure of ref. 23. The 148 mg of colorless plates had mp 138–140°C, $[\alpha]_D^{19.5}$ −147°C (*c* 1.04, $CHCl_3$) (lit. (23) mp 137.5–140°C); ir ($CHCl_3$): 1660 (conjugated C=O) and 1610 cm^{-1} (conjugated C=C); ^{1}Hmr ($CDCl_3$) δ: 6.04 (1H, bs, C=CH) and 7.10 ppm (1H, s, C=CH—C=C). M^+ calcd. for $C_{28}H_{43}ClO$: 430.3002; found: 430.3005.

(b) A*-Homo-5α-cholestan-3-one (***3a***)*

The chlorodienone (148 mg) from (*a*) was hydrogenated by the procedure of ref. 23 to give, after thick-layer chromatography and recrystallization from ether–MeOH, 72 mg of colorless needles of **3***a*, mp 83–84°C, $[\alpha]_D^{19}$ −21.6° (*c* 1.00, $CHCl_3$) (lit. (23) mp 81–82.5°C, lit. (14) $[\alpha]_D$ −21°); ir ($CHCl_3$): 1698 cm^{-1} (7-ring C=O). M^+ calcd. for $C_{28}H_{48}O$: 400.3705; found: 400.3708.

Synthesis of Authentic A*-Homo-5β-cholestan-3-one (***3b***)*

(a) 3,3-Dimethoxy-5β-cholestane

A solution of 50 mg of **2***b* and 2 mg of *p*-TsOH in 2.5 mL of MeOH was refluxed for 5 h. After basification with NaOMe–MeOH the reaction mixture was diluted with ether, washed with water, dried, and concentrated to leave 50 mg of a colorless oil (49); ir ($CHCl_3$): faint C=O at 1710 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.14 (3H, s, OCH_3) and 3.21 ppm (3H, s, OCH_3). M^+ calcd. for $C_{29}H_{52}O_2$: 432.3967; found: 432.3957.

Analysis by tlc showed ~5% of **2***b* remaining; the ketal was used without further purification.

(b) 3-Methoxy-5β-cholest-3-ene

The dimethyl ketal (50 mg) from (*a*) was evaporatively distilled in a tube at 200°C/1 Torr over a period of 3 h to give 35 mg of viscous oily enol ether containing ~5% of **2***b* (49); ir ($CHCl_3$): 1667 (C=C of enol ether) and faint C=O at 1710 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.53 (3H, s, OCH_3) and 4.24 ppm (1H, bs, C=CH). M^+ calcd. for $C_{28}H_{48}O$: 400.3705; found: 400.3697.

(c) 3β,4β-Dibromomethylene-3α-methoxy-5β-cholestane

To a stirred (magnetic bar) solution of 92 mg of enol ether from (*b*) in 2.5 mL of cyclohexane at 0–5°C was added 272 mg of KO *t*Bu followed by addition of a solution of 540 mg of $CHBr_3$ in 1.5 mL of cyclohexane during 3 min. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. Dilution with ether, washing with water, drying, and concentration left a viscous oil which was chromatographed on a preparative plate developed twice with hexanes. Extraction of the band at R_f 0.38 gave 82 mg (62%) of colorless solid. Recrystallization from ether–MeOH (1×) and from $CHCl_3$–MeOH (2×) gave glistening colorless plates of the dibromocyclopropyl steroid, mp 140–143°C (dec.), $[\alpha]_D^{20}$ +66° (*c* 0.90, $CHCl_3$); ir, no C=C absorption; ^{1}Hmr ($CDCl_3$) δ: 3.51 ppm (3H, s, OCH_3). M^+ calcd. for $C_{29}H_{48}Br_2O$: 572.2051; found: 572.2026. *Anal.* calcd. for $C_{29}H_{48}Br_2O$: C 60.83, H 8.45; found: C 60.98, H 8.46.

*(d) 4-Bromo-*A*-homo-5β-cholest-4-en-3-one*

A mixture of 59 mg of dibromocyclopropyl compound from (*c*), 30 mg of AgOAc, 2 mL of HOAc, and 2 drops of water was stirred (magnetic bar) and refluxed for 2 h. After evaporation

of HOAc and water, the $CHCl_3$-soluble material was chromatographed on a preparative plate developed in benzene–hexanes (75:25). Extraction of the band at R_f 0.40 gave 33 mg (67%) of colorless solid. Recrystallization from ether–MeOH (3×) afforded 23 mg of colorless needles of the bromo enone, mp 108–110°C, $[\alpha]_D^{19.5}$ −124° (*c* 0.80, $CHCl_3$); ir ($CHCl_3$): 1680 cm^{-1} (conjugated C=O); ^{1}Hmr ($CDCl_3$) δ: 7.07 (1H, d, J = 6.5 Hz, C=CH) ppm. M^+ calcd. for $C_{28}H_{45}BrO$: 476.2654; found: 476.2663. *Anal.* calcd. for $C_{28}H_{45}BrO$: C 70.41, H 9.50; found: C 70.58, H 9.45.

(e) A-Homo-5β-cholestan-3-one (3b)

A mixture of 98 mg of bromo enone from (*d*), 50 mg of 10% Pd/C, 50 mg of K_2CO_3, and 6 mL of benzene was hydrogenated with stirring (magnetic bar) at room temperature and atmospheric pressure for 17 h. The filtered solution was concentrated and chromatographed on a preparative plate developed with benzene–ether (95:5). Extraction of the band at R_f 0.44 gave 80 mg of colorless viscous oil which crystallized on standing. Recrystallization (2×) of a 68-mg portion from ether–MeOH gave 26 mg of colorless needles of pure **3***b*, mp 55.5–56°C, $[\alpha]_D^{19}$ +89° (*c* 0.88, $CHCl_3$); ir ($CHCl_3$): 1695 cm^{-1} (7-ring C=O). M^+ calcd. for $C_{28}H_{48}O$: 400.3705; found: 400.3697. *Anal.* calcd. for $C_{28}H_{48}O$: C 83.93, H 12.07; found: C 84.15, H 11.87.

Baeyer–Villiger Reactions

(a) 5α-Cholestan-3-one

A solution of 100 mg (0.26 mmol) of **2***a*, 100 mg (75%, 0.43 mmol) of *m*-chloroperbenzoic acid, and 3 mL of $CHCl_3$ was allowed to stand at room temperature for 36 h. The solution was washed with 10% aqueous Na_2SO_3, 5% aqueous $NaHCO_3$, water, and dried. Concentration left 94 mg (90%) of colorless solid lactone mixture **5***a* + **6***a* which gave a single tlc spot more polar than **2***a*, ir ($CHCl_3$): 1725 cm^{-1} (lactone C=O), *m/e* 402 (M^+). ^{13}C peaks integrated: δ 64.7 (C-2 of **6***a*) and 70.0 ppm (C-4a of **5***a*).

(b) 5β-Cholestan-3-one

A 100-mg sample of **2***b* oxidized as in (*a*) yielded 92 mg (88%) of colorless solid lactone mixture **5***b* + **6***b*; ir ($CHCl_3$): 1720 cm^{-1} (lactone C=O); *m/e* 402 (M^+). ^{13}C peaks integrated: δ 63.3 (C-2 of **6***b*) and 70.5 ppm (C-4a of **5***b*).

(c) 17β-Hydroxy-5α-androstan-3-one

A 50-mg sample (0.19 mmol) of **2***c* was oxidized with 48 mg (0.21 mmol) of *m*-chloroperbenzoic acid in 3 mL of $CHCl_3$ for 24 h to yield 48 mg (92%) of colorless solid lactone mixture **5***c* + **6***c* which contained ~20% of **2***c*; ir ($CHCl_3$) 1730 cm^{-1} (lactone C=O); *m/e* 306 (M^+). ^{13}C peaks integrated: δ 64.7 (C-2 of **6***c*) and 70.0 ppm (C-4a of **5***c*).

When 50 mg (0.19 mmol) of **2***c* was oxidized with 100 mg (0.43 mmol) of *m*-chloroperbenzoic acid for 2.5 days, the product was ~85% 17-oxo-A-ring lactones; *m/e* 304 (85%) and 306 (15%) (M^+).

(d) 5α-Cholestan-3-one + CF_3CO_3H

A solution of CF_3CO_3H made by stirring 0.1 mL of 63% H_2O_2 and 0.4 mL of $(CF_3C{=}O)_2O$ in 1 mL of CH_2Cl_2 at 5°C for 10 min was added to a solution of 125 mg of **2***a* in 2 mL of CH_2Cl_2 containing 250 mg of suspended Na_2HPO_4. The reaction was stirred (magnetic bar) at room temperature for 2 h. The organic solution was washed with 10% aqueous Na_2CO_3 and water, dried, and concentrated to leave 123 mg (95%) of oily solid lactone mixture **5***a* + **6***a* which was used for ^{13}C integration of the isolated peaks at δ 64.7 (C-2 of **6***a*) and 70.0 ppm (C-4a of **5***a*).

Authentic 4-Oxa-A-homo-5α-cholestan-3-one (5a)

(a) 2α-Bromo-A-homo-4-oxa-5α-cholestan-3-one

A solution of 200 mg (0.43 mmol) of 2α-bromo-5α-cholestan-3-one and 500 mg (~2 mmol) of *m*-chloroperbenzoic acid (Aldrich, 75%) in 5 mL of $CHCl_3$ was allowed to stand at room temperature. At the end of 4 h, tlc showed considerable starting material remaining, and two more 500-mg portions of the peracid were added during the next 4 h to increase the reaction rate. The $CHCl_3$ solution was washed thoroughly with 10% aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and water. Evaporation of the dried solution left 207 mg (100%) of colorless solid which gave a single tlc spot more polar than starting material. A 125-mg portion dissolved in 1 mL of CCl_4 was chromatographed on a column of 3 g of silica gel. Elution with hexanes–benzene (45:55) gave 79 mg of colorless solid. Recrystallization from acetone–hexanes (1×) and from ether – petroleum ether (1×) gave 34 mg of colorless needles of *bromo lactone*, mp 186–189°C, $[\alpha]_D^{20}$ −5.4° (*c* 1.60, $CHCl_3$) (lit. (40), mp 192–193°C, $[\alpha]_D$ −4.5°); ir ($CHCl_3$): 1750 cm^{-1} (lactone C=O); ^{1}Hmr ($CDCl_3$) δ: 3.82 (1H, d, 4a-H), 4.34 (1H, dd, 4a-H), and 4.96 ppm (1H, dd, 2β-H). The bromo lactone was a single pure isomer according to its ^{13}Cmr spectrum.

(b) Reductive Debromination

The method of Bolliger *et al.* (40) was used. A solution of $CrCl_2$ was made from 1.0 g of $CrCl_3{\cdot}6H_2O$, 2.0 g of Zn, and 1.6 g of $HgCl_2$ (50). To this stirred solution under N_2 was added a solution of 100 mg of the bromo lactone from (*a*) in 4 mL of HOAc, and the reaction mixture was stirred for 12 h. The product was isolated by ether extraction, and the ether solution was washed with aqueous $NaHCO_3$ and water. Evaporation of the dried solution left 64 mg (77%) of colorless solid. Recrystallization (3×) from $CHCl_3$–CH_3OH gave 23 mg of colorless needles of lactone **5***a*, mp 192–195°C (lit. (40), mp 199–200°C); ir ($CHCl_3$): 1725 cm^{-1} (lactone C=O); ^{1}Hmr ($CDCl_3$) δ: 3.68 (1H, d, 4a-H) and 4.29 ppm (1H, dd, 4a-H). M^+ calcd. for $C_{27}H_{46}O_2$: 402.3498; found: 402.3501. The ^{13}Cmr spectrum was that of a single lactone.

Schmidt Reactions

(a) 5α-Cholestan-3-one

The procedure of Doorenbos and Wu (43) was used. To a mixture of 1.25 g of polyphosphoric acid and 50 mg (0.13 mmol) of **2***a* at 65°C was added 10 mg (0.15 mmol) of NaN_3; the 65°C temperature was maintained for 12 h. After addition of ice, the mixture was basified with 50% aqueous NaOH and extracted with $CHCl_3$. The organic layer was washed with water, dried and concentrated. Since tlc examination of the product revealed some unreacted **2***a*, it was recycled through a second treatment with HN_3 as above to give 35 mg (67%) of colorless solid lactam mixture **7***a* + **8***a* (free of **2***a*), mp 262–264°C with a phase change ~230°C; ir ($CHCl_3$): 3430 (NH) and 1660 cm^{-1} (amide C=O); *m/e* 401 (M^+). ^{13}C peaks for integration: δ 21.0, 35.3, 44.4, 49.6, and 53.8 ppm from **7***a*; δ 21.3, 34.7, 42.0, 43.3, and 54.1 ppm from **8***a* (Table 1, entry 13).

(b) 5β-Cholestan-3-one

A 50-mg sample of **2***b* under the reaction conditions in (*a*) gave complete reaction after one treatment and yielded 45 mg (86%) of colorless solid lactam mixture **7***b* + **8***b* (free of **2***b*); ir ($CHCl_3$): 3430 (NH) and 1660 cm^{-1} (amide C=O); *m/e* 401 (M^+). ^{13}C peaks for integration: δ 27.0, 38.8, 42.2, 44.1, and 45.5 ppm from **7***b*; δ 26.0, 36.8, and 43.0 ppm from **8***b* (Table 1, entry 22).

Authentic Lactams 8a and 8b

(a) 3-Aza-A-homo-4a-cholesten-4-one (Part Structure 20)

The Beckmann rearrangement procedure of Mazur (51) was adapted. To a stirred (magnetic bar) solution of 300 mg of the oxime of 4-cholesten-3-one (~30% *syn*, ~70% *anti* OH:C=C)

in 4.5 mL of dry dioxane at 10°C was added 0.9 mL of freshly distilled $SOCl_2$. The cooling bath was allowed to warm to room temperature, and the dark yellow solution was stirred for 2 h. After addition of excess 5% aqueous $NaHCO_3$, the product was extracted with ether. Evaporation of the washed and dried organic solution left 285 mg of tan oily solid which was chromatographed on two preparative plates developed in EtOAc. Extraction of the band visible under uv on the lower half of the plate gave 160 mg of off-white solid. Recrystallization (2×) from benzene–acetone gave colorless granules of the *lactam* **20**, mp 245–247°C with a phase change ~220°C, $[\alpha]_D^{20}$ +24° (*c* 1.40, $CHCl_3$) (lit. (44, 52), mp 252–256°C, 255–260°C, $[\alpha]_D$ +20°); uv (MeOH): 222 (22 000) and 247 nm (20 000); ir ($CHCl_3$): 3440 (NH), 1660 (C=O), and 1625 cm^{-1} (conjugated C=C); ^{1}Hmr ($CDCl_3$) δ: 3.18 (2H, bm, O=$CNCH_2$), 5.75 (1H, bs, C=CH), and 6.55 ppm (1H, bs, NH). M^+ calcd. for $C_{27}H_{45}NO$: 399.3501; found: 399.3498.

*(b) 3-Aza-*A*-homo-5α-cholestan-4-one (**8**a)*

To a mixture of 100 mg of 10% Pd/C catalyst and 100 mg of powdered KOH in 5 mL of MeOH stirred (magnetic bar) under H_2 was added a solution of 100 mg of unsaturated lactam **20** in 25 mL of MeOH. After 12 h the catalyst was removed by filtration and the solvent evaporated. The residual solid was dissolved in $CHCl_3$, and the solution was washed with water, dried, and concentrated. Recrystallization (2×) from MeOH–$CHCl_3$ gave 42 mg of colorless granules of pure *lactam* **8***a*, mp 260–280°C (dec. and subl.) with a phase change to needles at ~210°C; when the melting point was taken in a sealed capillary, a narrower range, mp 280–282°C (dec.), was observed; $[\alpha]_D^{20}$ +35° (*c* 1.60, $CHCl_3$) (lit. (44) mp 294–296°C, $[\alpha]_D$ +41°); uv (MeOH) rising end absorption only; ir ($CHCl_3$): 3420 (NH) and 1660 cm^{-1} (amide C=O); ^{1}Hmr ($CDCl_3$) δ: 2.6–3.5 (2H, bm, O=$CNCH_2$) and 6.47 ppm (1H, bs, NH). M^+ calcd. for $C_{27}H_{47}NO$: 401.3658; found: 401.3655.

*(c) 3-Aza-*A*-homo-5β-cholestan-4-one (**8**b)*

To a mixture of 50 mg of PtO_2 in 1.5 mL of HOAc stirred (magnetic bar) under H_2 was added a solution of 140 mg of unsaturated lactam **20** in 4 mL of HOAc. After 18 h the catalyst was removed by filtration, and the product was isolated by partition between ether and water. The semi solid product was chromatographed on two preparative plates developed (3×) in EtOAc–MeOH (97:3). Extraction of the band at R_f 0.82 produced 78 mg of colorless solid which was recrystallized (2×) from MeOH to give 49 mg of colorless plates of pure *lactam* **8***b*, mp 230–232°C, $[\alpha]_D^{20}$ + 56.4° (*c* 1.00, $CHCl_3$); uv (MeOH) rising end absorption only; ir ($CHCl_3$): 3420 (NH) and 1655 cm^{-1} (amide C=O); ^{1}Hmr ($CDCl_3$) δ: 3.08 (2H, m, O=$CNCH_2$) and 6.18 ppm (1H, bs, NH). M^+ calcd. for $C_{27}H_{47}NO$: 401.3658; found: 401.3663.

Both **8***a* and **8***b* gave only 27 signals each in their ^{13}Cmr spectra.

Acknowledgements

We would like to thank the National Research Council of Canada for financial support, Cheryl DuCharme for the ^{13}Cmr spectra, Heather Schroeder for the 100 MHz ^{1}Hmr spectra, and Doug Hairsine for the mass spectra.

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