Nuclear Magnetic Resonance Spectra and Conformations of 10-Carbethoxy-1,1-dimethyldecalins. Conformational Effects on Proton Nonequivalence[1]

Walter L. Meyer, Daniel L. Davis,[2] Lincoln Foster,[2] Alfred S. Levinson, Virginia L. Sawin,[2] D. Craig Shew, and Richard F. Weddleton

Contribution No. 1270 from the Department of Chemistry, Indiana University, Bloomington, Indiana. *Received December 21, 1964*

The O-methylene protons of the ethoxyl groups in a series of 10-carbethoxy-1,1-dimethyl-trans-decalin (**4a–c**) *and 10-carbethoxy-1,1-dimethyl-Δ^8-octalin derivatives* (**5a–e**) *are magnetically nonequivalent, proton magnetic resonance spectra of the ethyl groups being characteristic of ABC_3 systems having chemical shifts of 0.07 to 0.16 p.p.m. between the methylene protons. Magnetic nonequivalence of the corresponding protons in an analogous series of 10-carbethoxy-trans-decalins and 10-carbethoxy-Δ^8-octalins without 1,1-dimethyl substituents* (**6a–f**) *could not be detected, the ethoxyl resonances being of the A_2B_3 type in each case. From these results it is concluded that steric interaction between the ester and the axial 1β-methyl group is of major importance in providing different magnetic environments for the O-methylene protons of the methylated derivatives, probably due to depopulation of some otherwise accessible conformations of the ester group. Nonequivalence of the O-methylene protons of 10-carbethoxy-1,1-dimethyl-trans-2-decalone* (**2**) *and 10-carbethoxy-1,1-dimethyl-Δ^8-2-octalone* (**3**) *could not be detected. Therefore it appears that in these two derivatives, the only ones examined with 1,1-dimethyl substitution and trigonal hybridization at C-2, the gem-methyl groups are differently oriented with respect to the ester than is the case for the other dimethylated compounds, and that the methylated ring in such 2-ketones thus is not in a chair conformation. Synthesis of several of the substituted decalins is reported. Hydrogenation of the 1,1-dimethyl-Δ^8-2-ketone* **3** *in acetic acid produces 1,1-dimethyl-2β-hydroxy-trans-decalin-10-carboxylic acid lactone* (**8**). *Successive saponification to the hydroxy acid* **9**, *Jones oxidation to the keto acid* **10**, *and ethylation afford the saturated keto ester* **2**. *That this in fact has a trans ring fusion is shown by its Wolff–Kishner reduction to the known 1,1-dimethyl-trans-decalin-10-carboxylic acid. 10-Carbethoxy-1,1-dimethyl-Δ^8-octalin* (**5d**) *was prepared by conversion of the corresponding Δ^8-7-ketone* **5b** *into its thioketal* **5c** *followed by Raney nickel desulfurization. 10-Carbethoxy-$\Delta^{1,9}$-2-octalone* (**6a**), *10-carbethoxy-trans-2-decalone* (**6b**,) *and the 1,1-dimethyl-Δ^8-2-ketone* **3** *were converted to their thioketals* (**6e, 6d,** *and* **5e**) *using the boron fluoride etherate technique.*

The conformation of ring A in 4,4-dimethyl-3-keto steroids and terpenoids has been a subject of considerable recent interest. In this system, which may be examined as a substituted 1,1,10-trimethyl-*trans*-2-decalone (**1**),[3] diaxial interactions of the 1β-methyl with the angular methyl and the 3β- and 8β-hydrogens and interaction of the equatorial 1α-methyl with the equatorial 8α-hydrogen destabilize the chair form of the methylated ring compared to the 1,1-desmethyl analogs. Some of these substituent interactions are relieved in certain nonchair[4] conformations of ring A, and the presence of the 2-keto group in that ring permits some of these nonchair forms to be occupied with less increase in energy due to eclipsed interactions in the ring or other new nonbonded interactions of the substituents than would result in an analogous C-2 saturated system.[5] Several studies have accumulated evidence to indicate that the relative magnitudes of these effects are sufficient to make nonchair conformations of lower energy than the chairs in such compounds.[5–11] We have now obtained some n.m.r. data of a type quite different from that usually considered to decide such conformational questions,[10,11g,h,12] on the basis of which we conclude that nonchair conformations are also important in 1,1-dimethyl-*trans*-2-decalones when the angular group is carbethoxyl (*e.g.*, **2**). These results also indicate that

(1) (a) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, Abstracts of papers, p. 85Q. (b) Abstracted in part from the Ph.D. Dissertation of A. S. Levinson, Indiana University, 1963.

(2) National Science Foundation Undergraduate Research Participant.

(3) For the sake of clarity all *gem*-dimethyldecalins herein discussed are named with the methylated position as C-1, and the methylated ring is referred to as ring A. The configurational notations α and β are used in the steroid sense, a β-substituent being *cis* to the angular group. Although all synthetic compounds were examined as racemic forms, the prefix *dl* is omitted and only one enantiomer is depicted in structural formulas.

(4) Throughout we use this term to refer to the conformations other than the true or slightly distorted chair which the six-membered ring may occupy. These may be, or approach, the boat, twist, or flat chair forms which other authors have discussed (*cf.* ref. 5 and references therein), but since our data cannot distinguish among these we prefer the less precisely descriptive term "nonchair" in the present context.

(5) N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Am. Chem. Soc.*, **86**, 4061 (1964), discuss in detail the conformational analysis of such systems.

(6) J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.*, 464 (1961).

(7) N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.*, **84**, 4561 (1962); *Tetrahedron Letters*, 676 (1961).

(8) J. M. Lehn, J. Levisalles, and G. Ourisson, *ibid.*, 682 (1961).

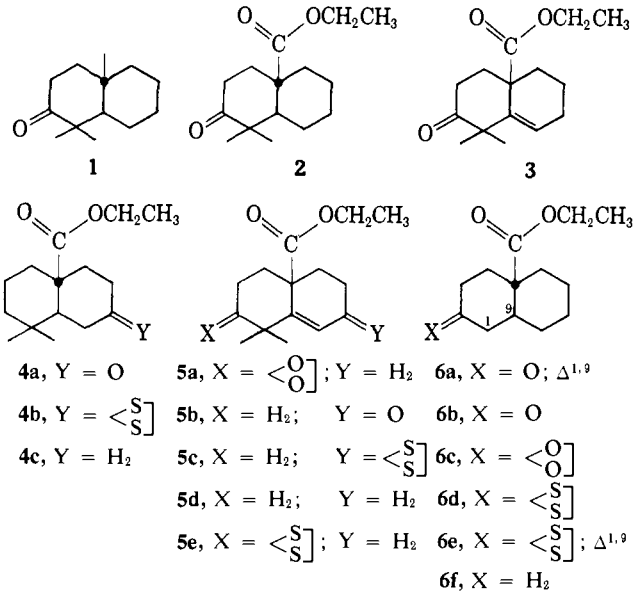
(9) J. M. Lehn and G. Ourisson, *Bull. soc. chim. France*, 1113 (1963).

(10) M. Gorodetsky and Y. Mazur, *Tetrahedron Letters*, 227 (1964).

(11) Nonchair forms have also been encountered in related systems containing additional substituents; for example, see (a) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957); (b) E. G. Cummins and J. E. Page, *ibid.*, 3847 (1957); (c) J. Levisalles, *Bull. soc. chim. France*, 551 (1960); (d) D. T. Cropp, B. B. Dewhurst, and J. S. E. Holker, *Chem. Ind. (London)*, 209 (1961); (e) D. R. Chaudry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2725 (1961); (f) I. G. Grant, J. A. Hamilton, T. A. Hamor, R. Hodges, S. G. McGeachin, R. A. Raphael, J. M. Robertson, and G. A. Sim, *Proc. Chem. Soc.*, 444 (1961); (g) B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, and J. Levisalles, *Chem. Ind.* (London), 1667 (1961); (h) R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1961). Reference 11c and M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962), have reviewed the literature in the general area of nonchair cyclohexane derivatives.

(12) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).

such is *not* the case when the 2-keto group is replaced by a methylene.



1 **2** **3**

4a, Y = O **5a**, X = <O,O>; Y = H_2 **6a**, X = O; $\Delta^{1,9}$

4b, Y = <S,S> **5b**, X = H_2; Y = O **6b**, X = O

4c, Y = H_2 **5c**, X = H_2; Y = <S,S> **6c**, X = <O,O>

5d, X = H_2; Y = H_2 **6d**, X = <S,S>

5e, X = <S,S>; Y = H_2 **6e**, X = <S,S>; $\Delta^{1,9}$

6f, X = H_2

We recently had occasion to prepare a number of 10-carbethoxy-1,1-dimethyl-*trans*-decalin (**4a–4c**) and 10-carbethoxy-1,1-dimethyl-Δ^8-octalin derivatives (**3**, **5a**, and **5b**), most of which contained additional functional substituents in one or both rings of the bicyclic system.[13] While proton n.m.r. spectra of all these esters in carbon tetrachloride solution are in other respects unexceptional, the multiplets from the O-methylene protons of the ethoxyl groups of all of them except the unsaturated keto ester **3** are characteristic of the AB parts of ABC_3 spectra (Figure 1) rather than

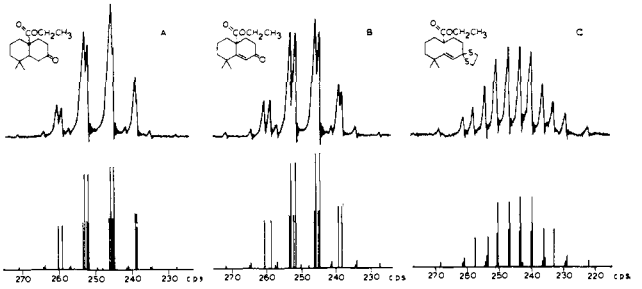


Figure 1. Observed and calculated O-methylene proton multiplets for A, 10-carbethoxy-1,1-dimethyl-*trans*-7-decalone, **4a** ($\Delta\nu_{AB}$ = 4.2 c.p.s.); B, 10-carbethoxy-1,1-dimethyl-Δ^8-7-octalone, **5b** ($\Delta\nu_{AB}$ = 5.7 c.p.s.); and C, 10-carbethoxy-1,1-dimethyl-7,7-ethylenedithio-Δ^8-octalin, **5c** ($\Delta\nu_{AB}$ = 9.4 c.p.s.); all in carbon tetrachloride at 31°, 60 Mc.p.s.

simple quartets which would be expected from A_2X_3 systems (or A_2B_3 systems with chemical shifts and coupling constants of the order of magnitude usually found in ethoxyl groups). Subsequently the saturated keto ester **2**, the unsaturated ester **5d**, and the unsaturated thioketals **5c** and **5e** were also prepared, and the last three of these derivatives likewise show nonequivalence of the ethoxyl methylene protons. The chemical shift between the two magnetically nonequivalent O-methylene protons ($\Delta\nu_{AB}$) varies from 4.2 to 9.4 c.p.s. at 60 Mc,[14] with methyl–methylene coupling constants (*ca.* +7 c.p.s.),[15] geminal methylene coupling constants (*ca.* −11 c.p.s.), O-methylene chemical shifts (*ca.* τ 6), and C-methyl chemical shifts (*ca.* τ 8.75) in the range characteristic of ethoxyl protons (Table I).

Table I. Chemical Shifts (ν) and Coupling Constants (J) of Ethoxyl Protons ($OCH^AH^BCH_3^C$) of Substituted 10-Carbethoxydecalins[a]

Compd.	ν_A[b]	ν_B[b]	$\nu_A - \nu_B$[c]	ν_C[b]	$\pm J_{AB}$[c]	$\pm J_{AC}$[c]
4a	250.8	246.6	4.2	77.9	10.8	7.0
4b	248.4	242.6	5.8	76.1	11.1	7.0
4c	246.4	242.1	4.3	75.3	11.0	7.0
5a	248.3	240.0	8.3	74.4	11.0	7.0
5b	251.7	246.0	5.7	75.7	11.0	7.0
5c	249.6	240.2	9.4	76.0	10.8	7.0
5d	247.9	239.9	8.0	74.3	10.8	6.9
5e	248.1	239.7	8.4	74.4	10.9	7.0
2	249.4	249.4	0	77.6	...	7.1
3	244.5	244.5	0	73.0	...	7.1
6a	253.5	253.5	0	77.0	...	7.0
6b	250.9	250.9	0	77.3	...	7.0
6c	246.5	246.5	0	74.3	...	7.2
6d	246.6	246.6	0	74.6	...	7.0
6e	247.2	247.2	0	74.5	...	7.1
6f	248.5	248.5	0	75.0	...	7.0

[a] Carbon tetrachloride solution, 31°. [b] C.p.s. downfield from internal tetramethylsilane, at 60 Mc./sec. [c] C.p.s. See ref. 17.

These carbethoxy groups, of course, are attached to asymmetric structures, and the magnetic nonequivalence thus arises from location of the methylene group in an asymmetric environment.[16,17] Many examples of such magnetically nonequivalent acyclic methylene protons can be found in systems having the methylene group directly attached to an asymmetric center (*e.g.*, methyl α,β-dibromopropionate[16]) or separated from an asymmetric center by two bonds (*e.g.*, diethyl sulfite[18–22] or acetaldehyde diethyl acetal[19]).[23] Fewer examples are available of compounds which, like these esters,

(13) W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2184 (1963).

(14) Throughout the discussion chemical shifts are expressed in τ units or in c.p.s. at 60 Mc./sec. downfield from internal tetramethylsilane. Peak positions are in c.p.s. at 60 Mc. downfield from tetramethylsilane.

(15) Absolute signs of these coupling constants are not, of course, derived from our data, but are assigned by analogy; *cf.* P. C. Lauterbur and R. J. Kurland, *J. Am. Chem. Soc.*, **84**, 3405 (1962), and F. A. L. Anet, *ibid.*, **84**, 3768 (1962). Our spectra are in satisfactory agreement with theoretical spectra which have opposite relative signs of the geminal and vicinal proton–proton coupling constants, as is expected; compare R. R. Fraser, R. U. Lemieux, and J. D. Stevens, *ibid.*, **83**, 3901 (1961); F. Kaplan and J. D. Roberts, *ibid.*, **83**, 4666 (1961); F. A. L. Anet, *ibid.*, **84**, 1053 (1962); and A. McLauchlan and D. H. Whiffen, *Proc. Chem. Soc.*, 144 (1962). No attempt was made to fit the spectra using coupling constants of like sign.

(16) P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 4565 (1957).

(17) In all the esters except **6f** discussed here, the O-methylene protons are, of course, stereochemically nonequivalent. Throughout, we use the term "nonequivalent" to refer to *magnetic* nonequivalence of observable magnitude. There is a lower limit to $\Delta\nu_{AB}$ below which instrument resolution and sensitivity do not permit differentiation of an ABC_3 from an A_2B_3 system. In the present cases we estimate this to be *ca.* 2 c.p.s. on the basis of line intensities and separations in theoretically calculated spectra. Thus throughout our discussion nonequivalent protons which differ by less than this value are considered as "equivalent."

(18) H. Finegold, *Proc. Chem. Soc.*, 283 (1960).

(19) P. R. Shafer, D. R. Davis, M. Vogel, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci. U. S.*, **47**, 49 (1961).

(20) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, **65**, 562 (1961).

(21) J. G. Pritchard and P. C. Lauterbur, *J. Am. Chem. Soc.*, **83**, 2105 (1961).

(22) F. Kaplan and J. D. Roberts, *ibid.*, **83**, 4666 (1961).

(23) *Cf.* E. I. Snyder, *ibid.*, **85**, 2624 (1963), and references cited therein for numerous additional examples.

have more than two bonds between an asymmetric center and nonequivalent geminal protons[24] or methyl groups,[25] although they have been observed. Whitesides, Holtz, and Roberts[25] examined the effect on the chemical shift difference ($\Delta\nu_{AB}$) between nonequivalent geminal methyls (*i.e.*, an isopropyl group) which resulted from increasing the separation of an asymmetric center and the geminal system; they found rapid attenuation of $\Delta\nu_{AB}$ in an acyclic system, only small (0–2.5 c.p.s.) effects being observed when more than two intervening bonds were involved. Three bonds separate the O-methylene of the carbethoxydecalins and the nearest asymmetric center, and yet $\Delta\nu_{AB}$ between the methylene protons is relatively large. In this system, however, the rigid bicyclic nucleus holds the carbethoxy group more or less over the ring system and hence closer to the asymmetric environment it provides than would be the case for a completely acyclic system. This seems to be a clear illustration of the fact that the number of bonds involved is really only a formal distinction which may not be particularly meaningful in rigid systems. On the other hand it also suggests that, due to its location over the rings, the angular group of a decalin may be a sensitive probe for various steric and electronic effects in the system.

In addition to dissymmetric substitution *per se*, however, it appears that the *gem*-dimethyl group is an important structural feature in conferring observable nonequivalence on the O-methylene protons of these 10-carbethoxydecalins. So far as we have been able to observe, electronic effects due to different substitution patterns in the two rings of the decalin system are ineffective in leading to O-methylene nonequivalence in the absence of the methyls. A series of 10-carbethoxy-*trans*-decalins **6** containing the 2-ketone **6b**,[26–29] the 2-ethylene ketal **6c**,[28] and the thioketal **6d**, as well as the $\Delta^{1,9}$-2-ketone **6a**,[26–29] its thioketal **6e**, and 1-methyl derivative[30] all have simple A_2B_3 O-methylene resonances,[17] as does, of course, the symmetric 10-carbethoxy-*trans*-decalin **6f**[26–29] itself. These compounds contain the same functional groups which on the 1,1-dimethyldecalin (**4a–4c**) or the 1,1-dimethyl-Δ^8-octalin (**5a–5e**) skeletons give rise to compounds with nonequivalent O-methylene protons. In every case introduction of only the *gem*-dimethyl group is sufficient to produce nonequivalence, and comparison of the simple esters **4c** and **6f** clearly demonstrates that the anisotropy of a functional group is not an added requirement (although it may distinctly affect the magnitude of $\Delta\nu_{AB}$, see below). Comparison of the nonmethylated ester **6f** with any of its functional derivatives, even the unsaturated thioketal **6e** (the methylated analog (**5e**) of which has the greatest $\Delta\nu_{AB}$ of any here observed), shows that simple introduction of electronically and magnetically anisotropic groups onto the decalin nucleus, without adding the *gem*-dimethyl, is ineffective in producing O-methylene nonequivalence.

(24) Dr. E. I. Snyder has informed us that he, too, has observed nonequivalent O-methylene protons in certain ethyl esters; *cf.* footnote 6 of ref. 23.

(25) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964).

(26) A. S. Hussey, H. P. Liao, and R. H. Baker, *ibid.*, **75**, 4727 (1953).

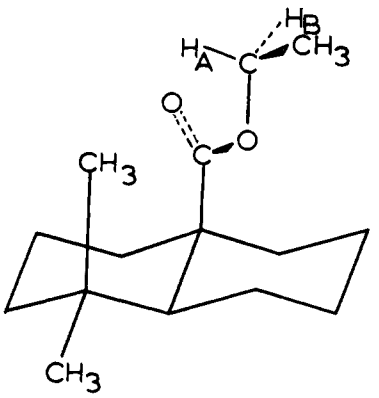
(27) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *ibid.*, 77, 48 (1955).

(28) A. S. Dreiding and A. J. Tomasewski, *ibid.*, 77, 411 (1955).

(29) M. Idelson and E. I. Becker, *ibid.*, **80**, 908 (1958).

(30) F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 586 (1941).

Since very anisotropic groups like the olefinic bond or the carbonyl group do not by themselves lead to nonequivalence, it seems unreasonable to ascribe the effect of *gem*-dimethyl substitution solely to an electronic effect of the methyl groups, and thus they must have a steric influence which leads to significantly different magnetic environments for the two O-methylene protons. When a bulky substituent such as ketal **5a** or thioketal **5e** occupies the 2β-position, the methylated ring is certainly in a chair or nearly a chair conformation, for a nonchair[4] would involve intolerable interaction between the 2-substituent and the angular group or the 1β-methyl (depending on which nonchair is considered). When the methylated ring is in a chair conformation, the axial 1β-methyl group offers considerable hindrance to rotation of the carbethoxyl group (Figure 2). This endows relatively high energy on several conformations of the ester about the C-10 carbonyl bond and these would not be similarly destabilized if the axial 1-substituent were hydrogen. Thus only some conformations, *e.g.*, **7** (*cf.* Figure 2), about the bridgehead carbonyl bond are significantly populated, and in each of these the two O-methylene protons are in different environments. For example proton B will be able to spend but little time in the area occupied by proton A in conformation **7**. The resulting average environment to which one proton is exposed over all accessible conformations which the ester group occupies during its rotations is no longer the same (or nearly the same) as that of the other proton, as was the case with a 1β-hydrogen. The observability of nonequivalence thus seems to be dependent upon the presence of an axial methyl group to hinder (not necessarily freeze) rotation of the ester, thereby depopulating certain of its otherwise occupied conformations.[31,32]



7

In the presence of 1,1-dimethyl substitution the nature of nuclear functionality clearly influences the magnitude of the chemical shift between the two O-methylene protons. The most profound effect is pro-

(31) Presumably other axial substituents could produce the same effect but we have not examined such derivatives. Nor have we had access to 1β-monomethyl compounds to confirm that it is only the axial methyl which is involved. Whether a similar result is obtained with the hindering axial substituent at C-3 is under investigation, as are systems in which the ester and axial methyl are interchanged (angular methyl, 1β-ester).

(32) The same spectra could result from molecules in which such rotation was frozen, only one conformation being significantly populated.[16] Examination of molecular models suggests that interaction of the carbethoxyl group with the methyl and other ring substituents should probably not be sufficiently severe to freeze completely its rotation, so we do not favor this possibility.

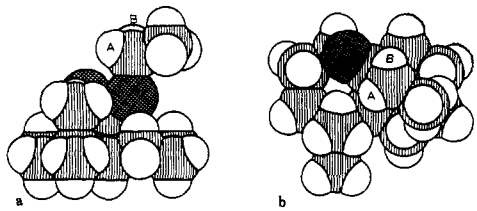


Figure 2. Molecular model of 10-carbethoxy-1,1-dimethyl-*trans*-decalin (**4c**) in conformation **7** viewed from side (a) and top (b).

duced by an 8,9-double bond. Those systems containing such unsaturation have $\Delta\nu_{AB}$ greater than 8 c.p.s. in each of four cases (**5a, c, d,** and **e**), including that (**5d**) in which it is the only nuclear function.[33] The only exceptions are the Δ^8-7-enone **5b** ($\Delta\nu_{AB}$ = 5.7 c.p.s.), in which the double bond is conjugated with the carbonyl group and thus has an appreciably different electron distribution than do the isolated olefins, and the Δ^8-2-enone **3** which is probably abnormal for different reasons (below). Inspection of structure **7** suggests that one area where the two protons in question spend quite different amounts of time when hindered by the axial 1β-methyl (but not when not thus hindered) is above the π-cloud of such an 8,9-olefin, so it is reasonable that one proton should be more shielded by the olefin than is the other. Functions other than the 8,9-olefin which we have thus far examined have much less effect, the compounds **4a** and **4b** showing about the same degree of nonequivalence ($\Delta\nu_{AB}$ = 4–6 c.p.s.) as does the parent ester **4c** (*ca.* 4 c.p.s.).

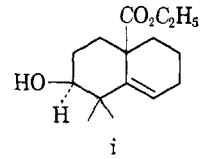
Of all the compounds examined, only two, the dimethylated keto ester **2** and its Δ^8 analog **3**, fail to fit into the pattern. In spectra of both derivatives the O-methylene resonances are simple quartets, like those of the unmethylated decalins. This is especially remarkable in the latter case (**3**) since the presence of 8,9-unsaturation would be expected to enhance the nonequivalence, and it seems unreasonable to argue that the effect of a 2-ketone exactly counterbalances that of an 8,9-olefin, for if this were the case one would anticipate a large $\Delta\nu_{AB}$ for the saturated ketone **2**. Hence it seems that in these two ketones the 1β-methyl group is not juxtaposed with the angular ester in the same way it is in all of the other *gem*-dimethyl compounds examined. If so, it is not truly axial, and thus *with the trigonal carbonyl group at C-2, either with or without 8,9-unsaturation, the 1,1-dimethylated ring is not in a chair conformation.*[34] Other recent evidence[5-11] has suggested that such is also the case in the presence of 1,1-dimethyl substitution when the angular group is methyl.

It should be observed that while these n.m.r. data serve as evidence for nonchair conformations of the *gem*-dimethylated ring when C-2 is trigonal, they also indicate that this ring is a chair when C-2 is a methylene group. The same sort of nonequivalence in the ethoxyl is observed when C-2 is a methylene (**5d**) as when it carries very bulky substituents (**5a** or **5e**). In the latter cases it is almost certainly a chair, and thus by inference the same is true when C-2 is methylene. While this has commonly been assumed to be the case, little evidence for it has previously been available.

The magnitude of magnetic nonequivalence between such diastereomeric[35] protons is well known to be solvent dependent in some instances,[23,25,35] and the direction and size of this effect are not quantitatively predictable at the present time. The spectra discussed above were all obtained from carbon tetrachloride solutions in order to keep such effects constant and hopefully to minimize them. However, in order to learn whether this was an unwittingly unfortunate choice, and whether the observability of nonequivalence would fit some different pattern in other solvents, spectra of the dimethyl-Δ^8-7-ketone **5b**, the unmethylated $\Delta^{1,9}$-2-ketone **6a** and both methylated 2-ketones (**2** and **3**) were also examined in deuteriochloroform, carbon disulfide, hexadeuterioacetone, benzene, pyridine, and acetic acid. These decalins were selected for the solvent study for the following reasons. The methylated Δ^8-7-ketone (**5b**) represents a typical methylated system with nonequivalent O-methylene protons, and $\Delta\nu_{AB}$ between them is of a magnitude (5.7 c.p.s. in carbon tetrachloride) that a change of *ca.* 2 c.p.s. in either direction would be visible simply on inspection (see Figure 1). Its unmethylated analog **6a** is a typical equivalent unmethylated system whose methylated analog (**5b**) has a large enough $\Delta\nu_{AB}$ that one would hope that solvent-induced nonequivalence would be of observable magnitude. And the methylated 2-ketones were examined because it is the difference between them and all other methylated compounds which leads to the conclusion concerning conformation of their A rings; hence it was important to learn whether the apparent equivalence of their O-methylene protons was only an accident of solvent selection for the initial study. In that event, although distinct chemical shift changes for some proton groups in the molecules were produced (Table II), no major alterations of $\Delta\nu_{AB}$ for any of the four systems were observed in any of the solvents. The three systems which had equivalent O-methylene protons in carbon tetrachloride also had equivalent protons[17] in the other solvents, and the $\Delta\nu_{AB}$ of the enone **5b** did not change markedly from 5.7 c.p.s. in any solvent (these latter spectra were not subjected to computer analysis, but visual inspection showed only small changes). Thus it seems safe to exclude capricious solvent effects from being the origin of the results in this instance. Furthermore, it would seem that the position of the chair–nonchair equilibria of the decalins here studied are not strongly solvent dependent.

In the foregoing discussion we have considered the nonequivalence of the O-methylene protons to have its

(33) A fifth example is probably provided by the unsaturated hydroxy ester i. The O-methylene multiplet in the spectrum of a crude sample of this compound qualitatively resembles that of **5e** much more than that of **5b**. However, a pure sample of the hydroxy ester was not obtained,[13] so its spectrum could not be precisely analyzed.



i

(34) This argument does not distinguish between sole (>99%) existence of the nonchair conformation and a rapidly interconverting chair–nonchair equilibrium mixture which contains a considerable proportion of the nonchair form. That is, the n.m.r. technique "sees" only the average conformation of the ring at these temperatures, but this average, we deduce, is appreciably if not completely nonchair in character in contrast to the situation when C-2 is tetrahedral.

(35) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, **86**, 1710 (1964).

Table II. Solvent Effect on Chemical Shifts of Methyl, O-Methylene, and Vinyl Protons in Selected 10-Carbethoxydecalin Derivatives

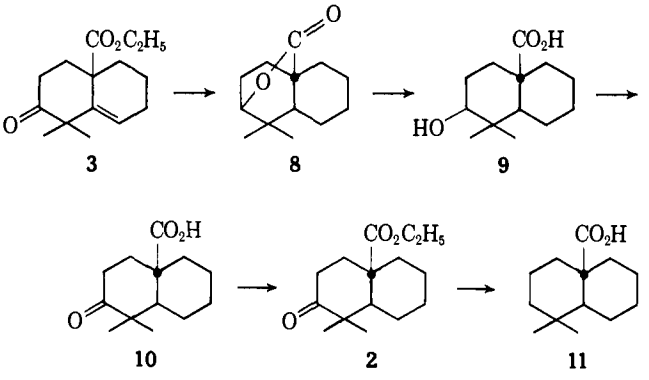
Compd., proton	Chemical shift[a] in CCl_4	$CDCl_3$	$(CD_3)_2CO$	CS_2	C_6H_6	C_5H_5N	CH_3CO_2H
5b, C-1 CH_3	61	62	62	58.5	55	59	62.5
C-1 CH_3	71	71	70.5	68	57	63	71
CH_2CH_3	75.5	75	74	73	55	66	74
OCH_2[b]	250[b]	253[b]	252[b]	247[b]	235[b]	249[b]	252.5[b]
$=CH$	357.5	369	360.5	355	370	373.5	375
6a, CH_2CH_3	76	76.5	75	74.5	53	67.5	75
OCH_2	252	254.5	253.5	248	234	252	255
$=CH$	347	355	349	342	356.5	362	361
2, C-1 CH_3	56	60	57.5	53	60	63	59.5
C-1 CH_3	61.5	66	62	58.5	68	70	64
CH_2CH_3	77.5	78	76	75	54.5	69	76.5
OCH_2	250	252	251.5	247	233.5	250	252
3, C-1 CH_3	71	75.5	73	69	71	76	75
C-1 CH_3	71	77	74.5	69	84	84	76
CH_2CH_3	71	73	71.5	69	57	66	71
OCH_2	245	248	246	241	234	246	247
$=CH$	344	349	349	342	336	346	350

[a] In c.p.s. ±1 c.p.s. downfield from internal tetramethylsilane, at 60 Mc./sec. [b] These two protons are in all instances nonequivalent, and the multiplet was not analyzed except in the CCl_4 spectrum. The figure quoted is the estimated mean of the two chemical shifts, ±2 c.p.s.

origin in differences in the populations of an assembly of molecular conformations, each of which provides different environments for the two protons, with these environments not averaging to the same value over all rapidly interconverting conformations involved.[32] Such "conformational control" was the factor originally suggested for the observed magnetic nonequivalence of the protons of a methylene group which undergoes rotation in an asymmetric environment,[16] and at least one attempt to invalidate it experimentally as an important contributing factor failed.[36] It has been pointed out, however, that in the general case one need not resort to such a conformational argument, for the two protons are fundamentally different for reasons of symmetry ("diastereomeric"), irrespective of conformer populations.[20,36] With respect to the present systems, we feel that some sort of conformational control must be at least an important contributing factor, however, for we find no satisfying rationalization of the results without recourse to it. If no conformational preferences were involved, the effect of the methyl groups would be electronic in nature. Should this be the case, as mentioned above, it would be surprising if other more anisotropic groups like the olefin were unable to induce analogous nonequivalence effects, but they do not. Furthermore it seems unlikely that the magnitude of such an electronic effect of the methyls would depend upon the nature of other substituents in the ring ($\Delta\nu_{AB}$ 4.2 c.p.s. for **4a** and 9.4 c.p.s. with similarly disposed methyls in **5c**, etc.). Thus we feel that these results show that conformational factors are in large measure responsible for the magnetic nonequivalence observed here. They do not, of course, exclude the possibility that nonconformational effects contribute to a small degree, although the magnitude of this is too small to be observed in the absence of the methyl-induced conformational effects. Nor do they eliminate the possibility that there may be systems in which conformational effects are not involved, although a convincing example is yet to be reported.

(36) G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **48**, 1112 (1962).

Synthesis of 10-Carbethoxydecalin Derivatives. In an earlier paper[13] we recorded the preparation of 10-carbethoxy-1,1-dimethyl-Δ^8-2-octalone (**3**) by methylation of 10-carbethoxy-$\Delta^{1,9}$-2-octalone (**6a**), together with our unsuccessful efforts to prepare the corresponding *trans*-fused saturated keto ester **2** by stereoselective hydrogenation of the double bond. Brown had independently studied this reduction,[37] and observed that a mixture of the *cis*- and *trans*-fused isomers of **2** results. Hence a more circuitous sequence for stereoselective preparation of the keto ester **2** was devised.



It had been observed that hydrogenation of the enone **3** over platinum in acetic acid gave rise predominantly to a single saturated lactone (**8**), which was presumed to have the *trans* configuration because it seemed likely that reduction of both the ketone and the olefin occurred from the same side of the molecule.[13] Saponification of this lactone affords the corresponding hydroxy acid (**9**). Although this hydroxy acid is quite sensitive toward relactonization,[38] it can be oxidized by Jones reagent[39] to the keto acid (**10**), and ethylation of the potassium salt of this product affords the *trans*-keto ester **2**, an oil Although the keto acid

(37) R. F. C. Brown, *Australian J. Chem.*, 17, 47 (1964).

(38) This is, incidentally, the best way to purify the lactone, which thus can be obtained in crystalline form.

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

10 exists extensively as its pseudo-acid tautomer in chloroform solution, as seen from its infrared absorption at 5.73 (lactone) as well as 5.87 μ (ketone and acid) and from the low extinction coefficient (12) of its ketonic n $\rightarrow$ π^* absorption, the ester must have the assigned normal structure since it has the expected infrared (5.79 and 5.87 μ) and ultraviolet (280 mμ, ϵ 55) spectral properties and forms normal ketone derivatives. It may be noted that the ketonic n $\rightarrow$ π^* absorptions of this keto ester and the 8,9-unsaturated analog **3** (ϵ 50)[13] are of comparable intensity, which gives further support[10] to assignment of a nonchair conformation to the enone **3**. That the saturated keto ester indeed has the same ring-fusion configuration as do the other dimethyl decalins **4a–4c,** all of which were prepared through the isomeric unsaturated keto ester **5b,**[13] was shown by Wolff–Kishner reduction[37] to the same acid, 1,1-dimethyl-*trans*-decalin-10-carboxylic acid (**11**), as was derived from them.[13]

Also in the earlier work,[13] from hydrogenation of the Δ^8-7-keto ester **5b** we isolated a by-product which was presumed to be 1,1-dimethyl-10-carbethoxy-Δ^8-octalin (**5d**) on the basis of its spectral properties. This material, obtained in less than 1% yield, was not available in sufficient quantity for further characterization. The unsaturated ester **5d** has now been prepared by conversion of the enone **5b** to its unsaturated thioketal **5c,** followed by desulfurization of the latter with deactivated Raney nickel.[40] This not only proved to be a useful source of the olefinic ester, but serves to confirm the earlier structural assignment, for the two samples were identical. It is useful to note that substantial amounts of the enone **5b** were regenerated in the desulfurization reaction unless the nickel was thoroughly washed to remove acetone which remained from the deactivation process. This suggests that the enone was formed through an exchange of the thioketal with acetone, and emphasizes the need of careful preparation of the nickel if high yields of desulfurized products are to be obtained.

The other three new compounds examined in the course of this work, the thioketals **5e, 6d,** and **6e,** were prepared by the usual boron trifluoride–ethanedithiol technique.[41] Their structures were attested by infrared and n.m.r. spectra. In particular, the unsaturated thioketal **6e** clearly corresponded to the assigned structure rather than a $\Delta^{8,9}$ derivative (resulting from double bond migration during thioketalization) because the n.m.r. spectrum showed the olefinic proton resonance as a somewhat broadened singlet rather than the triplet characteristic of spin coupling of such an olefinic proton to an adjacent methylene.

Experimental[42]

Nuclear Magnetic Resonance Spectra. Spectra were obtained from dilute (*ca.* 10%) solutions with tetramethylsilane as internal standard using a Varian A-60 spectrometer or a Varian DP-60 spectrometer operating at 60 Mc./sec. and equipped with a Model 3506 flux stabilizer. Band positions in DP-60 spectra were determined by the audio side-band technique, the average of a minimum of ten sweeps, five in each direction, being accepted. Separation of adjacent peaks in the ABC_3 multiplets ascertained in this manner were reproducible to $\pm$0.2 c.p.s. or better. Theoretical spectra were computed using the program described by Bothner-By and Naar-Colin[43] with an IBM 706 computer. In choosing trial parameters (chemical shifts and coupling constants) it was assumed that the vicinal and geminal proton coupling constants are of opposite sign,[15] and that both vicinal coupling constants are equal. Line positions in spectra computed from the parameters which best fit the observed spectrum agreed within $\pm$0.2 c.p.s. with the observed positions.

2β-Hydroxy-1,1-dimethyl-trans-decalin-10-carboxylic Acid Lactone (**8**). Hydrogenation of 10-carbethoxy-1,1-dimethyl-Δ^8-2-octalone (**3,** 80% pure according to g.l.c.[13]) was carried out at 75° in glacial acetic acid, using four times the relative total amount of platinum oxide previously described.[13] Under these conditions reduction was complete after 1.5 hr. at 3 atm. The crude distilled product contained approximately 20% of contaminants according to g.l.c. assay A pure sample was obtained by heating 100 mg. (0.48 mmole) of the purified hydroxy acid **9,** m.p. 173°, for 12 hr. under reflux in 25 ml. of 95% ethanol containing 2 drops of concentrated hydrochloric acid. The lactone was extracted into ether, washed with 5% potassium hydroxide, treated with activated charcoal, and isolated as a clear oil by evaporation of the ether. Distillation at 58–60° (1.5 mm.) afforded a colorless oil which crystallized upon refrigeration. An analytical sample, m.p. 55–56.6°, was collected by g.l.c.; $\lambda_{max}^{CHCl_3}$ 5.74 μ; n.m.r. (CCl_4) τ 6.07 (t), 8.93 (s), and 8.98 (s).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.69; H, 9.64.

2β-Hydroxy-1,1-dimethyl-trans-decalin-10-carboxylic Acid (**9**). A mixture of 9.0 ml. of the once-distilled hydrogenation product (80% lactone **8** according to g.l.c.) and 6.0 g. of potassium hydroxide in 50 ml. of water was refluxed for 12 hr., at which point the lactone had all dissolved. The hydroxy acid was isolated by chilling the solution, slowly acidifying with concentrated hydrochloric acid, and filtration. The product was washed thoroughly with cyclohexane and then recrystallized thrice from ethyl acetate to afford 4.8 g. (60%) of hydroxy acid as a fine white powder, m.p. 173°, λ_{max}^{KBr} 2.89 and 5.90 μ.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 69.00; H, 9.80. Found: C, 68.62; H, 9.53.

1,1-Dimethyl-trans-2-decalone-10-carboxylic Acid (**10**). Following Djerassi's[44] adaptation of the Jones oxidation, 0.8 ml. of 7.88 *N* chromium trioxide reagent was added dropwise to a cold (0–3°) solution of 750 mg. (3.3 mmoles) of hydroxy acid **9,** m.p. 173°, in 200 ml. of acetone. The mixture was diluted with water and extracted with ether which was extracted twice with 5% potassium hydroxide. The alkaline extract

(40) G. B. Spero and A. W. McIntosh, *J. Am. Chem. Soc.*, 70, 1907 (1948).

(41) L. F. Fieser, *ibid.*, 76, 1945 (1954).

(42) Infrared spectra were obtained on Perkin-Elmer Models 21 and 137 spectrophotometers and ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Microanalyses were by Alfred Bernhardt, Mulheim, Germany. Melting points were taken in open capillary tubes, and are corrected for stem exposure. N.m.r. spectra are described in the preparative sections by the abbreviations (s) for singlet, (d) for doublet, (t) for triplet, and (m) for multiplet.

(43) A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, 83, 231 (1961). We are extremely grateful to Dr. Bothner-By for providing us with the program.

(44) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).

was acidified with hydrochloric acid and extracted with ether, which after being dried and evaporated left the keto acid **10** as a creamy oil. This was crystallized and recrystallized from *n*-hexane to afford 365 mg. (49%) of colorless prisms: m.p. 88.5°; $\lambda_{max}^{CHCl_3}$ 2.8–3.1 (broad), 5.73, and 5.89 μ; $\lambda_{max}^{95\%\ EtOH}$ 287 mμ (ϵ 12); n.m.r. (CCl_4) τ 2.27 (broad), 8.92 (s), and 9.04 (s).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.57; H, 9.29.

10-Carbethoxy-1,1-dimethyl-trans-2-decalone (**2**). A solution of 336 mg. (0.67 mmole) of the keto acid **10**, m.p. 88.5°, and 59 mg. (1.05 mmole) of potassium hydroxide in 16.8 ml. of ethanol was refluxed for 10 min. Excess ethyl iodide (1.21 ml.) was added to the cooled mixture, and reflux was resumed for 9 hr. The mixture was diluted with water and extracted with ether, which was washed with 10% sodium thiosulfate and 5% potassium hydroxide. Evaporation of the ether left 192 mg. (52%) of colorless oil which distilled at 75° (0.5 mm.) to afford 186 mg. of colorless keto ester in greater than 95% purity as indicated by g.l.c. An analytical sample was collected by g.l.c.: $\lambda_{max}^{95\%\ EtOH}$ 280 mμ (ϵ 55); $\lambda_{max}^{CCl_4}$ 5.79 and 5.87 μ; n.m.r. (CCl_4) τ 5.83 (q), 8.73 (t), 8.98 (s), and 9.07 (s).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.62; H, 9.58.

1,1-Dimethyl-trans-decalin-10-carboxylic Acid (**11**). The Wolff–Kishner procedure was carried out as described by Brown[37] for a mixture of *cis*- and *trans*-fused keto esters. From 100 mg. (0.40 mmole) of keto ester **2** (95% pure according to g.l.c.) was obtained 70 mg. (84%) of crude oily acidic product. Fractional sublimation at 51° (1.5 mm.) afforded 51 mg. (62%) of colorless prisms, m.p. 95–98°, which showed melting point and mixture melting point behavior identical with an authentic sample.[13] The infrared spectrum was superimposable upon that of the authentic sample.

10-Carbethoxy-1,1-dimethyl-7,7-ethylenedithio-Δ^8-octalin (**5c**). Following the procedure of Sondheimer and Wolfe,[45] 0.4 ml. of freshly distilled boron fluoride etherate was added to a solution of 1.08 g. (0.00432 mole) of 10-carbethoxy-1,1-dimethyl-Δ^8-7-octalone (**5b**), m.p. 68.5–73°,[13] in 1 ml. of ethanedithiol. After the rapid exothermic reaction had subsided, precipitation of the thioketal was completed by addition of 3 ml. of methanol and cooling. The precipitate was collected, washed with methanol, and recrystallized from *n*-hexane to afford 1.03 g. (73%) of colorless cubes, m.p. 116–116.5°; $\lambda_{max}^{CHCl_3}$ 5.83 and 6.14 μ; n.m.r. (CCl_4) τ 4.25 (s), 5.84 and 6.00 (m), *ca.* 6.68 (m), 8.73 (t), 8.87 (s), and 9.10 (s).

Anal. Calcd. for $C_{17}H_{26}O_2S_2$: C, 62.56; H, 8.03; S, 19.64. Found: C, 62.38; H, 7.86; S, 19.49.

10-Carbethoxy-1,1-dimethyl-Δ^8-octalin (**5d**). About 2 teaspoons of W-2 Raney nickel was deactivated[40] by treatment with refluxing acetone (distilled from potassium permanganate and potassium carbonate) for 4.5 hr. This nickel was washed with three 40-ml. portions of absolute ethanol, the first wash being conducted by refluxing the ethanolic suspension for 5 min. To this nickel suspended in 35 ml. of absolute ethanol was added 0.704 g. (0.00216 mole) of the thioketal **5c**, m.p. 116°, and the mixture was refluxed for 14 hr. The nickel was removed by centrifugation and washed well with ethanol, and the crude unsaturated ester **5d** was obtained by evaporation of the ethanol. G.l.c. of this showed it to be contaminated by about 10% of enone **5b**, which was removed by chromatography over alumina, pure unsaturated ester **5d** being eluted in early cyclohexane fractions. On vacuum distillation in a micro apparatus this came over as a colorless oil, b.p. 107° (bath temperature) at 2 mm.; $\lambda_{max}^{CHCl_3}$ 5.84 and 6.24 μ; n.m.r. (CCl_4) τ 4.38 (t), 5.87 and 6.00 (m), 8.77 (t), 8.95 (s), and 9.13 (s).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.71; H, 10.25.

10-Carbethoxy-1,1-dimethyl-2,2-ethylenedithio-Δ^8-octalin (**5e**). Following the general Fieser procedure,[41] 5 ml. of boron fluoride etherate was added to a solution of 5 g. (0.02 mole) of 10-carbethoxy-1,1-dimethyl-Δ^8-2-octalone (**3**) (once distilled, *ca.* 80% pure by g.l.c[13]) in 5 ml. of ethanedithiol. Heat was evolved. After being allowed to stand for 120 hr. at room temperature, the mixture was dissolved in 25 ml. of benzene and chromatographed on 50 g. of Merck alumina which was overlayed with a mixture of 30 g. of sand and 15 g. of mercuric oxide covered with 15 g. of alumina. Elution with 250 ml. of benzene gave 6.70 g. (100%) of pale yellow oil, λ_{max}^{film} 5.6 (weak), 5.8, and 6.1 μ (weak); n.m.r. ($CDCl_3$) τ 4.15 (t), 5.87 and 6.00 (m), 6.84 (s), 8.60 (s), 8.74 (t), and 8.88 (s).

Anal. Calcd. for $C_{17}H_{26}O_2S_2$: C, 62.53; H, 8.03; S, 19.64. Found: C, 61.42; H, 7.58; S, 19.71.

10-Carbethoxy-2,2-ethylenedithio-trans-decalin (**6d**). Following the general Fieser procedure[41] a mixture of 4.1 g. of 10-carbethoxy-*trans*-2-decalone[29] (**6b**, 96% pure according to g.l.c. assay), 5 ml. of ethanedithiol, and 5 ml. of boron fluoride etherate was held at room temperature for 24 hr., poured into 25 ml. of saturated aqueous sodium chloride solution, extracted with ether, dried over sodium sulfate, and concentrated to produce 8.2 g. of foul-smelling oil. Crystallization and recrystallization from methanol afforded the pure thioketal **6d**, m.p. 46–47.5°; $\lambda_{max}^{CHCl_3}$ 5.81 μ; n.m.r. (CCl_4) τ 5.89 (q), 6.78 (s), and 8.76 (t).

Anal. Calcd. for $C_{15}H_{24}O_2S_2$: C, 59.96; H, 8.05; S, 21.34. Found: C, 60.43; H, 7.87; S, 21.20.

10-Carbethoxy-2,2-ethylenedioxy-trans-decalin (**6c**). The ketal was prepared as described by Dreiding and Tomasewski,[28] and was distilled in a Hickman still at 1 mm., bath temperature 110–115°, to obtain a pure sample with $n^{27}D$ 1.4820 (reported[28] b.p. 115–122° (0.2 mm.), $n^{23}D$ 1.4850); λ_{max}^{film} 5.80 μ; n.m.r. (CCl_4) 5.89 (q), 6.18 (s), and 8.76 τ (s).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.26; H, 8.61.

10-Carbethoxy-2,2-ethylenedithio-$\Delta^{1,9}$-octalin (**6e**). According to the general procedure of Sondheimer and Wolfe,[45] a mixture of 1.0 ml. of 10-carbethoxy-$\Delta^{1,9}$-2-octalone[29] (80% pure according to g.l.c.), 1.0 ml. of ethanedithiol, and 1.0 ml. of boron fluoride etherate was held at 0° for 35 min. Water (0.9 ml.) was added, the mixture was partitioned between water and ether, and the ether extracts were washed with 5% potassium hydroxide and saturated sodium chloride. Evaporation of the ether left the thioketal as a yellow oil which was distilled at 160–161° (0.75 mm.) to

(45) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

afford material of analytical purity in 80% yield; $\lambda_{max}^{CCl_4}$ 5.80 μ; n.m.r. (CCl_4) τ 4.83 (s), 5.17 (q), 7.92 (m), and 8.75 (t).

Anal. Calcd. for $C_{15}H_{22}O_2S_2$: C, 60.36; H, 7.43, S, 21.49. Found: C, 60.33; H, 7.39; S, 21.45.

Acknowledgment. We wish to express thanks to the National Institutes of Health, U. S. Public Health Service, for a grant (A4215) in support of this work, and the National Science Foundation for stipends for D. L. D., L. F., and V. L. S.[2] We are also grateful to Mr. A. O. Clouse for assistance with some of the n.m.r. determinations, and Mr. Steven W. Young of the Indiana University Research Computing Center for assistance with the computations.

General Methods of Synthesis of Indole Alkaloids. IV. A Synthesis of *dl*-Eburnamonine[1,2]

Ernest Wenkert[3] and Börje Wickberg

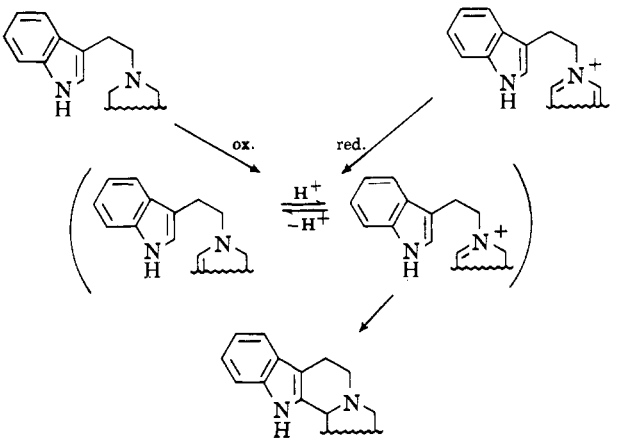
Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa. *Received November 2, 1964*

The hydrogenation of 1-[β-(3-indolyl)ethyl]-3-acetylpyridinium bromide to a tetrahydropyridine derivative is described. Transformation of the product into the alkaloid eburnamonine is discussed. The stereochemistry of the alkaloid and its possible biosynthesis are portrayed.

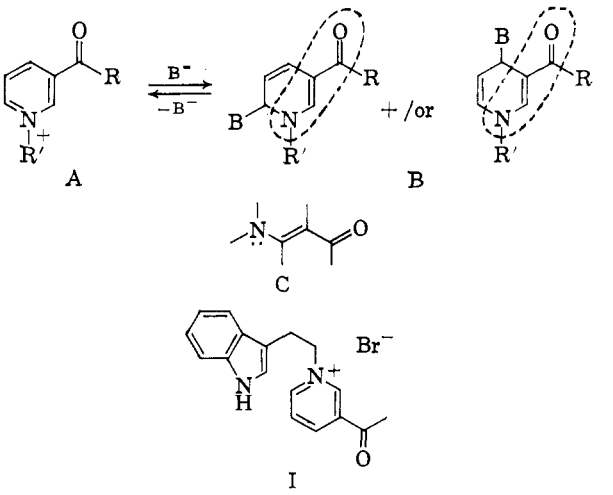
Previous reports[2,4] from this laboratory have illustrated three new methods of synthesis of indole alkaloids of the tetrahydrocarboline type, which were based on oxidative or reductive cyclizations of indole derivatives *via* Δ^1- and Δ^2-piperideine intermediates (*cf.* Chart I). The reductive cyclization scheme had involved hydride reductions of N-alkylpyridinium salts.[2,5] As a follow-up of this method a search for a scheme based on partial hydrogenation of the pyridinium salts was undertaken.

Since catalytic hydrogenation of N-alkylpyridinium salts yields N-alkylpiperidines,[6] it was clear from the beginning of our study that only a special experimental design might permit hydrogenation stoppage at the Δ^1- (or Δ^2-) piperideine stage. On the assumption that the presence of a pyridine substituent which would stabilize the double bond of the piperideine intermediate, while itself being impervious to hydrogen attack, might cause the desired interruption of the hydrogenation, a β-acyl group was chosen as the stabilizing substituent. Furthermore, reduction in alkaline medium was considered another important prerequisite of the reaction, since N-alkyl-β-acyl-

Chart I



pyridinium salts (A) would be expected to be transformed in this environment to compounds B which already possess the all-important vinylogous amide chromophore C (see dotted lines in B), on whose inertness to hydrogenation success of the reaction depended. The salt I, prepared from β-acetylpyridine and tryptophyl bromide,[2] was selected as the model for our study.



(1) This work was first presented as part of a lecture by E. W. at the 17th National Organic Chemistry Symposium of the American Chemical Society at Bloomington, Ind., June 26–29, 1961. The authors acknowledge gratefully herewith the financial support of the work by the U. S. Department of Health, Education, and Welfare (MY-5815) and the Swedish Natural Science Research Council.

(2) Part III: E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

(3) Department of Chemistry, Indiana University, Bloomington, Ind.

(4) (a) E. Wenkert and J. Kilzer, *J. Org. Chem.*, **27**, 2283 (1962); (b) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

(5) For other recent syntheses of tetrahydrocarbolines by reductive cyclization, *cf.* (a) J. Thesing and W. Festag, *Experientia*, **15**, 127 (1959); (b) K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3066 (1963); (c) J. H. Supple, D. A. Nelson, and R. E. Lyle, *Tetrahedron Letters*, 1645 (1963).

(6) *Cf.*, *inter alia*, K. Hohenlohe-Oehringen, *Monatsh.*, **93**, 586 (1962).