(no observable ultraviolet absorption maximum corresponding to 367 mμ C.D. extremum and corresponding O.R.D. Cotton effect).

Experimental[28]

Cholestan-3-one (I), C.D. (Fig. 2) in methanol: *c* 1.25 (327–240 mμ), $[\theta]_{292}$ +4230; ultraviolet in methanol: $\lambda^{\max}_{279}$ log ε 1.76.

Coprostan-3-one (II), C. D. (Fig. 2) in methanol: *c* 2.27 (330–245 mμ), $[\theta]_{291}$ −1455.

Cholestan-1-one (III), C. D. (Fig. 2) in methanol: *c* 1.81 (340–240 mμ); $[\theta]_{301}$ −1270, $[\theta]_{250}$ +80; ultraviolet in methanol: $\lambda^{\max}_{285}$ log ε 1.83.

Cholestan-7-one (IV), C.D. (Fig. 2) in methanol: *c* 1.71 (330–245 mμ), $[\theta]_{291}$ −2320; O.R.D. (Fig. 1) in methanol, *c* 0.106 (410–235 mμ): $[\phi]_{366}$ −2290°, $[\phi]_{262}$ +640°.

5α-Pregnan-20β-ol methyl xanthate (V), (Fig. 3) C.D. in isoöctane: *c* 1.015 (400–305 mμ), $[\theta]_{375}$ + 6190; ultraviolet in isoöctane: $\lambda^{\max}_{354}$ log ε 1.72, $\lambda^{\max}_{276}$ log ε 4.03.

Methyl-α-D-glucopyranoside-6-(S-benzyl)-xanthate (VI) (Fig. 4) C.D. in dioxane: *c* 3.50 (395–315 mμ), $[\theta]_{359}$ −420; ultraviolet in dioxane: $\lambda^{\max}_{354}$ log ε 1.81, $\lambda^{\max}_{281}$ log ε 4.08.

D-(−)-**Mandelic acid ethyl dithiocarbonate** (VII), (Fig. 5) C.D. in dioxane: *c* 0.954 (410–320 mμ), *c* 0.191 (320–310 mμ), *c* 0.00954 (310–260 mμ); $[\theta]_{386}$ + 150, $[\theta]_{354}$ −2520, $[\theta]_{289}$ −10000; O.R.D. in dioxane, *c* 0.1065 (420−320 mμ); $[\phi]_{368}$ −4030°, $[\phi]_{336}$ −1825°; ultraviolet in dioxane: $\lambda^{\max}_{354}$ log ε 1.88, $\lambda^{\max}_{283}$ log ε 4.23.

D-(−)-**Lactic acid ethyl dithiocarbonate** (VIII), (Fig. 6) C.D. in methanol: *c* 0.426 (430–315 mμ), *c* 0.00426 (260–232 mμ); $[\theta]_{393}$ +50, $[\theta]_{355}$ −1010; ultraviolet in methanol: $\lambda^{\max}_{355}$ log ε 180, $\lambda^{\max}_{279}$ log ε 4.14, $\lambda^{\max}_{227}$ log ε 3.88.

N-Dithiocarbethoxy-L-alanine (IX), (Fig. 7) C.D. in methanol: *c* 0.738 (395–320 mμ), *c* 0.147 (320–300 mμ); *c* 0.00738 (300–260 mμ); $[\theta]_{340}$ +2580, $[\theta]_{275}$ +6100; ultraviolet in methanol: $\lambda^{\text{shoulder}}_{325\text{-}35}$ log ε 1.87, $\lambda^{\max}_{273}$ log ε 4.04, $\lambda^{\max}_{252}$ log ε 4.04.

N-Dithiocarbomethoxy-L-proline (X), (Fig. 8) C.D. in methanol: *c* 0.936 (390–315 mμ), *c* 0.187 (315–300 mμ); *c* 0.00936 (315–285 mμ); $[\theta]_{336}$ +5120; ultraviolet in methanol: $\lambda^{\text{shoulder}}_{320\text{-}30}$ log ε 1.80, $\lambda^{\max}_{275}$ log ε 4.16, $\lambda^{\max}_{250}$ log ε 4.05.

N-Dithiocarbethoxy-D-aspartic acid (XI), (Fig. 9) C.D. in dioxane: *c* 1.15 (370–320 mμ); *c* 0.115 (320–295 mμ); *c* 0.0115 (295–260 mμ); $[\theta]_{340}$ −2500, $[\theta]_{275}$ + 5600; O.R.D. in dioxane: *c* 0.119 (400–320 mμ), *c* 0.0119 (320–290 mμ); $[\phi]_{356}$ −760°, $[\phi]_{310}$ +5980°; ultraviolet in dioxane: $\lambda^{\max}_{339}$ log ε 1.81, $\lambda^{\max}_{274}$ log ε 4.37, $\lambda^{\max}_{251}$ log ε 4.36.

N-Thionocarbethoxy-L-hydroxyproline (XII), (Fig. 10) C.D. in dioxane: *c* 0.78 (330–284 mμ), $[\theta]_{302}$ −780; O.R.D. in dioxane: *c* 0.112 (400–300 mμ), *c* 0.0224 (300–270 mμ); $[\phi]_{315}$ −1130°, $[\phi]_{285}$ +770°; ultraviolet in dioxane: $\lambda^{\text{shoulder}}_{295}$ log ε 2.20, $\lambda^{\max}_{248}$ log ε 4.29.

N-Thionocarbethoxy-L-phenylalanine (XIII), (Fig. 11) C.D. in dioxane: *c* 0.585 (320–275 mμ), *c* 0.0585 (275–260 mμ); $[\theta]_{297}$ +860; ultraviolet in dioxane: $\lambda^{\text{shoulder}}_{285\text{-}95}$ log ε ∼ 210, $\lambda^{\max}_{245}$ log ε 4.14.

1,5-Cyclotrimethylene-3-phenyl-2-thiohydantoin (XIV), (Fig. 12) C.D. in dioxane: *c* 0.618 (365–305 mμ), *c* 0.309 (305–295 mμ), *c* 0.00309 (295–240 mμ); $[\theta]_{328}$ +3740, $[\theta]_{277}$ − 42000, $[\theta]_{252}$ +50000; O.R.D. in dioxane: *c* 0.108 (400 − 290 mμ), $[\phi]_{345}$ + 1330°; ultraviolet in dioxane: $\lambda^{\max}_{327}$ log ε 1.96, $\lambda^{\max}_{272}$ log ε 4.24.

5-Methyl-3-phenyl-2-thiohydantoin (XV), (Fig. 13) C.D. in methanol: *c* 0.67 (355–305 mμ), *c* 0.335 (305–298 mμ); $[\theta]_{321}$ +760; ultraviolet in methanol: $\lambda^{\text{shoulder}}_{305\text{-}315}$ log ε ∼2.25, $\lambda^{\max}_{265}$ log ε 4.24.

(−)-(R)-**Hydratropyl-morpholinothiocarbamide** (XVI), (Fig. 14) C.D. in dioxane: *c* 0.290 (400–330 mμ), *c* 0.0425 (330–315 mμ), *c* 0.0084 (315–270 mμ), *c* 0.00116 (270–235 mμ); $[\theta]_{349}$ + 10400, $[\theta]_{315}$ +1700, $[\theta]_{288}$ +15500, $[\theta]_{243}$ − 50000; O.R.D.[29] in dioxane: *c* 0.110 (410–315 mμ), *c* 0.0022 (315–260 mμ); $[\phi]_{368}$ +4800°, $[\phi]_{322}$ 8600°, $[\phi]_{295}$ + 100°; ultraviolet in dioxane: $\lambda^{\max}_{343}$ log ε 2.59, $\lambda^{\max}_{285}$ log ε 4.12.

(+)-(S)-α-(2-**Naphthyl)-propionyl-morpholinothiocarbamide** (XVII), (Fig. 15) C.D. in dioxane: *c* 0.655 (400–330 mμ), *c* 0.131 (330–310 mμ), *c* 0.00524 (310-265 mμ); $[\theta]_{249}$ − 7450, $[\theta]_{315}$ O, $[\theta]_{289}$ −40000; O.R.D. in dioxane: *c* 0.82 (420–305 mμ); $[\phi]_{360}$ −3500°, $[\theta]_{320}$ + 5250°; ultraviolet in dioxane: $\lambda^{\max}_{343}$ log ε 2.55, $\lambda^{\max}_{279}$ log ε 4.21.

(+)−**1,2-Dithiane-3**,6-dicarboxylic acid (XVIII), (Fig. 16) C.D. in dioxane: *c* 0.300 (360–270 mμ), *c* 0.150 (270–250 mμ); $[\theta]_{280}$ +3450; O.R.D. in dioxane: *c* 0.021 (400–270 mμ), $[\phi]_{300}$ +3580°; ultraviolet in dioxane: $\lambda^{\text{shoulder}}_{270\text{-}90}$ log ε ∼ 2.4.

(+)-1,**2-Diselenane-3**,6-dicarboxylic acid (XIX), (Fig. 17) C.D. in dioxane: *c* 0.900 (420–318 mμ), *c* 0.090 (318–265 mμ), *c* 0.018 (265–240 mμ); $[\theta]_{351}$ +4740, $[\theta]_{277}$ −7900), $[\theta]_{249}$ + 16200; O.R.D. in dioxane: *c* 0.0198 (400–270 mμ, *c* 0.0232 (270–240 mμ); $[\phi]_{390}$ + 2500°, $[\phi]_{313}$ −6200°, $[\phi]_{255}$ +15600°; ultraviolet in dioxane: $\lambda^{\max}_{340}$ log ε 2.38, $\lambda^{\text{shoulder}}_{265\text{-}75}$ log ε ∼ 2.85, $\lambda^{\text{shoulder}}_{230\text{-}40}$ log ε ∼ 3.35.

6,8-Thioctic Acid (**XX**) (Fig. 18). (−)-**Antipode**, C.D. in dioxane: *c* 1.55 (425–355 mμ), *c* 0.18 (355–285 mμ), *c* 0.045 (285–250 mμ); $[\theta]_{367}$ −230, $[\theta]_{320}$ +460, $[\theta]_{265}$ −295; O.R.D. in dioxane: *c* 0.155 (420–370 mμ), *c* 0.076 (370–300 mμ), *c* 0.019 (300–250 mμ); $[\phi]_{386}$ −400°, $[\phi]_{336}$ −156°; ultraviolet in dioxane: $\lambda^{\max}_{328}$ log ε 2.16, $\lambda^{\text{shoulder}}_{255\text{-}70}$ log ε ∼ 2.24.

(+)-**Antipode**, C.D. in dioxane: *c* 1.61 (425–360 mμ), *c* 0.644 (360–285 mμ), *c* 0.322 (285–255 mμ); $[\theta]_{365}$ +255, $[\theta]_{321}$ −520, $[\theta]_{266}$ +240; O.R.D. in dioxane: *c* 1.61 (420–390 mμ), *c* 0.0644 (390–300 mμ), *c* 0.0322 (300–260 mμ); $[\phi]_{380}$ +420°, $[\phi]_{340}$ +160°.

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(28) All circular dichroism measurements were performed with a Baird–Atomic/Jouan Dichrograph, utilizing dilutions so as to maintain the slit width below 1.3 mm. Molecular ellipticities [θ] were calculated as outlined in ref. 11, the concentration *c* being defined in g./l. Optical rotatory dispersion results (peaks and troughs in terms of molecular rotation [φ]) are listed in the Experimental section (*c* being defined as g./100 cc.) only for those substances where new measurements were performed, in which case an automatically recording Nippon-Bunko (Japan Spectroscopic Manufacturing Co., Ltd.) spectropolarimeter was utilized.

(29) The lower amplitude observed in methanol solution (ref. 23) has been confirmed, thus demonstrating a significant solvent effect.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

Conformational Analysis. XXXII. The Conformation of Ring A in 2,2- and 4,4-Dimethyl-3-ketosteroids[1,2]

BY NORMAN L. ALLINGER AND MARGARET A. DAROOGE[2b]

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Dipole moment and rotatory dispersion data for a series of 3-ketosteroids containing the 2,2- or 4,4-*gem* dimethyl group have shown that with these compounds ring A does not exist as a regular chair or as a boat, but rather has a flattened chair structure. Similarly, it was shown that in the analogous 4,4-dimethyl-19-nor-3-ketone, ring A is an ordinary chair.

A determination of the conformation of ring A in 2,2-dimethyl and 4,4-dimethyl substituted 3-keto-5α-steroids was of particular interest because of the widespread occurrence of this type of structure in nature. Recently boat forms for ring A in similar compounds have been proposed in a number

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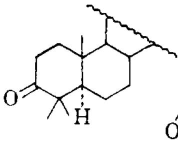
(1) (a) Paper XXXI, N. L. Allinger, L. A. Freiberg and S. Hu, *J. Am. Chem. Soc.*, **84**, 2836 (1962). (b) A brief description of a portion of the present work has been published in *Tetrahedron Letters*, 676 (1961).

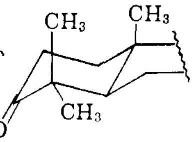
(2) (a) This work was supported in part by Grant No. A-5836 from the Public Health Service, National Institutes of Health. (b) Predoctoral National Institutes of Health Fellow, Division of Medical Sciences, 1960–1962.

of cases.[3-8] Numerical values have been recently reported for the enthalpies of two quantities related to this question, namely the 1,3-dimethyl interaction[9] (3.7 kcal./mole) and the chair → boat transformation of a cyclohexanone[10] (2.8 kcal./mole). Other interactions must also be considered, but a first approximation would seem to indicate that ring A in compounds I and VI might be more comfortable in boat forms than as undeformed chairs (II and VII).

An examination of models indicates that the boat form under consideration has a certain amount of flexibility, and if I is considered first, the most stable arrangement of the boat may be either of two extremes, III or IV, or it may be somewhere in between. Another possibility must also be considered, which is V. Here C-3 is moved upward (relative to II) toward the plane defined by carbons 1, 2, 4 and 5.[11] Such a structure is similar to the transition state between boat and chair forms, which for cyclohexanone can be estimated roughly as the sum of two "half-eclipsed" ethanes (3 kcal.) plus two acetone barriers (perhaps 2 kcal.).[12] The angular distortion appears to be quite small and is neglected. The energy of this distorted chair (*ca.* 5 kcal.) is therefore comparable in magnitude to the other possibilities and this form must also be considered.



I



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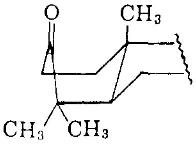
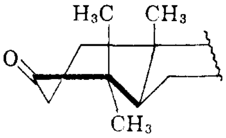
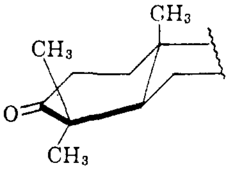


III



IV



V

The non-chair structure for 3-ketones is commonly represented as III.[3-8] A general objection to this arrangement in this case is that it contains two eclipsed ethanes (6 kcal.), while a boat of type IV contains but one (3 kcal.). Offsetting this difference, IV has a 1,3-diaxial dimethyl interaction which III is lacking. Something in between III and IV can probably minimize the total energy of the boat form by having each of these unfavorable effects present to a small degree.

In an effort to obtain a decision as to the conformational structure of ring A, a series of dipole moments was measured for the compounds listed in Table I. Compounds 1 through 4 and 7 through 9 were all obtained by standard methods and had properties in good agreement with the literature values. Compounds 5 and 6 were obtained by oxidation of the known 17-alcohols.[13,14]

TABLE I

DIPOLE MOMENTS OF VARIOUS KETONES IN BENZENE SOLUTION AT 25°

	Compound	Moment, D.
(1)	Cholestan-3-one	3.01[15]
(2)	Androstan-17-one	2.98
(3)	Androstan-3,17-dione	2.94[16]
(4)	4,4-Dimethylcholestan-3-one[17]	2.78
(5)	4,4-Dimethyl-19-nor-androstan-3,17-dione[13]	2.68
(6)	4,4-Dimethylandrostan-3,17-dione[14]	2.28
(7)	19-Norandrostan-3,17-dione	2.90
(8)	2,2-Dimethylcholestan-3-one	2.85
(9)	2,2-Dimethylandrostan-3,17-dione	2.64

The moments of 1 and 2 gave the group moments of 3. A calculated value for the resultant moment of the latter was arrived at by projecting a Dreiding model of the molecule into a coördinate system, and determining the angle between the carbonyl groups and the resultant moment by standard trigonometric methods. It is estimated that the angle between the dipoles could be determined on the models to within 2 or 3° which gave errors of 0.1–0.2 D. in the calculated moments. The moment calculated for 3 was 2.82 D., and the experimental value is 2.94 D.; hence the model seems to portray the system to within the accuracy of measurement. As a check, the moment of 7 was determined and found to be 2.90 D., within experimental error of the value found for 3.

The presence of the 4,4-dimethyl grouping lowers the moment of the 3-ketone somewhat (from 3.01 in 1 to 2.78 in 4). Using the group moments from 2 and 4, the moment of 5 was calculated, assuming a chair form. This assumption seems justified since there is no 1,3-diaxial dimethyl interaction. Here again the calculated (2.69 D.) and the experimental (2.68 D.) values are in good agreement.

Compound 6 was then examined. The angle between the dipoles of the ordinary chair was as for 3 and 5, 124° (Table II). For boat IV this angle was measured as slightly smaller (121°),

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[3] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957).

[4] F. Sondheimer, Y. Klibansky, Y. M. Y. Haddad, G. H. R. Summers and W. Klyne, *ibid.*, 767 (1961).

[5] C. Djerassi, N. Finch, R. C. Cookson and C. W. Bird, *J. Am. Chem. Soc.*, **82**, 5488 (1960).

[6] D. T. Cropp, B. B. Dewhurst and J. S. E. Holker, *Chemistry & Industry*, 209 (1961).

[7] J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.*, 464 (1961), and private communication.

[8] J. Lehn, J. Levisalles and G. Ourisson, *Tetrahedron Letters*, 682 (1962).

[9] N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

[10] N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961).

[11] In order to carry out numerical calculations, it was assumed that in form V (and also form X) these carbons were as near as possible to being in the same plane. This assumption is not exactly true (*vide infra*).

[12] J. D. Swalen and C. C. Costain, *J. Chem. Phys.*, **31**, 1562 (1959).

[13] A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 424 (1959).

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

[15] N. L. Allinger, H. Blatter, M. A. DaRooge and L. A. Freiberg, *ibid.*, **26**, 2550 (1961).

[16] H. R. Nace and R. B. Turner, *J. Am. Chem. Soc.*, **75**, 4063 (1953), reported a dipole moment of 3.1 D for this compound. Since they did not account for atomic polarization in calculating the moment, their value is slightly higher than ours.

[17] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958).

TABLE II

DIPOLE ANGLES AND MOMENTS FOR POSSIBLE STRUCTURES OF 6

Structure	Angle, °	μcalcd., D.
II	124	2.69
III	110	3.30
IV	121	2.82
V	131	2.38

while III has a dipolar angle of only 110°. These are the extremes of the flexible form, and any angle between these limits is in principle possible. The calculated moment of any boat form then is predicted to be higher than that of II. The experimentally determined moment of 6 was, however, only 2.28 D., much smaller than that calculated for the chair, and well outside of the range defined by the flexible form. It may be noted that while the calculation of resultant moments from models is somewhat inaccurate, the qualitative experimental result here is unambiguous. Thus any boat form for ring A requires that the moment of 6 be increased over that of 5. The observed difference is small, but the conclusion necessary is that neither the regular chair, nor any arrangement of the flexible form, nor any mixture of these forms can yield the observed result.

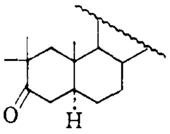
A structure similar to the flattened form V appears to be the only arrangement which will lower the calculated resultant moment. The value calculated for this structure is 2.38 D., within experimental error of the measured value.

The near-planar form V should have the angle between C-2 and C-4 expanded slightly above its normal value. Such a bond angle expansion has previously been detected[18] by the shift in carbonyl frequency, the relationship having been suggested by Halford.[19] In the present work the carbonyl frequencies of 1, 4 and of 4,4-dimethyl-19-nor-androstan-17β-ol-3-one were measured in chloroform solution. The latter showed absorption at 1706 cm.$^{-1}$, as did 1, while compound 4 showed the predicted decrease to 1699 cm.$^{-1}$. Such shifts in carbonyl frequency have been observed in similar compounds by earlier workers.[20,21]

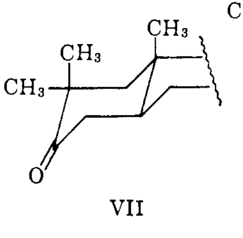
The infrared spectrum of 6 was run, both in carbon tetrachloride solution, and as a mull. No bands could be detected in solution which were not present in the solid, although there were some changes in the relative intensities of a few bands. With a complicated molecule such a result is not definitive, but it suggests that the molecule has a single conformation.

The structure of ring A in 6 which best fits both the infrared and dipole moment data is not a boat or simple chair, nor any mixture of the two, but rather a deformed or flattened chair.

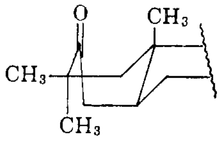
Because of the unusual results obtained from the studies of the 4,4-dimethyl compounds, it was thought that studies of the 2,2-dimethyl substituted steroids might also prove to be interesting, and the dipole moments of a series of the latter compounds were also examined. An examination of a Dreiding stereomodel of 2,2-dimethylcholestan-3-one indicated that besides the ordinary chair form VII, the conformations VIII, IX and X had to be considered. The ordinary chair form VII was again unlikely because of the 1,3-dimethyl interaction between the C-2 axial methyl group and the C-10 angular methyl. It also appeared that the form IX was not likely because of the interaction between the α-methyl at the prow of the boat (C-2) with the C-5 hydrogen. Structure VIII is unfavorable because it contains two eclipsed ethane units, and it seems likely that the best arrangement for the flexible form is here again in between VIII and IX. Since with the 4,4-dimethyl derivative a structure analogous to X appears to be preferred, the latter was considered as a likely possibility here also.



VI



VII



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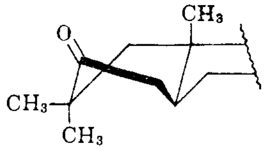
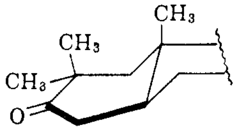


IX



X

To determine the conformational structure of ring A in the 2,2-dimethyl series, the dipole moments of 2,2-dimethylcholestan-3-one (8) and 2,2-dimethylandrostan-3,17-dione (9) were measured. The moments are listed in Table I. The compounds were synthesized by standard methods and had properties in good agreement with the literature values.

To find the conformation of ring A in this series the angle between the dipoles in 2,2-dimethylandrostan-3,17-dione (9) was determined by measuring the moment of the compound together with the individual group moments which were obtained from 2,2-dimethylcholestan-3-one (8) and androstan-17-one (2). The presence of the 2,2-dimethyl group lowers the dipole moment of the 3-keto group slightly, from 3.01 D. in 1 to 2.85 D. in 8. The angles between the dipoles for the ordinary chair and for the various boats, together with the calculated resultant moments, are listed in Table III. The moment calculated for any boat form is higher than that calculated for the regular chair VII. The experimentally determined moment of 9 was 2.64 D., which is within experimental error of VII and just slightly outside of the range calculated for the flexible form. A planar form (X) also gives a range which does not quite include the experimental value for the moment of 9.

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[18] N. L. Allinger and S. Greenberg, *J. Am. Chem. Soc.*, **81**, 5733 (1959).

[19] J. O. Halford, *J. Chem. Phys.*, **24**, 830 (1956).

[20] Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).

[21] E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957), and references therein.

TABLE III

DIPOLE ANGLES AND MOMENTS FOR POSSIBLE STRUCTURES OF 9

Structure	Angle, °	μcalcd., D.
VII	124	2.73
VIII	110	3.34
IX	121	2.87
X	131	2.42

If compound 9 exists with ring A in conformation X, again a shift in the carbonyl frequency should appear due to the expansion of the angle between C-2 and C-4. This is what was found. 2,2-Dimethylcholestan-3-one showed absorption in chloroform at 1700 cm.$^{-1}$ compared to 1706 cm.$^{-1}$ for cholestan-3-one.

If all of the data so far presented are now taken together, the best agreement between theory and experiment is obtained by considering that those compounds of the present group which contain a 1,3-diaxial dimethyl interaction all have ring A in a flattened chair form (V or X), but the flattening may not have been carried far enough to get C-3 up to the approximate plane defined by C1, C2, C4 and C5.

An independent check on the conclusions reached from the dipole moment and infrared data is also available, since the rotatory dispersion curves for most of the compounds discussed have been reported by Djerassi and his co-workers.[17]

Previous workers[3–8,17] have made attempts to interpret the rotatory dispersion curves of compounds of the type under discussion in terms of conformational situations which might exist. These interpretations have been qualitative, and have not given a fully accurate picture of the actual situation.

When the rotatory dispersion curves of 2,2-dimethyldihydrotestosterone and 2α-methyldihydrotestosterone were compared, a positive shift in the Cotton effect was observed.[17] Qualitatively the conclusions which can be drawn by application of the octant rule[22] are these: conformation VIII can clearly be eliminated as the structure since it would show a large negative shift in the Cotton effect. The observed shift is consistent with VII, and may or may not be consistent with X, depending on the extent to which flattening is carried. Not enough is yet known about structures like IX or those between VIII and IX to make firm predictions as to what their Cotton effect curves would look like.

TABLE IV

EXPERIMENTAL COTTON EFFECT AMPLITUDES OF 3-KETOSTEROIDS[a]

Derivative of 3-ketone	Cholestane series	[A] Dihydrotestosterone series
Parent	+66	+54[b]
2α-Me	+63	>+30
2β-Me	+73	..
2,2-Me$_2$	..	+80
4α-Me	+54	..
4β-Me	+11	..
4,4-Me$_2$	−11	−14
19-Nor-series		
Parent	..	+56
4,4-Me$_2$	..	−20
2,2,17-Me$_3$	..	+139
4,4,17-Me$_3$	..	−16

[a] The rotatory dispersion curve of 19-nordihydrotestosterone was determined in the present work. The other values were calculated from the data of Djerassi (ref. 17). [b] This value has recently been given for the acetate (ref. 26). It is probably more accurate than the value (+46) given earlier for the free alcohol (ref. 17). Use of the latter value would not alter the arguments or conclusions.

On the basis of a deformed chair ring A structure, a rather detailed and at least semi-quantitative[23] series of changes in the amplitudes[25] [A] of the rotatory dispersion curves of cholestan-3-one derivatives can be predicted as methyl groups are substituted for hydrogens in ring A. In Table IV are given the molecular amplitudes [A] of the Cotton effect curves for the pertinent compounds. For cholestan-3-one [A] is +66 and for dihydrotestosterone acetate the corresponding value is +54. We can thus take the average of these values (+60) as typical of a 3-keto-5α-steroid, and certainly the bulk of this amplitude is due to the interactions of methylene groups C-6 and C-7 with the carbonyl.[27] If now an α-methyl (equatorial) is substituted at C-2 or at C-4 (Table IV), there is a rather small change in [A]. On the other hand, a β-methyl (axial) at C-2 or C-4 would be expected to yield a large change. Because of the interaction of such a methyl with the C-19 methyl, as indicated by the dipole moment work, ring A flattens out, and there are two aspects of the flattening which are important as far as the changes that are predicted in the Cotton effect curve. First, the methyl at C-2 or at C-4 is not in a fully axial position and should contribute less to the resultant Cotton effect curve than in simple cases and, second, because of the ring flattening the C-6 and C-7 methylenes in these compounds come up toward the *xy*-plane (the plane defined by the carbonyl and carbons 2 and 4). The latter distortion should therefore reduce the Cotton effect of the basic ring system of the 3-keto steroid. It was found that the [A] values are +73 for the 2β-methyl and +10 for the 4β-methyl. Consequently the contribution of the C-6 and C-7 methylenes appears to be reduced from +60 in cholestanone to +42 in the 2β- and 4β-methylcholestanones, and the axial methyl contributes ±31 (the sign being that predicted by the octant rule).

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(22) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(23) The theoretical basis for such a treatment is discussed in footnote 16 of ref. 22; for an earlier experimental application see ref. 24.

(24) N. L. Allinger, J. Allinger, L. E. Geller and C. Djerassi, *J. Org. Chem.*, **25**, 6 (1960).

(25) By definition[23]

$$[A] = ([\alpha_1] - [\alpha_2]) \times (\text{mol. wt.}) \times 10^{-4}$$

where $[\alpha_1]$ is the specific rotation of the compound at the first extremum (with due regard to sign), and $[\alpha_2]$ the similar quantity at the second extremum. The [A] values are more convenient in magnitude than ordinary molecular rotations (designated in earlier papers by [ϕ] and by [α]).

(26) C. Djerassi, E. Lund and A. A. Akhrem, *J. Am. Chem. Soc.*, **84**, 1249 (1962).

(27) It may be noted that Djerassi has assigned a value of ±25 to the (equatorial) β-methyl in 3-methylcyclohexanone. In this molecule, however, some 5–10% of the molecules presumably are in the chair form with an axial methyl, and the latter is contributing a positive Cotton effect, which reduces the apparent effect of the methyl. Probably only about 1% of boat form is present, and it seems unlikely that this small amount would profoundly affect the rotatory dispersion curve.

The shifts expected for the 2,2-dimethyl and 4,4-dimethyl derivatives should be and are roughly similar to those of the corresponding β-methyl compounds, but there are quantitative differences. While the change in [*A*] was ±31 for the introduction of an axial methyl, the corresponding change was ±47 for the *gem*-dimethyl grouping. The C-6 and C-7 methylenes contributed +33 in the latter case, compared to +42 in the monomethyl case and +60 in the parent.

These quantities are rationalized in the following way. When two or three carbons and two or one hydrogens are bound to the same carbon, the C–C–C angles are widened relative to a regular tetrahedron at the expense of the others; for example the C–C–C bond angle in propane[28] is 112.4°. Hence the β-methyl is naturally bent outward from the ring to a greater extent than is the β-methyl of the *gem*-dimethyl. In addition, bending of the former is probably easier than for the latter, since this bending compresses the equatorial group, and this compression would be more serious with methyl than with hydrogen. In the latter case, relief of the 1,3-diaxial repulsion requires a greater flattening of the ring. Consequently, the *gem*-dimethyl group causes a greater shift in amplitude due to its axial methyl (±47) than does an axial monomethyl (±31) since the latter is nearer the *xy*-plane. Because the flattening of the ring is less in the monomethyl case, the contribution of the C-6 and C-7 methylenes is greater (+42) than with the *gem*-dimethyl compound (+33).

This interpretation of the rotatory dispersion data, while self-consistent, is not proven by the available information. There is a check on this interpretation that can be made, however, using the 19-nor series of compounds. In the latter series introduction of the *gem*-dimethyl grouping at either position 2 or 4 should produce shifts which differ from those obtained in the cholestanone series because there is no 1,3-diaxial methyl–methyl repulsion, which means that ring A is in an ordinary chair form and not flattened. Since the chair is regular in this case, there are two ways in which the shifts here should differ from those in the cholestanone series. First, in this case the methyl should not be bent toward the equatorial position, it should be more axial-like, and hence the shift in [*A*] due to the β-methyl should be larger than in the cholestanone series. Second, the C-6 methylene should contribute to the net curve together with the methyl in a strictly additive way.

A comparison of the appropriate 19-nor compounds was then made, but the data could not be reconciled with the above interpretation. Such a reconciliation appeared to be possible only if the rotatory dispersion curve reported in the literature for 19-nordihydrotestosterone was seriously in error. Since the curve for this compound appears to have been reported only once, and because of the well known difficulty of making quantitative amplitude measurements, the curve for this compound was redetermined. The [*A*] value found in the present work differed appreciably from that in the literature, and the former has been used throughout the following discussion.

The [*A*] for 19-nordihydrotestosterone was found to be +56, while the values reported for 2,2,17-trimethyl-19-nordihydrotestosterone and for the 4,4,17-trimethyl analog are +139 and −16, respectively. Hence the shift which results upon introduction of the *gem*-dimethyl grouping in this series (±77) is much larger than the value (+47) obtained when the 19-methyl was present. Further, the shift relative to the parent brought about by the 2,2-dimethyl grouping is +83, while that for the 4,4-analog is −72. Hence these quantities are very nearly additive with that from the C-6 methylene, which means the ring is essentially undistorted. In the compounds where the 19-methyl is present, on the other hand, the corresponding shifts are +20 and −72. The difference in the latter values indicates the reference point has moved, that is the C-6 and C-7 methylenes do not contribute +60 here as in the parent, but only +26 since they are nearer the *xy*-plane.

The perfect agreement of the complicated rotatory dispersion interrelationships is strong support for the proposed form, which is perhaps best designated as a flattened chair, and suggests the potential usefulness of quantitative rotatory dispersion measurements.

Lehn, Levisalles and Ourisson[8] have preferred to interpret their data on similar 4,4-dimethyl compounds as indicating an equilibrium between boat and chair forms. It may be that their system in fact behaves differently from the one studied by us, and this is possible, since their system contains an 8-β-methyl, and therefore is not exactly comparable to those compounds studied here. As these authors have pointed out, the data given in their paper can also be interpreted in terms of a single deformed chair structure (in between their forms C and P). We do not regard the exactly planar form (P) as particularly favorable, and said[1b] of this form only that "C-3 is moved upward (relative to II) approximately to the plane defined by carbons 1, 2, 4 and 5." The dipole moment work was not sufficiently sensitive to detect just how close to the plane C-3 was moved. The rotatory dispersion data cited here are only consistent with C-6 remaining in a positive octant, and hence the form which actually exists in the systems studied in the present work must not be quite planar, but rather must be between the planar and chair forms. Such a form appears to be consistent with all the available data for the systems described in the present work.[28a]

There is no evidence requiring a boat form, although the presence of a small amount cannot be eliminated with certainty.

Experimental

5α-Androstan-3,17-dione.—The dione was prepared from epiandrosterone[29] by chromic acid oxidation; needles from acetone, m.p. 129–131° (reported[30] 133°).

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[28] D. R. Lide, Jr., *J. Chem. Phys.*, **33**, 1514 (1960).

[28a] While the evidence for the flattened chair in the 4,4-dimethyl-3-ketone seems compelling, the possibility of some type of boat structure, although unlikely, has not been definitely eliminated in the 2,2-dimethyl-3-ketone case.

[29] The authors are indebted to Professor Carl Djerassi, Stanford University, for a gift of this material.

[30] A. Butenandt and K. Tschirning, *Z. physiol. Chem.*, **229**, 167, 185 (1934).

4,4-Dimethyl-5α-androstan-3,17-dione.—4,4-Dimethyl-5α-androstan-17β-ol-3-one (prepared from testosterone acetate as described),[14] m.p. 140–143°, was dissolved in 50 ml. of acetone (previously distilled from potassium permanganate) and treated with an excess of 8 *N* chromic acid (Jones reagent)[31] for 5 min. The mixture was poured into water and the solid was collected. Crystallization from acetone yielded 0.83 g. of material, m.p. 159–161.5°. From methanol the melting point was 154.7°.

TABLE V

DIPOLE MOMENT DATA; BENZENE SOLVENT, 25°

N_2	d_{12}	ϵ_{12}
Androstan-17-one, M_R 81.55 cc.		
0.00000000	0.873092	2.2711
.00024062	.873284	2.2744
.00064687	.873500	2.2798
.00099070	.873612	2.2843
.00161294	.873942	2.2923
$\alpha = 13.138$	$\epsilon_1 = 2.2712$	$d_1 = 0.87313$
$\beta = 0.512$	$P_{2\infty} = 271.2$	$\mu = 2.98 \pm 0.03$ D.
Androstan-3,17-dione, M_R 81.47 cc.		
0.00000000	0.873162	2.2714
.00047266	.873574	2.2775
.00128910	.874121	2.2879
.00233197	.874910	2.3016
.00134156	.874124	2.2891
$\alpha = 12.966$	$\epsilon_1 = 2.2714$	$d_1 = 0.87318$
$\beta = 0.737$	$P_{2\infty} = 266.6$	$\mu = 2.94 \pm 0.05$ D.
4,4-Dimethylcholestan-3-one, M_R 128.03 cc.		
0.000000000	0.873160	2.2717
.000285375	.873297	2.2749
.000531309	.873385	2.2779
.000704488	.873525	2.2803
.000977205	.873665	2.2830
$\alpha = 11.800$	$\epsilon_1 = 2.2717$	$d_1 = 0.87314$
$\beta = 0.524$	$P_{2\infty} = 298.9$	$\mu = 2.78 \pm 0.04$ D.
19-Nor-4,4-dimethylandrostan-3,17-dione, M_R 86.17 cc.		
0.00000000	0.873268	2.2713
.00031480	.873448	2.2753
.00056695	.873607	2.2780
.00092333	.873769	2.2816
.00113738	.873947	2.2835
$\alpha = 10.637$	$\epsilon_1 = 2.2717$	$d_1 = 0.87326$
$\beta = 0.583$	$P_{2\infty} = 241.8$	$\mu = 2.68 \pm 0.08$ D.
4,4-Dimethylandrostan-3,17-dione, M_R 99.90 cc.		
0.00000000	0.873151	2.2715
.00031348	.873400	2.2733
.00088809	.873795	2.2780
.00151501	.874136	2.2835
.00252560	.874727	2.2913
$\alpha = 7.961$	$\epsilon_1 = 2.2712$	$d_1 = 0.87319$
$\beta = 0.618$	$P_{2\infty} = 206.1$	$\mu = 2.28 \pm 0.04$ D.
19-Norandrostan-3,17-dione, M_R 76.88 cc.		
0.00000000	0.873226	2.2711
.00027981	.873433	2.2748
.00061547	.873653	2.2791
.00105299	.873983	2.2845
.00170021	.874432	2.2924
$\alpha = 12.524$	$\epsilon_1 = 2.2712$	$d_1 = 0.87323$
$\beta = 0.709$	$P_{2\infty} = 256.1$	$\mu = 2.90 \pm 0.04$ D.
2,2-Dimethylcholestan-3-one, M_R = 128.03 cc.		
0.00000000	0.873536	2.2760
.00056563	.873795	2.2835
.00131051	.874209	2.2914
.00167053	.874336	2.2969
.00202439	.874496	2.3009
$\alpha = 12.281$	$\epsilon_1 = 2.2763$	$d_1 = 0.87354$
$\beta = 0.483$	$P_{2\infty} = 307.1$	$\mu = 2.85 \pm 0.04$ D.
2,2-Dimethylandrostan-3,17-dione, M_R 99.90 cc.		
0.00000000	0.873566	2.2759
.00101689	.874288	2.2868
.00173637	.874990	2.2939
.00297891	.875615	2.3074
.00324819	.875850	2.3104
$\alpha = 10.588$	$\epsilon_1 = 2.2759$	$d_1 = 0.87360$
$\beta = 0.701$	$P_{2\infty} = 242.0$	$\mu = 2.64 \pm 0.03$ D.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.60; H, 10.07.

19-Norandrostan-3,17-dione was prepared by chromic acid oxidation[31] of 19-norandrostan-17β-ol-3-one (obtained from a lithium and liquid ammonia reduction of 19-nortestosterone as described[32]; m.p. 147–149° (reported[33] m.p. 150°).

4,4-Dimethyl-19-norandrostan-3,17-dione.—4,4-Dimethyl-19-norandrostan-17β-ol-3-one (prepared from 19-nortestosterone acetate as previously described[13]), 1.3 g. was treated with an excess of Jones reagent[31] as described for the preparation of 4,4-dimethylandrostan-3,17-dione; yield 1.0 g., m.p. 156–158°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.45; H, 9.99. Found: C, 79.24; H, 10.21.

4,4-Dimethylcholestan-3-one was prepared as described[34,35]; m.p. 99–100.5° (reported 100–101°).

5α-Androstan-17β-ol.—5α-Androstan-3β-ol-17-one tosylate (3.0 g.) was dissolved in 100 cc. of ether and added dropwise to 100 cc. of anhydrous benzene and 25 cc. of ether containing 1 g. of lithium aluminum hydride. The mixture was allowed to reflux 30 hours and the excess lithium aluminum hydride was decomposed with 1:1 acetic acid–water. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were washed with water, bicarbonate solution and water, were dried and the ether was evaporated. The residue (2.3 g.) was crystallized from methanol to give 1.2 g. of material, m.p. 145–148.5°; reported[36] for 5α-androstan-17β-ol, m.p. 148°.

5α-Androstan-17-one.—5α-Androstan-17β-ol (1.2 g.) was oxidized with an excess of Jones reagent as previously described for the 4,4-dimethyl ketones. The product was obtained as plates, wt. 1.12 g., m.p. 119–121° (reported[37] m.p. 122°).

2,2-Dimethylcholestan-3-one was prepared essentially by the procedure previously described by Mazur and Sondheimer.[20] Crystallization from methanol–ether afforded plates, m.p. 112.5–113.5° (reported[20] m.p. 111–113°).

2,2-Dimethylandrostan-17β-ol-3-one was prepared essentially by the procedure of Ringold, *et al.*[38] Crystallization from acetone afforded flakes, m.p. 134–135° (reported[38] m.p. 134–136°).

2,2-Dimethylandrostan-3,17-dione.—2,2-Dimethylandrostan-17β-ol-3-one was oxidized with an excess of Jones reagent as previously described for the 4,4-dimethyl ketones. Several crystallizations from acetone afforded 1.6 g., m.p. 127–128° (reported[38] m.p. 127–127.5°).

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

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(33) C. Chen, *Tetrahedron*, **3**, 43 (1958).

(34) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

(35) J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *J. Chem. Soc.*, 753 (1957).

(36) G. Rosenkranz, *J. Am. Chem. Soc.*, **71**, 3689 (1949).

(37) C. W. Shoppee, *Chemistry & Industry*, 454 (1950).

(38) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

19-Nordihydrotestosterone.[39]—The rotatory dispersion curve was determined in methanol (c 0.018) at 25°, "max." $[\alpha]_{305}$ +1101°, "min." $[\alpha]_{265}$ −928°.

Dipole Moments.—The dipole moments of the various ketones were run at 25° in benzene solution, and the data are given in Table V. The dipole moment apparatus has been described previously.[15] The moments were calculated by essentially the method of Halverstadt and Kumler,[41] utilizing an IBM 650 computer programmed as described earlier.[42] Because of the high molecular weights of the compounds, an attempt was made to account approximately for atomic polarization by taking $P_e + P_a$ = 1.10 MD where the latter was found from the table of Vogel.[43]

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[39] The authors are indebted to Dr. A. Bowers, Syntex, for a sample of this material. The rotatory dispersion curve was measured by L. Tushaus and J. Maul using the previously described[40] instrument.

[40] C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).

[41] I. F. Halverstadt and W. D. Kumler, *ibid.*, **64**, 2988 (1942).

[42] N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

[43] A. I. Vogel, W. T. Cresswell, G. J. Jeffrey and J. Leicester, *Chemistry & Industry*, 358 (1950).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES, NORTH CHICAGO, ILL.]

Neighboring Group Reactions. VI. Reactions of 3-(ω-Haloalkyl)-3-phenyl-2-benzofuranones with Secondary Amines. Trapped Tetrahedral Intermediates in a Carbonyl Addition Reaction[1]

BY H. E. ZAUGG, F. E. CHADDE AND R. J. MICHAELS

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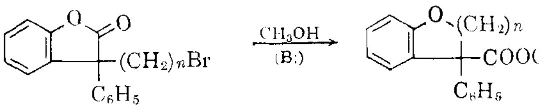
The reactions of a series of ω-bromoalkylbenzofuranones I (n = 0–4) with morpholine are described. The first and last two members of the homologous series (I; n = 0, 3, 4) merely undergo direct displacement to give IV (n = 0, 3, 4). The bromomethyl homolog (n = 1) reacts exclusively with rearrangement to produce the amide III; and the bromoethyl derivative (n = 2) yields mainly (>90%) the trapped tetrahedral intermediate V. A more detailed study of the last reaction is reported. Although solvents of low polarity exert little influence on its course (sp^2 attack), dimethylformamide and dimethyl sulfoxide alter it completely. Then, the sole product IV (n = 2) arises from direct sp^3 displacement of the bromine atom. Other secondary amines, alone or in non-polar media, likewise give corresponding *ortho* amides of type VII; but with increasing basicity of the amine larger quantities of the rearranged amide VI are produced at the expense of VII. Possible mechanisms for these reactions are discussed. The structure VII assigned to these products is documented spectroscopically (infrared, ultraviolet and n.m.r.) and chemically. *Ortho* amides VII are extremely stable bases of widely divergent base strength (spectrophotometrically determined), but each one is less basic than the amine from which it is derived. Protonation occurs on the phenyl oxygen atom, rather than on nitrogen, to give the cyclic quaternary imidate salt VIII as the more reactive acid form. On the other hand, quaternization with methyl iodide of the pyrrolidine *ortho* amide VII occurs on nitrogen to give XIV.

Previous papers[2] have described the base-catalyzed rearrangement of the three homologous benzofuranones I to the corresponding methyl esters II.



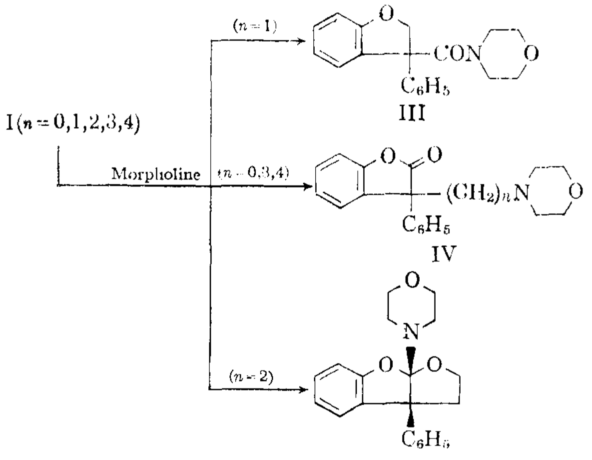
I(n = 1, 2, 3) II(n = 1, 2, 3)

With methoxide ion in methanol, the first two members of this series reacted with extreme rapidity (titration conditions). The third member (n = 3) rearranged more slowly but no less completely (97% yield). In the presence of a weak base (sodium acetate or triethylamine) in refluxing methanol, rearrangement was restricted to the first two members (n = 1,2), and lengthening the chain further (n = 4) exceeded the steric requirements of the reaction so that no rearrangement occurred under any conditions.

All of these reactions clearly proceed through primary attack of the carbonyl carbon atom by a nucleophilic oxygen atom. Naturally it was of interest to find out what would happen to these bromides in the presence of nitrogen nucleophiles. This paper reports the outcome of such investigations with secondary amines.

Results

In order to examine the effect of chain length on the reaction course, each of the five homologous bromides I (n = 0–4) was dissolved in excess morpholine and allowed to stand at room temperature for several days. Results are summarized as



Reactions of all but the bromoethyl derivative (n = 2) can be disposed of briefly. With the bromomethyl derivative (n = 1) rearrangement occurred exclusively and the amide III was the only product

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[1] Paper V, H. E. Zaugg and R. J. Michaels, *Tetrahedron*, **18**, 893–901 (1962).

[2] (a) H. E. Zaugg, R. W. DeNet and R. J. Michaels, *J. Org. Chem.*, **26**, 4821 (1961); (b) **26**, 4828 (1961).