(+)-Isothujylamine (IIIa) from (+)-(1*S*,3*R*,4*S*)-3-Nitrothujane (XXVII).—A solution of 1.80 g (9.82 mmoles) of XXVII in 200 ml of 95% ethanol saturated with sodium bicarbonate was boiled for 8 hr. After partial removal of the ethanol, addition of water, extraction with hexane, drying, and evaporation of the hexane, there was obtained 1.15 g of (+)-(1*S*,3*S*,4*S*)-3-nitrothujane (XXVIII) (64%) as a residual oil, $[\alpha]^{25}D$ +96° (*c* 2.5, methanol). Without further purification, 1.06 g (5.78 mmoles) of this oil was reduced with iron powder in glacial acetic acid, and there was obtained 0.61 g of a crude amine product. Addition of this oil to an equivalent amount of 0.016 *M* aqueous nitric acid gave a precipitate. Recrystallization of this precipitate from water gave 0.52 g of (+)-isothujylamine nitrate (60% based on crude amine), mp 171-173° dec, $[\alpha]^{25}D$ +71° (*c* 0.8, water) [lit.[3b] mp 176.9°, $[\alpha]^{25}D$ +70.48° (water)]. The infrared spectrum of this substance was identical with that of authentic (+)-isothujylamine nitrate,[38] mp 172-173° dec, $[\alpha]^{25}D$ +72° (*c* 1.0, water).

Acknowledgment.—We wish to thank the National Science Foundation for a grant (G-14524) supporting the earlier stages of this work. We also wish to thank those[32,33,37-39,47] who aided us with equipment, materials, and unpublished observations.

Terpenes. III. The Nuclear Magnetic Resonance Spectra and Absolute Configurations of the Thujylamines[1]

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The nmr spectra at 60 and 100 Mc/sec were measured for (+)-isothujylamine and (+)-neoisothujylamine, for the N-*p*-nitrobenzoyl derivative of (−)-thujylamine, and for the N-benzoyl derivatives of (−)-neothujylamine, (+)-isothujylamine, and (+)-neoisothujylamine. The absolute configurations at the ring-junction carbon atoms being known with certainty, interpretation of these spectra confirms for the amino and methyl groups the configurational assignments recently deduced on the basis of the preparation of the amines from the related thujyl alcohols and thujones. Since these assignments previously depended explicitly on the configurational assignments for the hydroxyl and methyl groups in the alcohols and ketones, this present work, when taken together with the chemical evidence, also confirms the corresponding configurational assignments in the thujyl alcohols and thujones.

In the preceding paper in this series,[1b] the absolute configurations of the four isomeric thujylamines (Ia–IVa, Chart I)[3] were deduced on the basis of their preparation from the related thujyl alcohols (Ib–IVb)[4] and thujones (V and VI),[4] and, as shown in Table I, a name consistent with that applied to the related thujyl alcohol[4] was given to each amine.

TABLE I

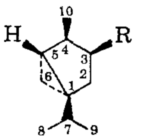
THE THUJYLAMINES

Compound	Name	$\alpha^{25}D$[a]
Ia	(−)-Thujylamine	−22.07
IIa	(−)-Neothujylamine	−14.15
IIIa	(+)-Isothujylamine	+94.94
IVa	(+)-Neoisothujylamine	+27.80

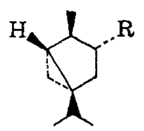
[a] Rotation in degrees for 1 dm without solvent.

In these amines, the configurations at C-1 and at the dependent asymmetric center at C-5 follow from those at C-1 and C-5 for (−)-thujone (V) and (+)-isothujone (VI), these assignments first being deduced on the basis of the asymmetric synthesis of (−)-*cis*-umbellularic acid,[5] a degradation product of (−)-umbellulone (VII).[6] This latter terpene was shown previously to be enantiomorphic at C-1 and C-5 with (−)-thujone by the conversions of (−)-umbellulone and (−)-thujone to (+)- and (−)-homothujadicarboxylic acid (VIII), respec-

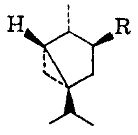
CHART I



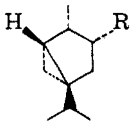
Ia, R = NH_2
b, R = OH
c, R = $NHCOC_6H_4NO_2$-*p*



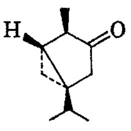
IIa, R = NH_2
b, R = OH
c, R = $NHCOC_6H_5$



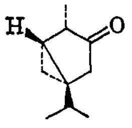
IIIa, R = NH_2
b, R = OH
c, R = $NHCOC_6H_5$



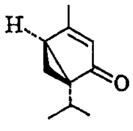
IVa, R = NH_2
b, R = OH
c, R = $NHCOC_6H_5$



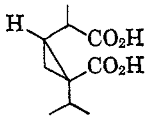
V



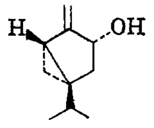
VI



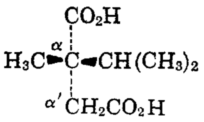
VII



VIII



IX



$$H_3C\blacktriangleright\overset{\alpha}{C}\blacktriangleleft CH(CH_3)_2 \quad \text{with } CO_2H \text{ above and } {}^{\alpha'}CH_2CO_2H \text{ below}$$

X

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[1] (a) Presented at the Southeast–Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Dec 1965; Abstracts of Papers, p 50. (b) Paper II: E. H. Massey, H. E. Smith, and A. W. Gordon, *J. Org. Chem.*, **31**, 684 (1966). (c) This is also paper VII in the series entitled Optically Active Amines. Paper VI is ref 1b.

[2] National Defense Education Act Fellow, 1961–1964.

[3] H. L. Dickison and A. W. Ingersoll, *J. Am. Chem. Soc.*, **61**, 2477 (1939).

[4] M. S. Bergqvist and T. Norin, *Arkiv Kemi*, **22**, 137 (1964).

[5] H. M. Walborsky, T. Sugita, M. Ohno, and Y. Inouye, *J. Am. Chem. Soc.*, **82**, 5255 (1960).

[6] F. Tutin, *J. Chem. Soc.*, **89**, 1104 (1906).

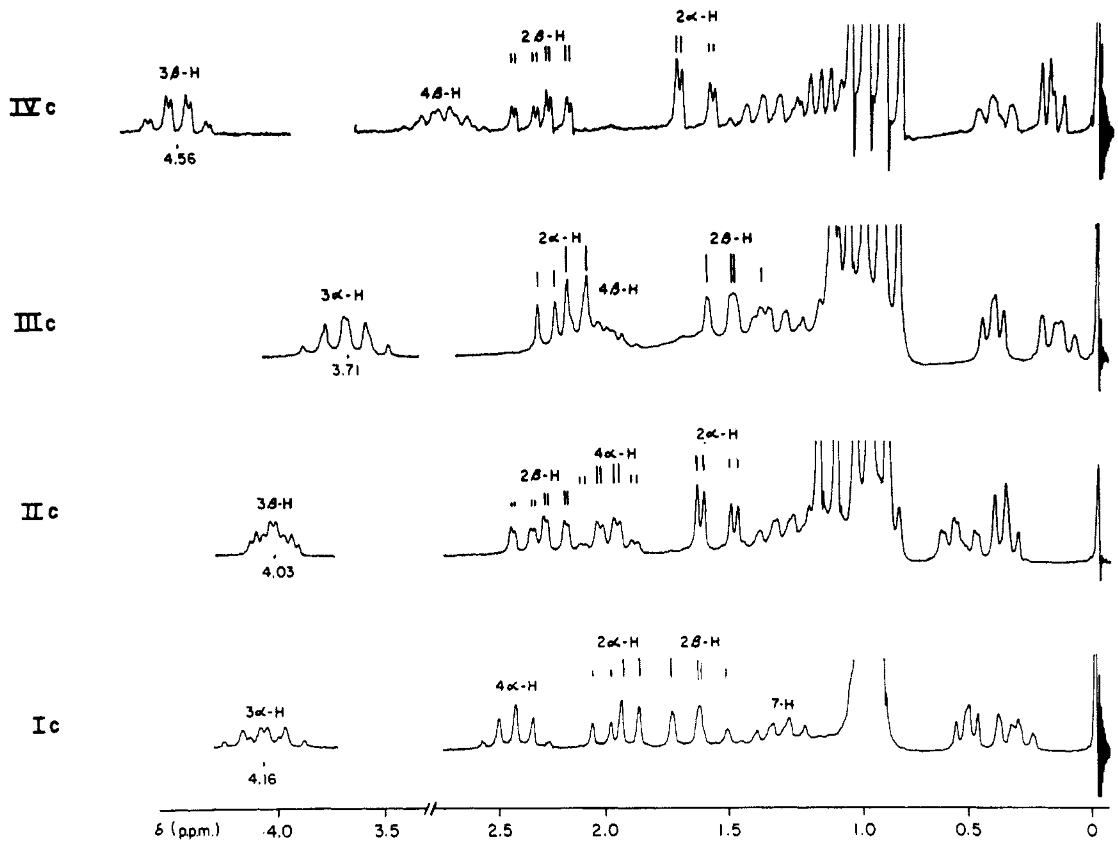

Figure 1.—The 100-Mc/sec nmr spectra of (−)-N-*p*-nitrobenzoylthujylamine (Ic), (−)-N-benzoylneothujylamine (IIc), (+)-N-benzoylisothujylamine (IIIc), and (+)-N-benzoylneoisothujylamine (IVc) in deuteriochloroform. (The horizontal scale in these spectra is somewhat irregular.)

tively.[7] These assignments were subsequently confirmed by the degradation of (+)-sabinol (IX) to (+)-(*S*)-α-methyl-α-isopropylsuccinic acid (X),[8] the latter, a compound of established absolute configuration,[9] and the former, configurationally the same at C-1 and C-5 as (−)-thujone and (+)-isothujone.[10] In addition, as reported in a preliminary communication[11] and described in the previous paper in this series,[1b] (−)-umbellulone has also been degraded to (+)-(*S*)-α-methyl-α-isopropylsuccinic acid (X), following the route previously used for the establishment of the structure of (+)-umbellulone dibromide.[12] The fact that (+)-sabinol and (−)-umbellulone both are converted to (+)-(*S*)-α-methyl-α-isopropylsuccinic acid resides in the circumstance that with the former it is C-2 and with the latter it is C-5 which eventually becomes the α′-methylene carbon atom in the succinic acid.

In the amines, since the configurational assignments at C-3 and C-4 depend explicitly on the assignments at these same positions recently established for the thujyl alcohols and thujones,[4] we now wish to report nmr measurements which confirm these assignments at C-3 and C-4 in the amines and which depend only on the configuration at C-5. This seems especially important since these amines provide suitable model compounds for investigations of the optical rotatory dispersion and circular dichroism of amines and amine derivatives[13] and studies of cations of the bicyclo[3.1.0]hexyl type.[14] In addition, when taken together with the chemical evidence previously reported,[1b] these present measurements confirm the configurational assignments made for the thujyl alcohols and thujones.[4]

Results and Discussion

The nmr spectra at 60 and 100 Mc/sec were measured in deuteriochloroform for (+)-isothujylamine (IIIa) and (+)-neoisothujylamine (IVa), for the N-*p*-nitrobenzoyl derivative of (−)-thujylamine (Ic), and for the N-benzoyl derivatives of (−)-neothujylamine (IIc), (+)-isothujylamine (IIIc), and (+)-neoisothujylamine (IVc). The spectra of the amines and amides (Figure 1) show an expected resemblance to one another and to the spectra of the isomeric thujyl alcohols.[4] The proton chemical shifts vary somewhat with the functional group (alcohol, amine, or amide), with those of the amides being the best separated. For the amines and amides, the assigned proton chemical shifts and coupling constants are summarized in Table II.[15]

The key to the configurational assignments at C-3 and C-4 lies principally in the coupling patterns and chemical shifts assigned to the ring protons at C-2, C-3, and

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[12] R. H. Eastman and A. Oken, *ibid.*, **75**, 1029 (1953).

[13] H. E. Smith and R. Records, *Tetrahedron*, in press.

[14] S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3244 (1961), and earlier papers referred to therein; E. J. Corey and R. L. Dawson, *ibid.*, **85**, 1782 (1963); E. J. Corey and H. Uda, *ibid.*, **85**, 1788 (1963); T. Norin, *Tetrahedron Letters*, 37 (1964).

[15] In Table II and elsewhere in this section α and β refer to the orientation of the hydrogen atoms and substituent groups attached to the three- and five-membered rings, signifying, respectively, below and above a ring when the latter is viewed as shown in I–IV.

TABLE II

SUMMARY OF THE NMR DATA FOR THE THUJYYLAMINES AND THEIR N-*p*-NITROBENZOYL OR N-BENZOYL DERIVATIVES

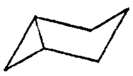
Protons[a]	Ic	IIc	IIIa	IIIc	IVa	IVc
	Chemical shifts assigned, ppm from TMS = 0					
$2\alpha/2\beta$	1.95/1.64	1.56/2.28	1.97/1.4[b]	2.18/1.52	1.45/2.05	1.66/2.32
$3\alpha/3\beta$	4.16/..	.../4.03	2.23/...	3.71/...	.../3.37	.../4.56
$4\alpha/4\beta$	2.4[b]/...	2.0[b]/...	.../1.6[b]	.../2.1[b]	.../*c*	.../2.73
$6\alpha,6\beta$[d]	0.34, 0.5[b]	0.38, 0.56	0.1[b], 0.25	0.15, 0.40	0.05–0.35[e]	0.18, 0.44
8, 9[d]	0.93, 0.93	0.90, 0.95	0.87, 0.94	0.84, 0.93	0.86, 0.93	0.84, 0.93
10	0.92	1.10	0.98	1.05	0.97	1.00
N*H*R	6.48	6.27	1.25	6.36	0.85	5.9[b]
	Coupling constants assigned, cps					
2α-2β	12	14	12[f]	12	13	14
2α-3/2β-3	8/11	3/8	7/9	7.5/10	1.5/7.5	2.3/8
3–4/4–5	7[f]/0[f]	2[f]/0[f]	8–9/*c*	*c*/*c*	7.5[f]/*c*	7[f]/7[f]
4–10/7–8, 7–9	7/5.5	7/5.5	7/5.5	7/6.5	7/5.5–6	7/5.5
3-N*H*R	8[f]	6[f]	0[f]	9[f]	0[f]	*g*

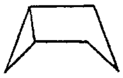
[a] For the significance of α and β, see footnote 15. [b] Chemical shift is approximate. Signal is partially obscured by another multiplet. [c] Value was not obtained owing to signal being obscured by another signal. [d] No differentiation between these protons is made or implied. [e] Two signals were not distinguishable. [f] Approximate value; may not be true coupling constant where perturbed. [g] Broad multiplet

C-4. The 3-H signals occur at lowest field, apart from nitrogen-attached and aromatic protons in the amides, and can be identified unambiguously. The splitting present in the 3-H signals shows the effect of coupling with N–H in the amide spectra, but not in the amine spectra.

The 2α-H and 2β-H signals are identified by the large geminal coupling (12–14 cps) superimposed on the coupling with 3-H. The 2-H signals then comprise the AB part of an ABX···· spin system. The 4-H resonance occurs close to the lower-field component of the 2-H signals, the 4-H and 2-H signals being distinguished from one another by their coupling patterns. Once the 2-H, 3-H, and 4-H signals are assigned and their coupling interpreted, the configurations at C-3 and C-4 relative to that at C-5 may be deduced using the Karplus relationship.[16] For this purpose only the general shape of the Karplus curve need be accepted. Dihedral angles of 70–110° are assumed to lead to small coupling constants (0–3 cps), whereas the constants associated with angles in the range 0–30 or 150–180° were taken as moderate to large (>6 cps). A more rigorous analysis, involving further hazards in estimating corrections,[17] does not seem to be called for.

Using the complete set of amide spectra (Figure 1) and Drieding models, we compared the expectations for the chair (XI) and boat (XII) conformations of each amide configuration (Ic–IVc) with the four spectra, taking into consideration the chemical shifts and spin splittings observed for the 2-H, 3-H, and 4-H signals. Final assignment of 2α-H and 2β-H signals was made after the configurations at C-3 and C-4 had been identified. On this basis the chair conformation of configuration IIIc does not fit any of the spectra, and the boat conformation of this configuration corresponds only to the spectrum of (+)-N-benzoylisothujylamine (spectrum IIIc in Figure 1).[18] (The same notation is used, respectively, for compounds, configurations, and spectra to avoid the confusion of extra sets of notations.)


XI


XII

Likewise, only the boat conformation of configuration IVc fits the spectrum of (+)-N-benzoylneoisothujylamine (IVc). (The chair conformation of configuration IVc could be compatible with spectrum IIIc, but, if this assignment were made, it becomes impossible to match all four spectra and configurations.) For configuration Ic, none of the spectra is consistent with a chair conformation although spectrum Ic and possibly IIIc are compatible with the boat conformation of this configuration. Configuration IIIc, however, has already been assigned, leaving configuration Ic for the spectrum of (−)-N-*p*-nitrobenzoylthujylamine (Ic). Finally, since both spectra Ic and IIIc, which could be compatible with the chair conformation of configuration IIc, have already been assigned, the boat conformation of this configuration fits only the spectrum of (−)-N-benzoylneothujylamine (IIc). Accordingly, there is a unique correlation of spectra and configurations if, and only if, *the four amides exist preferentially in the boat conformation*, the preferred conformation also deduced for the thujones[4,21] and thujyl alcohols.[4]

The assignment of proton chemical shifts and coupling constants in the two thujylamine spectra (IIIa and IVa) and the respective configurations to the four thujylamines (Ia–IVa) follow from these assignments made for the amides.

Experimental Section[22]

(−)-N-*p*-Nitrobenzoylthujylamine (Ic) had mp 147–148°, $[\alpha]^{25}\text{D}$ −49° (*c* 1.1, chloroform); lit.[3] mp 146.5°, $[\alpha]^{25}\text{D}$ −51.25° (chloroform).

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[16] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

[17] M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

[18] This key assignment is supported by the unusually high shielding associated with the 3α-H, resulting from the combined effects of the cyclopropyl[19] and methyl[20] groups.

[19] T. Norin, *Svensk Kem. Tidskr.*, **76**, 97 (1964); K. Tori and K. Kitahonoki, *J. Am. Chem. Soc.*, **87**, 386 (1965), and references cited therein.

[20] J. L. Jungnickel, D. O. Schissler, C. A. Reilly, and G. G. Henry, 3rd Pacific Meeting of the Northern California Society for Spectroscopy and 5th Meeting in Miniature of the Northern California and Santa Clara Sections of the American Chemical Society, Conference on Spectroscopy, Instrumentation, and Chemistry, San Francisco, Calif., Oct 1964; Abstracts of Papers, p 6.

[21] K. Tori, *Chem. Pharm. Bull.* (Tokyo), **12**, 1439 (1964).

[22] Melting points were taken in capillary tubes and are corrected. Boiling points are not corrected. Optical rotations were measured in 1-dm tubes.

(−)-**N-Benzoylneothujyalmine** (IIc) had mp 95–97°, $[\alpha]^{25}_{D}$ −13° (*c* 2.1, methanol); lit.[3] mp 94.5°, $[\alpha]^{25}_{D}$ −12.16° (methanol).

(+)-**Isothujylamine** (IIIa) had bp 113° (62 mm), n^{25}_{D} 1.4559, $[\alpha]^{25}_{D}$ +114° (*c* 2.4, 95% ethanol); lit.[3] bp 76.8° (11 mm), n^{25}_{D} 1.4564, $[\alpha]^{25}_{D}$ +107.9, +108.4° (*c* 1.6, ethanol).

(+)-**N-Benzoylisothujylamine** (IIIc) had mp 132–135°, $[\alpha]^{25}_{D}$ +89° (*c* 1.1, methanol); lit.[3] mp 131.5°, $[\alpha]^{25}_{D}$ +87.74° (methanol).

(+)-**Neoisothujylamine** (IVa) had bp 110° (52 mm), n^{25}_{D} 1.4658, $[\alpha]^{25}_{D}$ +52.2° (*c* 2.2, 95% ethanol); lit.[3] bp 77.0° (12 mm), n^{25}_{D} 1.4654, $[\alpha]^{25}_{D}$ +51.27° (*c* 3, ethanol).

(+)-**N-Benzoylneoisothujylamine** (IVc) had mp 74–75°, $[\alpha]^{25}_{D}$ +95° (*c* 1.0, methanol); lit.[3] mp 73–75°, $[\alpha]^{25}_{D}$ +91.44° (methanol).

Nmr Measurements.—The nmr spectra at 60 and 100 Mc/sec were recorded on Varian A-60 and HR-100 spectrometers, using samples dissolved in deuteriochloroform containing tetramethylsilane (TMS) as an internal standard. All chemical shifts are reported in parts per million downfield from TMS.

Acknowledgment.—We wish to thank the National Science Foundation for a grant (G-14524) supporting the earlier stages of this work, Professor Arthur W. Ingersoll, Vanderbilt University, for a generous gift of thujylamine salts and thujylamides, and Professor Carl Djerassi for his hospitality to H. E. S. during the summer of 1964 at Stanford University.

Steroids. CCLXVI.[1] A Series of C-19 Modified Analogs of Testosterone and Related Compounds[2]

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Received September 22, 1965

The preparation of the 10β-angular hydroxymethyl, formyl, carboxyl, chloromethyl, vinyl, ethyl, N,N-dimethylcarboxamido, and N,N-diethylaminomethyl analogs of various 3,17-bisoxygenated Δ^4- and Δ^5-androstenes as well as a series of 6β,19-oxides is described. A new synthesis of 17α-ethinyl-19-nortestosterone acetate is presented.

The marked difference in biological properties between testosterone or several structural modifications of testosterone and their corresponding 19-nor analogs[3] clearly indicates that the nature of the 10β-angular substituent plays an important role in structure–activity relationships. However, variations of the angular substituent have been extremely limited owing to the chemical inaccessibility of the C-19 angular methyl group.[4] Functionalization of the nonactivated 19-carbon became possible through the pioneering work of Barton and his collaborators.[5] Recent work in our laboratories[6-9] and independent studies by the CIBA group[10-12] have led to ready syntheses of 19-oxygenated steroids from the reaction of readily available 6β-hydroxy precursors with lead tetraacetate, and hence made the way clear to the preparation on industrial scale of a variety of 19-substituted compounds. Other independent investigators have pursued different routes to 19-substituted steroids.[13] This paper describes the preparation of the 10β-angular hydroxymethyl, formyl, carboxyl, chloromethyl, vinyl, ethyl, N,N-dimethylcarboxamido, and N,N-diethylaminomethyl analogs of various 3,17-bisoxygenated Δ^4- and Δ^5-androstenes (Chart I).

Cleavage of 3β-hydroxy-5α-bromo-6β,19-oxidoandrostan-17-one acetate (Ia)[8] with zinc dust in ethanol under reflux afforded the Δ^5-19-alcohol (IIa) in high yield. When this reaction was carried out in acetic acid, the product was the corresponding diacetate IIb. Acetylation of IIa with acetic anhydride in pyridine solution gave the diacetate IIb. Tosylation of IIa proceeded normally to yield the C-19 tosylate IIc which underwent displacement with lithium chloride in isopropyl alcohol solution under reflux for 5 hr to afford 3β-hydroxy-19-chloroandrost-5-en-17-one acetate (IId).[14] Similarly, treatment of IIc with lithium bromide led to 19-bromoandrost-5-en-17-one acetate (IIe). Alkaline hydrolysis of IId furnished the alcohol IIf, which upon Oppenauer oxidation gave 19-chloroandrost-4-ene-3,17-dione (IIIa). Reduction of IIIa with lithium aluminum hydride gave a product which did not exhibit any selective absorption in the ultraviolet above 210 mμ but which was readily oxidized with dichlorodicyanobenzoquinone (DDQ) in dioxane solution[15] at room temperature to 19-chlorotestosterone (IIIb).

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[1] Part CCLXV: J. C. Orr, A. de la Roz, and A. Bowers, *J. Org. Chem.*, **29**, 3300 (1964).

[2] A part of this work was presented by A. B. at the Gordon Research Conference for Steroids and Natural Products, New Hampton, N. H., on July 16, 1962, and as a preliminary communication, O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963).

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[4] For a summary of the biochemical methods (adrenal incubation and microbiological hydroxylations) used for the oxygenation of the C-19 methyl group, *cf.* ref 5 and T. Takahashi, *Agr. Biol. Chem.* (Tokyo), **27**, 639 (1963).

[5] A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

[6] For a recent review and relevant references, see A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

[7] A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.* (London), 1299 (1960).

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[9] B. Berkoz, E. Denot, and A. Bowers, *Steroids*, **1**, 251 (1963).

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[14] Reactions of the Δ^5-19-tosylate system with anions usually afford 5,19-cyclo steroids as the major reaction products: *cf.* O. Halpern, P. Crabbe, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

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