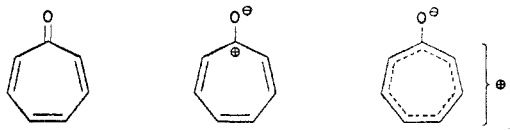
COMMUNICATIONS TO THE EDITOR

SYNTHESIS OF TROPONE

Sir:

Indications of aromaticity in the tropolones[1a] and in azulene[1b] direct attention to the need for determining the necessary minimum structural features for and the nature of this property in seven-membered ring systems. We wish to report the synthesis of 2,4,6-cycloheptatrien-1-one (tropone) (I)[2] and evidence bearing on its aromatic character.



(I) (II) (III)

2-Cyclohepten-1-one on treatment with four equivalents of bromine in acetic acid and heating for fifteen hours yields 38% 2,4,7-tribromotropone, cream needles (MeOH), m.p. 182–183° (calcd. for $C_7H_3OBr_3$: C, 24.51; H, 0.88; Br, 69.93. Found: C, 24.61; H, 1.11; Br, 70.80) (u.v. max. (EtOH): 275 mμ (22,100), 345 mμ (9400)), which absorbs (Pd–$BaSO_4$, EtOH) 6.0 moles of hydrogen to give cycloheptanone, is inert to ethanolic silver nitrate, and dissolves in ethanolic sodium hydroxide to furnish 88% dibromobenzoic acid(s), hydrogenolyzed to benzoic acid or fractionally crystallized to 2,5-dibromobenzoic acid.

Hydrogenolysis of tribromotropone in absolute ethanolic potassium acetate using poisoned palladium–barium sulfate catalyst interrupted at 2.9 moles yields 95% ionic bromine and 40% tropone (I), b.p. 104–105.5° (10 mm.), $n^{25}D$ 1.6070, viscous, almost colorless, hygroscopic (limited analyses to *ca.* C_7H_6O), (u.v. max. (HOH): 225 mμ (21,200); 228 mμ (22,100); 231.5 mμ (22,100); 239 mμ (12,700); 304 mμ inflection (8000); 312.5 mμ (8400)), (i.r. max.(liq.), 5–8 μ region; 5.86 μ (m); 6.09 μ (s); 6.35 μ (s); 6.60 μ (s); 6.75 μ (s); 7.98 μ (s); 8.22 μ (s). Reactions of tropone: (i) *salt formation:* hydrochloride, white hygroscopic needles by ether–hydrogen chloride and sublimation; picrylsulfonate, m.p. 266–267°, pale needles from aqueous picrylsulfonic acid (calcd. for $C_{13}H_9O_{10}N_3S$: C, 39.10; H, 2.27. Found: C, 38.93; H, 2.54); dipicrate, m.p. 100–101°, yellow needles from aqueous picric acid, (calcd. for $C_{19}H_6O_{15}N_6$: C, 40.43; H, 2.14. Found: C, 39.99; H, 2.44); (ii) *hydrogenation:* (Pd–$BaSO_4$, EtOH) 3.0 moles (only) in 17 min. to give 91% cycloheptanone; (PtO_2, HOAc) 4.0 moles in 28 min.; (iii) *carbonyl reactions:* no 2,4-dinitrophenylhydrazone in ethanol-sulfuric acid or acetic acid; hydroxylamine consumption (titration) only on heating (0.67 equiv., 2 hr.); (iv) *ring reactions:* aqueous permanganate, rapidly decolorized; benzenediazonium chloride in aqueous sodium acetate, immediate orange precipitate; bromination at 25°, moderately rapid in water, slower in aqueous acetic acid, very slow in carbon tetrachloride, to give addition products which eliminate hydrogen bromide partially during preparation but more readily on heating to furnish crystalline bromotropones.

These reactions and properties of tropone resemble strikingly those of its isostere, 4-pyrone, and this similarity suggests that aromatic character in tropone may originate from analogous carbonyl polarization (II) and resonance of six π-electrons among seven π-orbitals (III). This system would acquire a benzene-like $2p_\pi$ molecular orbital energy pattern which has been considered[3] as being largely responsible for aromatic behavior. Aromaticity in tropolone and azulene may arise from this type of resonance, stabilized by exocyclic structural features, or from other types.

(1) Pertinent references in (a) M. J. S. Dewar, *Nature*, **166**, 790 (1950); (b) A. G. Anderson, Jr. and J. A. Nelson, THIS JOURNAL, **72**, 3824 (1950).

(2) *Cf.* 4,5-benztropone, J. Thiele and E. Weitz, *Ann.*, **377**, 1 (1910).

(3) *Cf.* F. O. Rice and E. Teller, "The Structure of Matter," John Wiley and Sons, New York, N. Y., 1949, p. 107.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF WASHINGTON HYP J. DAUBEN, JR.
SEATTLE 5, WASH. HOWARD J. RINGOLD

RECEIVED JANUARY 16, 1951

CYCLOHEPTATRIENYLIUM OXIDE

Sir:

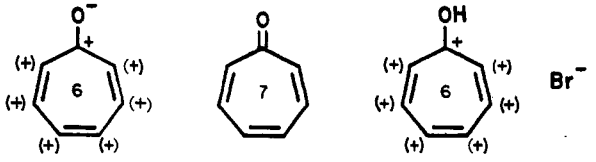
The general molecular orbital theory ascribing peculiar stability to cyclic molecular orbitals containing $2 + 4n$ electrons[1] has, among others, the corollary that the cycloheptatrienylium ion (I) should be more stable than the cyclopentadienylium ion (II) whereas the stability of the anions, $C_7H_7^-$ and $C_5H_5^-$, should be reversed. We have now synthesized C_7H_6O (III) and found its properties to be represented by the structure cycloheptatrienylium oxide (IIIa) in accord with the theory.

I II

Hydroxycycloheptatrienylium bromide (IV) is obtained from methoxytropilidene, prepared by the photochemical decomposition of diazomethane in anisole, by treatment with one equivalent of bromine, either directly or after preliminary acid hydrolysis to cycloheptadienone. IV is a colorless, sublimable salt from which aqueous sodium bicarbonate liberates III: m.p. −8 to −5°; b.p. 113° at 15 mm.; $n^{22}D$ 1.6172; d^{22}_4 1.095; M_D 33.9 (calcd. for "cycloheptatrienone" (IIIb), 30.9); C, 79.07; H, 5.88; miscible with water; crystallizable from ether. III is reconverted to IV with hydrogen bromide and forms a picrate: m.p. 99–100°; C, 46.65; H, 2.84. The infrared spectrum (we thank Mr. Alfred P. Wolf, Columbia University)

(1) E. Hückel, "Grundzüge der Theorie ungesättigter und aromatischer Verbindungen," Verlag Chemie, Berlin, 1938, pp. 71-85.

has prominent maxima at 3425, 2970, 1638, 1582, 1524, 1475, 1225, 1217, 1009, 936, 898, 834 and 785 cm.$^{-1}$. The ultraviolet spectrum in isoöctane shows maxima at 225 mu (log E 4.33), 297 (3.74) and 310 (3.67). Both III and IV react with three



IIIa IIIb IV

molecules of hydrogen with Adams platinum catalyst in ethanol to give *cycloheptanone*, identified as the semicarbazone, m.p. and m.p. mixed with authentic material 162.5–163°. The possible presence of an O–H bond inferred from the 3425 cm.$^{-1}$ band is excluded by the failure of III to exchange more than negligibly with deuterium oxide (analysis by Mr. Arthur K. Hoffmann, Columbia University). The arrangement of atoms in III is unquestionable (IIIa or IIIb).

As an extreme electronic structure, IIIa and not IIIb satisfactorily expresses (a) the basicity which reflects a high electron density on oxygen and a stabilization of positive charge (IV), (b) the large dipole moment implied by the high boiling point (*cf.* benzaldehyde, b.p. 68° at 15 mm.), miscibility with water and the large exaltation, and (c) the shift of the carbonyl frequency. The stability of IIIa relative to IIIb and the very existence of III in contrast to the non-existence of cyclopentadienones (having fewer than two phenyl substituents),[2] find insufficient theoretical explanation in terms of resonance structures (IIIa) alone, but are explained by the molecular orbital theory which predicts peculiar stability from *six* electrons in a cyclic resonating system.

This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service.

(2) C. F. H. Allen and J. A. VanAllan, THIS JOURNAL, **72**, 5165 (1950).

HICKRILL CHEMICAL RESEARCH LABORATORY
KATONAH, NEW YORK
W. VON E. DOERING
FRANCIS L. DETERT

RECEIVED JANUARY 16, 1951

COUNTERCURRENT DISTRIBUTION OF INSULIN

Sir:

Our success in applying the technique of countercurrent distribution to the study of the purity of polypeptides in the molecular weight range of a few thousand has encouraged us to attempt a similar study with proteins. Insulin as a type substance has given promise from the first attempts and has now been studied in several systems.

Active material has been found to give an interchange between phases sufficiently rapid to permit a true partition ratio to hold. This in itself would appear to be a finding of considerable interest. Although runs involving approximately 100 transfers did not clearly reveal more than a single major component, higher numbers of transfers were more revealing. The major band did not continue to behave as a single component.

For example, an experiment made with 500 mg. of a sample of beef insulin (activity 27 μ/mg. Sample No. T 2344), supplied by the Eli Lilly Company, gave the result shown in Fig. 1 at 424 transfers (System 2-butanol/1% aqueous dichloroacetic acid; temp. 24°; pH of system 2.7; single withdrawal procedure[1] used). The distribution apparatus contained 220 equilibration cells in the train and was operated automatically.[2]

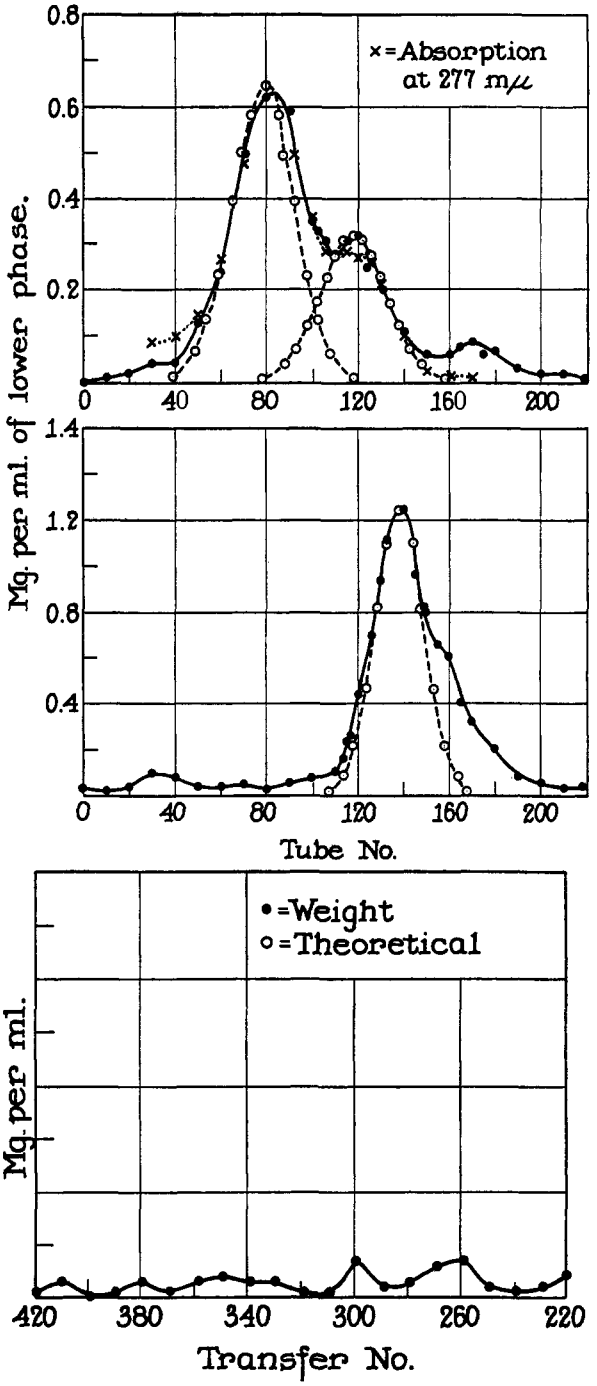


Fig. 1.—Distribution patterns of insulin: ●, weight; ○, theoretical: lower 424 transfers; upper 909 transfers.

(1) L. C. Craig and O. Post, *Anal. Chem.*, **21**, 500 (1949).
(2) L. C. Craig, *ibid.*, **22**, 1345 (1950).

Aside from small percentages of impurities or transformation products appearing in most of the fractions, the main solute band showed an interesting shoulder. In order to learn whether or not the shoulder really indicated a major second component, the apparatus was adjusted for the "recycling procedure"[2] and permitted to operate until 909 transfers had been accomplished. The upper pattern shown in Fig. 1 was thus obtained.

Although such a result strongly indicates two major components with slightly different partition ratios, further study is required, particularly since Fredericq and Neurath[3] have studied this same sample and, among other criteria, found it to give a solubility curve indicative of a single component.

It proved relatively easy to crystallize material from each peak of Fig. 1. Though identical in crystalline form, the largest component, A, showed a lower partition ratio in the system than did the faster moving B component. The partition ratios calculated from the pattern are 0.49 and 0.59. The activity[4] of the recovered material, if at all different, appeared to be slightly lower, *e. g.*, 22 and 26 μ/mg., respectively, for A and B, rather than higher than that of the starting material. No difference was found in the C, H and N analyses of A and B.

An attempt to redistribute material from each peak and to determine the quantitative amino acid composition will be made at the earliest opportunity. It is possible these results may have a bearing on the inconsistency of the proposed minimum molecular weight[3] of 6000 for the dissociated form and the published quantitative amino acid analyses[4] for insulin.

We are indebted to Dr. E. D. Campbell of the Eli Lilly Company for the insulin and for the bioassays.

(3) E. Fredericq and H. Neurath, THIS JOURNAL, **72**, 2684 (1950).

(4) F. Sanger, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **XLV**, 287 (1948).

THE ROCKEFELLER INSTITUTE
FOR MEDICAL RESEARCH ELIZABETH J. HARFENIST
NEW YORK 21, N. Y. LYMAN C. CRAIG

RECEIVED JANUARY 17, 1951

THE PARTIAL SYNTHESIS OF ESTRONE-16[1] AND OF ISOANDROSTERONE-16 (HEARD'S OXYKETONE)

Sir:

In our studies[2] of the various reductive methods as applied to 16-keto-17-hydroxysteroids we have found that the Clemmensen reduction of such a steroid unexpectedly gives rise to the 16-keto-17-desoxy compound. Thus, from 16-keto-estradiol[3] is obtained 3-hydroxy-16-keto-$\Delta^{1,3,5}$-estratriene (estrone-16) melting[4] at 243.5–245.5° dec. and having an optical rotation of $[\alpha]^{25}D$ −87° (in 95% ethanol). *Anal.*[5] Calcd. for $C_{18}H_{22}O_2$: C, 79.96, H, 8.20. Found: C, 80.04, 79.93; H, 8.22, 8.15. That this compound possesses the unaltered naturally-occurring $\Delta^{1,3,5}$-estratriene nucleus was established by hydrogenolysis of the 3-benzoxy-16-diethyl thioketal[2] to desoxoestrone benzoate (followed by saponification to desoxoestrone) as shown by mixed melting point comparison using authentic desoxoestrone benzoate[6] (and using authentic desoxoestrone[6]).

Estrone-16 was further characterized by preparation of the analytically pure semicarbazone (m.p. 246.5–248° dec.), acetate (m.p. 132–133°), benzoate (m.p. 223.5–224.5°, slight dec.), palmitate (m.p. 110.5–111.5°), methyl ether (m.p. 124–124.5°), and benzyl ether (m.p. 156–156.5°).

In 1939 Heard and McKay[7] isolated from mares' pregnancy urine a 3β-hydroxy-keto-androstane in which the position of the ketonic oxygen was not determined. Oppenauer[8] later confirmed this isolation. Much speculation has ensued concerning the exact location of the carbonyl in this androstane derivative.

The Clemmensen reduction of 3β,17-dihydroxy-16-keto-androstane (m.p. 217–218° dec.), prepared by the sequence of nitrosation[9] and Stodola reduction[9] of isoandrosterone, furnished 3β-hydroxy-16-keto-androstane (isoandrosterone-16) melting at 186–186.5° and possessing an optical rotation of $[\alpha]^{25}D$ −180° (in dioxane). *Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.55, 78.62; H, 10.36, 10.37. Isoandrosterone-16 gave a benzoate melting at 208.5–209° and an oxime melting at 199°.

Heard characterized his oxyketone ($C_{19}H_{30}O_2$) in part as follows: melting point, 187–187.5°; optical rotation, $[\alpha]^{24}D$ −160° (in dioxane); benzoate, m.p. 206–208°; oxime, m.p. 194–195°. Although a direct comparison between our isoandrosterone-16 and Heard's oxyketone has not yet been possible, it is highly probable that they are identical.

[Since this manuscript was submitted for publication a direct comparison between synthetic isoandrosterone-16 and the urinary androstanolone of Heard and McKay (supplied by Professor R. D. H. Heard) has been possible. A mixed melting point test showed no depression.]

We wish to thank G. D. Searle and Company and the Graduate Research Institute of Baylor University at Dallas for financial support of this research.

(1) The research concerning estrone-16 was completed in the Department of Biochemistry, Southwestern Medical School, Dallas, Texas.

(2) M. N. Huffman and M. H. Lott, THIS JOURNAL, **71**, 719 (1949).

(3) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **172**, 325 (1948).

(4) All melting points are uncorrected.

(5) Analyses were performed and optical rotations determined by Dr. E. W. D. Huffman, Denver.

(6) Kindly supplied by Dr. O. Wintersteiner of the Squibb Institute for Medical Research.

(7) R. D. H. Heard and A. F. McKay, *J. Biol. Chem.*, **131**, 371 (1939).

(8) R. Oppenauer, *Z. physiol. Chem.*, **270**, 97 (1941).

(9) F. H. Stodola, E. C. Kendall and B. F. McKenzie, *J. Org. Chem.*, **6**, 841 (1941).

THE OKLAHOMA MEDICAL RESEARCH INSTITUTE
MAX N. HUFFMAN
OKLAHOMA CITY, OKLAHOMA MARY HARRIET LOTT

RECEIVED DECEMBER 14, 1950

TOMATIDINE, A STEROID SECONDARY AMINE[1]

Sir:

Crystalline tomatine, a new glycosidal alkaloid having antifungal activity, was first isolated in our laboratory from the tomato plant and found to consist of an aglycone portion, tomatidine,[2] and a tet-

(1) Report of a study in which certain phases were carried on under the Research and Marketing Act of 1946.

(2) T. D. Fontaine, G. W. Irving, Jr., R. M. Ma, J. B. Poole, and S. P. Doolittle, *Arch. Biochem.*, **18**, 467 (1948).

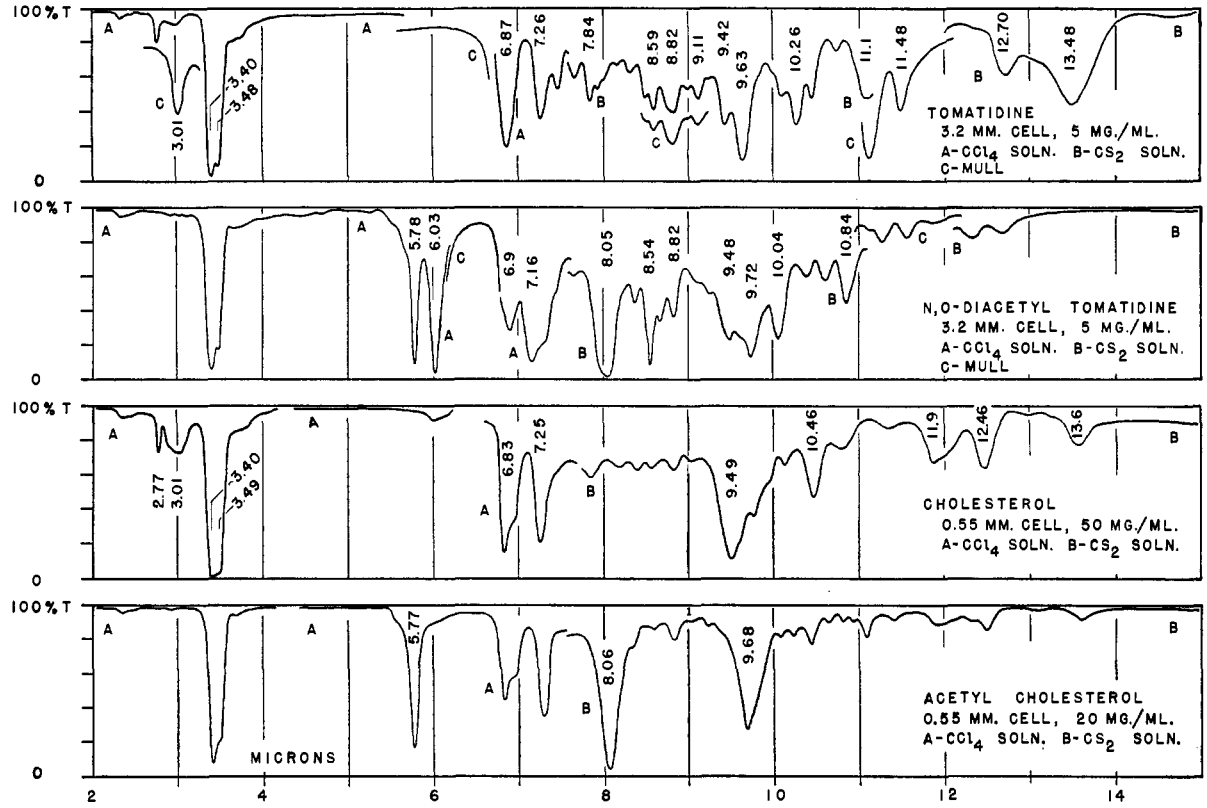


Fig. 1.—Infrared spectra of tomatidine, N,O-diacetyltomatidine, cholesterol, and acetylcholesterol.

rasaccharide moiety, composed of xylose, galactose, and two glucose units.[3] We now wish to report some of the chemical and physical data which have suggested a steroid structure for tomatidine. These products and some derivatives are here assigned the following empirical formulas:

Tomatine.—*Anal.* Calcd. for $C_{50}H_{83}O_{21}N$: C, 58.07; H, 8.09; N, 1.35. Found: C, 57.62; H, 8.15; N, 1.37.

Tomatidine, m.p. 210–211°[4]. *Anal.* Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91; N, 3.37. Found: C, 78.02; H, 10.97; N, 3.37; CH_3O, absent.

N,O-Diacetyltomatidine.—By the treatment of tomatidine with acetic anhydride in pyridine at room temperature, m.p. 193–194°. *Anal.* Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88; N, 2.80. Found: C, 74.36; H, 9.78; N, 2.84.

Dihydrotomatidine.—By the reduction of tomatidine with $LiAlH_4$ in diethyl ether solution, m.p. 194–195°. *Anal.* Calcd. for $C_{27}H_{47}O_2N$: C, 77.64; H, 11.34. Found: C, 76.92; H, 11.14.

N,O,O′-Triacetyldihydrotomatidine.—By the treatment of dihydrotomatidine with acetic anhydride in pyridine at room temperature. *Anal.* Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.83. Found: C, 72.87; H, 9.78.

Kuhn, *et al.*,[5] have confirmed our results on the sugars in tomatine but have differed by assigning an ethylenic linkage and, therefore, two less hydrogen atoms to these compounds.[5,6] We have found no evidence of an ethylenic group by either ultraviolet or infrared analysis (Fig. 1). The absorption of one mole of hydrogen by tomatidine[5] may have resulted in the opening of an oxidic linkage, as reported by Marker, *et al.*,[7] for sapogenins. Further evidence of the opening of an oxidic ring is that after $LiAlH_4$ reduction, as reported here, an additional hydroxyl group appeared, after which acetylation added three instead of two acetyl groups.

Tomatidine forms an alcohol insoluble digitonide, which is evidence of a 3(β)-ol sterol configuration. The steroid structure of tomatidine has been confirmed by Sato, *et al.*,[8] who have degraded it to Δ^{16}-allo-pregnen-3(β)-ol-20-one.

The infrared spectra of tomatidine and diacetyltomatine are compared with those of cholesterol and acetylcholesterol in Fig. 1. In the spectrum of diacetyltomatidine, a strong band appears at 6.03 microns from acetylation of the nitrogen, which together with the absence of bands at 3.0 and 6.5 microns, is characteristic of a secondary amine structure of the original base.[9,10]

(3) R. M. Ma and T. D. Fontaine, *ibid.*, **27**, 461 (1950).

(4) All melting points were taken on samples sealed in evacuated tubes and are corrected.

(5) R. Kuhn, I. Löw and A. Gauhe, *Ber.*, **83**, 448 (1950).

(6) R. Kuhn and I. Löw, *ibid.*, **81**, 552 (1948).

(7) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

(8) Y. Sato, A. Katz, E. Mosettig, *ibid.*, **73**, 880 (1951).

(9) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949.

(10) A preliminary report of some of this work was presented at the American Society of Biological Chemists Meeting, Atlantic City, N. J., April 17–21, 1950; T. D. Fontaine, J. S. Ard, R. M. Ma, C. L. Ogg and C. O. Willits, *Federation Proc.*, **9**, 171 (1950).

BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY
THOMAS D. FONTAINE
AGRICULTURAL RESEARCH CENTER J. S. ARD
BELTSVILLE, MARYLAND ROBERTA M. MA

RECEIVED DECEMBER 8, 1950

DEGRADATION OF TOMATIDINE

Sir:

In view of the recent interest in tomatidine[1,2,3] we wish to report our results on the degradation of tomatidine.[4]

Our analytical data of tomatidine and derivatives agree with the empirical formula $C_{27}H_{45}NO_2$ proposed by Fontaine, *et al.*,[5] rather than $C_{27}H_{43}NO_2$, suggested tentatively by Kuhn, *et al.*[3] Tomatidine. *Anal.* Calcd. for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37; for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.02; H, 10.96; N, 3.43.

Tomatidine hydrochloride. *Anal.* Calcd. for $C_{27}H_{46}ClNO_2$: C, 71.73; H, 10.26; for $C_{27}H_{44}ClNO_2$: C, 72.05; H, 9.85. Found: C, 71.83; H, 10.35.

N,O-Diacetyltomatidine.[6]—*Anal.* Calcd. for $C_{31}H_{49}NO_4$: C, 74.50; H, 9.88; for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52. Found: C, 74.66; H, 9.92.

Tomatidine forms a sparingly soluble digitonide. On treatment with sodium nitrite in acetic acid a N-nitroso derivative is obtained, m.p. 234–237°[7]; λ_{max} 233 mμ, log ε 3.87: λ_{max} 360, log ε 1.83 (ethanol). *Anal.* Calcd. for $C_{27}H_{44}N_2O_3$: N, 6.30. Found: N, 6.36.

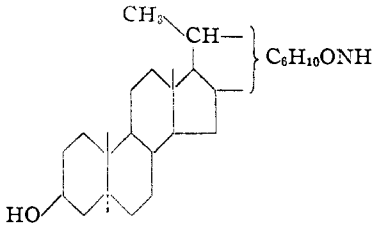
Treatment of tomatidine with acetic anhydride yielded an unsaturated triacetyl derivative (A), m.p. 105–107°. *Anal.* Calcd. for $C_{33}H_{51}NO_5$: C, 73.16; H, 9.49. Found: C, 73.12; H, 9.78.

A gave with dilute alkali a monoacetyl derivative, m.p. 210–215°. *Anal.* Calcd. for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 76.11; H, 10.42; N, 3.08.

Oxidation of A with chromic acid anhydride in acetic acid, and subsequent hydrolysis resulted in the formation of Δ^{16}-allopregnen-3(β)-ol-20-one, m.p. 205–206°, no depression when admixed with an authentic sample. *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.55; H, 10.30.

The acetate of the compound likewise agrees well (m.p. 167–168°, mixed m.p., ultraviolet and infrared spectra) with authentic samples.[8] *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05: H, 9.56. Found: C, 77.58; H, 9.80.

The isolation of the allopregnenolone establishes the structure of the steroidal moiety of tomatidine (I) and the attachment of the portion containing the secondary nitrogen, at C-20. The second point of attachment is most likely at position 16.



I

(1) Fontaine, Irving, Ma, Poole and Doolittle, *Arch. Biochem.*, **18**, 467 (1948).
(2) Kuhn and Löw, *Chem. Ber.*, **81**, 552 (1948).
(3) Kuhn, Löw and Gauhe, *ibid.*, **83**, 448 (1950).
(4) Kindly supplied to us by Dr. Thomas D. Fontaine, Bureau of Agricultural and Industrial Chemistry.
(5) Fontaine, Ard and Ma, THIS JOURNAL, **73**, 000 (1951).
(6) Purified by chromatography.
(7) All melting points were taken on the Kofler block and are uncorrected.
(8) A sample was kindly supplied to us by Dr. R. B. Wagner of Pennsylvania State College. Another generous sample was given to us by Dr. George Rosenkranz of Syntex, S. A.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND
YOSHIO SATO
ALFRED KATZ[9]
ERICH MOSETTIG

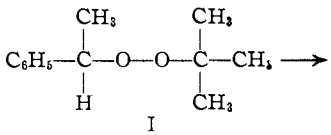
RECEIVED DECEMBER 8, 1950

(9) Organisch-chemische Anstalt, University of Basel.

THE BASE CATALYZED DECOMPOSITION OF A DIALKYL PEROXIDE

Sir:

We have found that bases, such as potassium hydroxide, sodium ethoxide, or piperidine, catalyze the decomposition of 1-phenylethyl-*t*-butyl peroxide (I)



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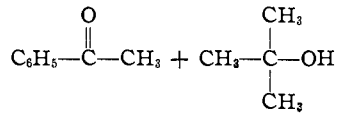
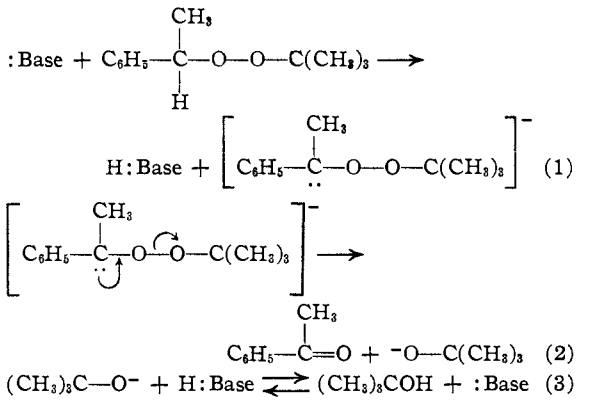


This reaction takes place smoothly at room temperature and apparently is the first demonstration of the instability of a dialkyl peroxide toward base. The facile decomposition of I contrasts sharply with the inertness of di-*t*-butyl peroxide to potassium hydroxide[1] or piperidine.

The following mechanism, which is in accord with all the known facts, emphasizes the relationship of this reaction to the well-known elimination reaction[2]; steps (1) and (2) presumably are synchronous.



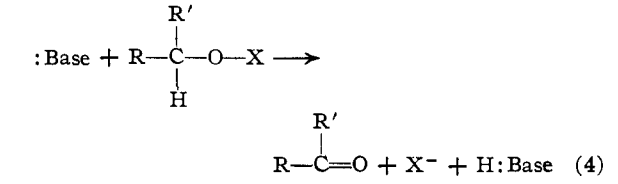
This mechanism also affords a reasonable explanation for the conversion of α-tetralin hydroperoxide (II) to α-tetralone under the influence of sodium hydroxide.

It is a consequence of this mechanism that only those dialkyl peroxides and alkyl hydroperoxides having a hydrogen on the carbon attached to the peroxide linkage will undergo base catalyzed decomposition. That the aromatic nucleus in I and II is not a necessary structural feature is indicated

(1) N. A. Milas and D. M. Surgenor, THIS JOURNAL, **68**, 205 (1946).
(2) E. D. Hughes, C. K. Ingold, *et al.*, *J. Chem. Soc.*, 2093 (1948).

by the report that isopropyl hydroperoxide, which is relatively stable to acidic and neutral solutions, under alkaline conditions rapidly gives acetone.[3] Similarly, peroxides and hydroperoxides such as *i*-propyl-*t*-butyl peroxide and cyclohexene hydroperoxide will be expected to exhibit instability toward bases.[4]

The base-catalyzed decompositions of peroxides and hydroperoxides apparently exemplify a rather general type of elimination reaction which may be anticipated for compounds in which an atom or group X, capable of giving a relatively stable anion X^-, is attached to oxygen



Thus the decomposition of nitrate esters (X = $-NO_2$) under the influence of hydroxide ion is an analogous process; $HO^- + C_6H_5CH(H)O\overset{\curvearrowright}{N}O_2 \downarrow$ $C_6H_5CH{=}O + NO_2^- + H_2O$.[5] To test the generality of reaction (4) the following suggest themselves for study: X = $C(C_6H_5)_3$, NR_2, mesitoyl, —C≡C—Aryl, etc.[6]

Peroxide I was obtained by the action of potassium *t*-butyl peroxide on 1-phenylethyl bromide; b.p. 56.3–57° (1.3 mm.); $n^{20}D$ 1.4809 (calcd. for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 74.35, 74.51; H, 9.18, 9.14). When I (0.08 mole) was dissolved in piperidine (0.40 mole) the temperature rose to 50° within fifteen minutes. At this point the solution was cooled to 25° and then maintained at 25° for eighty hours. Acetophenone was isolated in 79% yield; *t*-butyl alcohol, in 25% yield. When 0.05 mole I was mixed with 0.01 mole piperidine the temperature did not rise; after eighty-four hours at 25°, a 32% yield of acetophenone was obtained.

(3) S. S. Medwedew and E. Alexejewa, *Ber.*, **65**, 133 (1932).

(4) Compare V. L. Vaiser, *C. A.*, **44**, 3446 (1950); F. F. Rust, F. H. Seubold, and W. E. Vaughan, THIS JOURNAL, **72**, 338 (1950).

(5) J. W. Baker and D. M. Easty, *Nature*, **166**, 156 (1950).

(6) The base-catalyzed decomposition of hypohalites has been formulated as in eq. 4; X = Cl. Private communication from Dr. Saul Winstein.

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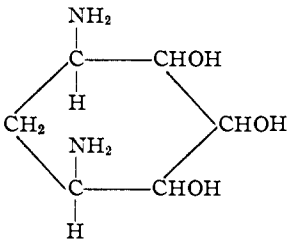
RECEIVED DECEMBER 1, 1950

STREPTOMYCES ANTIBIOTICS. XXIII. 1,3-DIAMINO-4,5,6-TRIHYDROXYCYCLOHEXANE FROM NEOMYCIN A.

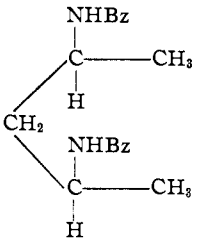
Sir:

Neomycin A has been degraded to a new compound which has been established as a *meso* form of 1,3-diamino-4,5,6-trihydroxycyclohexane (I).

Hydrolysis of Neomycin A[1] by heating a solution of it in 6 *N* hydrochloric acid at 140° for sixteen hours yielded the dihydrochloride of an optically inactive diacidic base. *Anal.* Calcd. for $C_6H_{14}N_2O_3 \cdot 2HCl$: C, 30.66; H, 6.86; N, 11.93; Cl, 30.17; eq. wt., 117.5. Found: C, 30.89; H, 6.71; N, 12.19; Cl, 29.44; eq. wt., 120 (potentiometric titration). Benzoylation of this base gave a pentabenzoate. *Anal.* Calcd. for $C_6H_9N_2O_3(C_6H_5CO)_5$: C, 72.12; H, 5.02; N, 4.10. Found: C, 71.77; H, 5.05; N, 4.04. Selective oxygen-debenzoylation of the pentabenzoate with barium methoxide in methanol yielded an N,N′-dibenzoyl derivative. *Anal.* Calcd. for $C_6H_{12}N_2O_3(C_6H_5CO)_2$: C, 64.85; H, 5.99; N, 7.55. Found: C, 65.05; H, 5.90; N, 7.70.



I

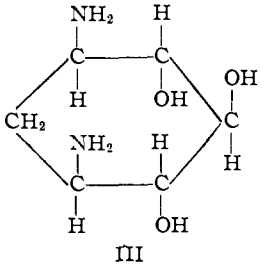


II

The original free base consumed four moles of periodate whereas its N,N′-dibenzoyl derivative utilized two moles. These combined data suggested that the structure of the base was that of a 1,3-diamino-4,5,6-trihydroxycyclohexane (I).

Confirmation of structure I was obtained by the following series of reactions and products. Periodate oxidation of the N,N′-dibenzoyl derivative yielded a dialdehyde, which was not separated, but which upon treatment with ethyl mercaptan and hydrogen chloride gave a dimercaptal; m.p. 140–141°. *Anal.* Calcd. for $C_{13}H_{28}N_2S_4(C_6H_5CO)_2$: C, 58.87; H, 6.95; N, 5.09; S, 23.3. Found: C, 58.97; H, 6.91; N, 5.40; S, 23.8. The dimercaptal was converted by hydrogenolysis with Raney nickel to an N,N′-dibenzamido-pentane (II); m.p. 197–197.5°. *Anal.* Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.53; H, 6.96; N, 8.50.

The higher-melting *meso* isomer[2] of 1,3-dibenzamido-pentane was prepared by stepwise catalytic reduction and benzoylation of acetylacetone dioxime. It melted at 197.5–198°, and caused no depression of melting point upon admixture with the degradation product.



III

The nitrogen atoms of this *meso* isomer of 1,3-diamino-4,5,6-trihydroxycyclohexane must have a *cis* relationship, and if the molecule is biogenetically related to streptidine, which has an all-*trans*-

(1) Peck, Hoffhine, Gale and Folkers, THIS JOURNAL, **71**, 2590 (1949).

(2) Dippel, *Rec. trav. chim.*, **50**, 525 (1931).

configuration,[3] its configuration would be all-*trans* also (III).

(3) Wolfrom and Olin, THIS JOURNAL, **72**, 1724 (1950).

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MARY NEALE BISHOP
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RECEIVED JANUARY 4, 1951

A NEW REACTION IN ORGANOSILICON CHEMISTRY

Sir:

We wish to report a new reaction which proceeds readily with certain organosilicon structures in the presence of concentrated sulfuric acid and involves cleavage of *one* methyl group from trimethylsilyl, Me_3Si, in a variety of compounds containing functional groups linked to carbon. This reaction makes possible the synthesis of a large number of hitherto unavailable new-type organosiloxanes.[1]

β-Trimethylsilylpropionic acid[2] (294 g.) was added dropwise with stirring to 400 cc. of cold (10°) concentrated sulfuric acid during one and one-half hours. A vigorous evolution of methane (identified by infrared absorption spectrum) occurred during the addition. Reaction was completed by warming on the steam-bath for one hour until gas evolution ceased. The reaction mixture was cooled and poured onto cracked ice, giving immediate formation of a white solid. Recrystallization from *n*-hexane gave 265 g., 95% yield, of 4,4,6,6-tetramethyl-4,6-disila-5-oxanonanedioic acid, m.p. 53–54°. *Anal.* $C_{10}H_{22}Si_2O_5$: Si, 20.16; neut. equiv., 139. Found: Si, 20.02; neut. equiv., 140.

$$2\ Me_3SiCH_2CH_2CO_2H \xrightarrow{H_2SO_4} \xrightarrow{H_2O} (H_2OCCH_2CH_2SiMe_2)_2O + 2\ CH_4$$

Reaction of β-trimethylsilylethylamine,[3] $Me_3SiCH_2CH_2NH_2$, with concentrated sulfuric acid by the procedure described above, followed by treatment with base, gave a 76% yield of 1,7-diamino-3,3,5,5-tetramethyl-3,5-disila-4-oxa-heptane, $(NH_2CH_2CH_2SiMe_2)_2O$, b.p. 115° (13 mm.), $n^{20}D$ 1.4473. *Anal.* $C_8H_{24}Si_2N_2O$: Si, 25.51. Found: Si, 25.46.

Similarly, reaction of 4-trimethylsilyl-2-butanone,[4] $Me_3SiCH_2CH_2COCH_3$, with concentrated sulfuric acid, followed by treatment with water, gave 42% yield of 5,5,7,7-tetramethyl-5,7-disila-6-oxa-2,10-undecanedione, $(CH_3COCH_2CH_2SiMe_2)_2O$, b.p. 142° (6 mm.), $n^{20}D$ 1.4390. *Anal.* $C_{12}H_{26}Si_2O_3$: Si, 20.46; mol. wt., 274. Found: Si, 20.60; mol. wt., 283.

The general scope, definitive constitutional factors, and the mechanism of the above reaction, are under investigation.

(1) It is, of course, important to recognize that organosilicon structures capable of yielding a β-carbonium ion (Me_3-Si-C-C$^+$) with concentrated sulfuric acid will give cleavage of the organic group containing the functional group, and hence cannot undergo the above reaction: *cf.* F. C. Whitmore, L. H. Sommer, J. Gold and R. E. Van Strien, THIS JOURNAL, **69**, 1551 (1947); L. H. Sommer, L. J. Tyler and F. C. Whitmore, *ibid.*, **70**, 2872 (1948); J. Gold, L. H. Sommer and F. C. Whitmore, *ibid.*, **70**, 2874 (1948).

(2) L. H. Sommer, J. Gold, G. M. Goldberg and N. S. Marans, *ibid.*, **71**, 1509 (1949).

(3) β-Trimethylsilylethylamine, b.p. 121° (734 mm.), $n^{20}D$ 1.4241, Si, 24.06% (calcd. 23.93), was prepared by the Hofmann reaction from β-trimethylsilylpropionamide, m.p. 95–96°, Si, 19.43% (calcd. 19.31); which was in turn prepared from β-trimethylsilylpropionyl chloride, b.p. 92° (65 mm.), Si, 16.84% (calcd. 17.03). The latter resulted from treatment of β-trimethylsilylpropionic acid[2] with thionyl chloride.

(4) L. H. Sommer and N. S. Marans, *ibid.*, **72**, 1935 (1950).

THE WHITMORE LABORATORY
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L. H. SOMMER
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J. ROCKETT
R. P. PIOCH

RECEIVED DECEMBER 18, 1950

LIGHT SCATTERING STUDIES ON FIBRINOGEN: PRELIMINARY REMARKS

Sir:

In view of the wide interest appertaining to the fibrinogen-fibrin system and the numerous workers currently engaged upon it, we wish to present here some pertinent results obtained by the light scattering method.[1,2,3,5] These results will also be reported in greater length and detail later.

Fibrinogen was prepared by fractionation of Armour plasma fraction I.[4] A product was obtained which displayed only a single boundary in the ultracentrifuge and with a minimum of 95% polymerizable protein.

Measurements upon three different samples at *p*H's 8.40 and 7.00 at ionic strength 0.35 gave for the native fibrinogen an average molecular weight of 540,000 and a length from the extrapolated dissymmetry coefficient of 850Å. It is apparent that the fibrinogen molecule is an asymmetric, rod-like particle.

The addition of thrombin to an activity of about 0.1 unit/ml. to a 0.14% solution of fibrinogen at *p*H 8.40 and ionic strength 0.35 brought about a rapid increase in dissymetry and turbidity. The increase in length calculated from the dissymetry was linear in time throughout the early stages of the reaction. A comparison of the average degrees of polymerization calculated from the increase in length of fibrinogen molecules as well as end to end association occurred.

Prior to gelation under these conditions the dissymmetry coefficient did not increase beyond the limiting value for a rod-like molecule. At a time immediately preceding gelation the weight average molecular weight was about 4,000,000 and the average length about 2500 Å. It was indicated that rod-like units averaging about three times the length of native fibrinogen and about eight times its molecular weight exist in solution prior to gelation under these conditions.

After gelation a slow increase in both turbidity and dissymmetry occurs. The process at *p*H 7.00 with other conditions unchanged is qualitatively quite similar except that after gelation the turbidity of the gel increased to a slightly higher value than at *p*H 8.40.

The action of papain is qualitatively similar to that of thrombin in producing a gel. The hydrolytic action of the papain slowly dissolved the gel formed, yielding eventually a product of a weight average molecular weight 200,000.

(1) J. T. Edsall, J. F. Foster and H. Scheinberg, THIS JOURNAL, **69**, 2731 (1947).

(2) J. L. Oncley, G. Scatchard and A. Brown, *J. Phys. Colloid Chem.*, **21**, 184 (1947).

(3) K. Laki, *Studies Inst. Med. Chem. Univ. Szeged*, **2**, 27 (1942).

(4) K. Laki, to be published.

(5) J. D. Ferry and P. R. Morrison, THIS JOURNAL, **69**, 388 (1947).

The gel formed by thrombin dissolved readily in 6 *M* urea at *p*H 8.40 to give products of the same molecular weight as native fibrinogen under the same conditions. It was not however possible for the present to ascertain the absolute value of the molecular weight because of uncertainties as to the contribution of selective adsorption to the scattering of such a three component system.

Further work is in progress with the aim of ascertaining the nature of the sub-units involved in the actual formation of the three dimensional network and whether they correspond in size and shape to the aggregates found immediately prior to gelation.

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NATIONAL NAVAL MEDICAL CENTER
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NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND KALOMAN LAKI

RECEIVED DECEMBER 16, 1950

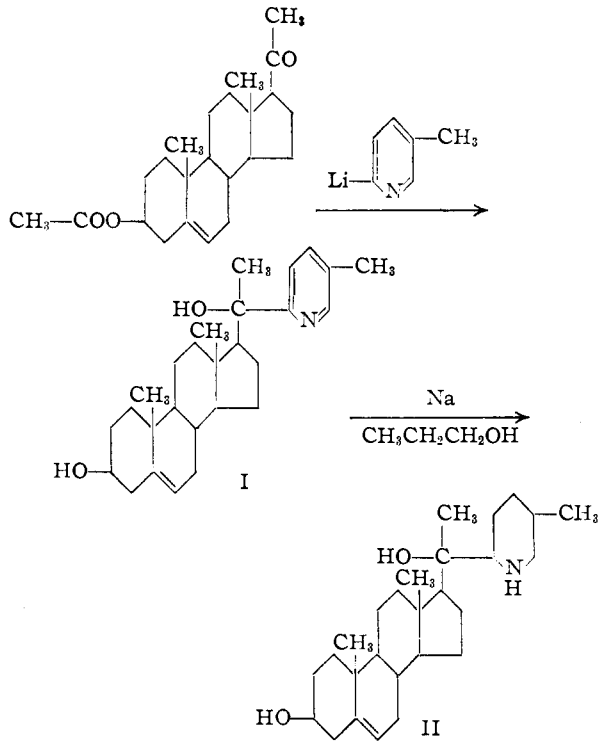
STEROID SECONDARY AMINES[1]

Sir:

The *veratrum*, and closely related *solanum*, alkaloids may be divided into two groups on the basis of the character of the nitrogen function, a separation reaffirmed in a parallel differentiation as a result of pharmacological studies. Because of the wide diversity of pharmacodynamic effects which they exhibit,[2] tertiary veratrum bases of the type of veratridine have been of interest to biologists for nearly a century, while protoveratrine and germitrine, powerful vasodepressor ester alkaloids derived from multiply oxygenated alkamines of this series, have been employed with a certain degree of success in the clinical management of hypertension.[3] The tertiary alkamines, which have been shown to be hexacyclic octahydropyrrocoline derivatives constructed from the perhydrocyclopentanophenanthrene ring system, have been obtained by partial synthesis as exemplified by the conversion of sarsasapogenin to 5-isosolanidane-3β-ol, one of the stereoisomeric dihydro derivatives of solanidine.[4]

The secondary alkamines of the class of veratramine and jervine, on the other hand, have only very recently been shown to exhibit an unprecedented type of remarkable specificity in their ability to annul the effects of accelerans stimulation, as well as to antagonize the positive chronotropic, or cardioaccelerator, properties of epinephrine and related sympathomimetic amines without disturbing the positive inotropic and vasopressor properties of these substances.[5] Steroid secondary amines characterized by the skeletal structure postulated for the naturally occurring secondary veratrum alkamines[6] and for the hydrogenation products of secondary solanum bases of the type of solasodine,[7] have now been obtained by partial synthesis.

2-Bromo-5-methylpyridine[8] has been converted to the 2-lithium derivative with *n*-butyllithium and allowed to react with Δ^5-pregnen-3β-ol-20-one 3-acetate[9] in ether solution to yield the pyridylcarbinol I, m.p. 281–282°; $[\alpha]^{25}D$ −76.8° ($CHCl_3$). *Anal.* Calcd. for $C_{27}H_{39}NO_2$: C, 79.17; H, 9.60; N, 3.42. Found: C, 79.39; H, 9.61; N, 3.42. 3-Acetate, m.p. 225–226°; $[\alpha]^{25}D$ −80.3° ($CHCl_3$); $\Delta^{Ac}_{MD} = -48°$. *Anal.* Calcd. for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.07; H, 9.11; N, 3.21. Reduction of I with sodium and *n*-propanol has afforded a fraction yielding an N-nitroso derivative and a slightly soluble picrate, m.p. 248–250°. *Anal.* Calcd. for $C_{33}H_{48}N_4O_9$: C, 61.47; H, 7.50; N, 8.69. Found: C, 61.38; H, 7.60; N, 8.82, which, on conversion to the base with dilute aqueous lithium hydroxide solution, has yielded 20-(5′-methyl-2′-piperidyl)-Δ^5-pregnen-3β,-20-diol (II) m.p. 207–208°; $[\alpha]^{25}D$ −54.8° ($CHCl_3$). *Anal.* Calcd. for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 78.15, H, 10.92; N, 3.64. Hydrochloride, m.p. 294–296°. *Anal.* Calcd. for $C_{27}H_{45}NO_2 \cdot HCl$: C, 71.72; H, 10.26; N, 3.10. Found: C, 71.28; H, 10.20; N, 3.04.



The synthetic alkaloid II, when examined by Dr. Otto Krayer, was found to display the antagonism to the cardioaccelerator properties of epinephrine characteristic of veratramine and jervine at a potency of the order of that exhibited by the latter naturally occurring substance.

DEPARTMENT OF PHARMACOLOGY
HARVARD MEDICAL SCHOOL
BOSTON 15, MASSACHUSETTS FREDERICK C. UHLE

RECEIVED JANUARY 8, 1951

(1) This work was supported in part by a grant from the United States Public Health Service and in part by funds of the Higgins Trust of Harvard University.

(2) Krayer and Acheson, *Physiol. Rev.*, **26**, 383 (1946).

(3) Meilman and Krayer, *Circulation*, **1**, 204 (1950); Fried, White and Wintersteiner, THIS JOURNAL, **72**, 4621 (1950).

(4) Uhle and Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

(5) Krayer, *J. Pharm. Ex. Therap.*, **96**, 422 (1949).

(6) Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., p. 603.

(7) Briggs, Harvey, Locke, McGillivray and Seelye, *J. Chem. Soc.*, 3013, 3020 (1950).

(8) Case, THIS JOURNAL, **68**, 2574 (1946).

(9) The pregnenolone used in this work was supplied by the Schering Corporation, Bloomfield, New Jersey, and the Lederle Laboratories, Pearl River, New York.