(found: C, 67.08; H, 7.44); and also was oxidized with chromium trioxide in pyridine to 9α-fluoro-17α-acetoxy-4-pregnene-3,11,20-trione (IX); m.p. 256–258°; $[\alpha]_D$ +112° ($CHCl_3$); $\lambda_{max.}^{methanol}$ 235 mμ, ε = 16,990; (found: C, 68.62; H, 7.07).

When tested orally in the Clauberg assay[8] at a level producing a +2 degree of glandular arborization the compounds had these relative potencies (subcutaneous progesterone = 1); V = 5; VII = 25; VIII = 10; IX = 10. In our hands compound VII is 2500 times as potent as progesterone is orally, 25 times as potent as Norlutin,[1] and 5 times as potent as 6α-methyl-17α-acetoxyprogesterone.[9]

(8) C. W. Emmens, "Hormone Assay," Academic Press, Inc., New York, N. Y., 1950, p. 422.

(9) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, THIS JOURNAL, **80**, 2904 (1958).

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RECEIVED JUNE 15, 1959

A NOVEL RESOLUTION OF 1-PHENYL-2-PROPYLHYDRAZINE

Sir:

In view of the recent paper by Biel and coworkers[1] on the chemistry and structure-activity relationships of aralkyl hydrazines as central stimulants and the current interest in several of these compounds as possible therapeutic agents,[2] we wish to report at this time a unique resolution of 1-phenyl-2-propylhydrazine by means of its L-pyroglutamoyl derivative. L-Pyroglutamic hydrazide,[3] $[\alpha]^{25}_D$ − 10.1 (*c*,1.0 in water) was condensed with 1-phenyl-2-propanone to yield N-L-pyroglutamoyl-N′-(1-phenyl-2-propylidene)-hydrazine, m.p. 152–154°, $[\alpha]^{27}_D$ +17° (*c*, 1.0 in ethanol). *Anal.* Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.84; H, 6.61. Found: C, 65.07; H, 6.39. Reduction of this hydrazide with sodium borohydride in aqueous methanol yielded a mixture of isomers which were separated by fractional crystallization from water or acetonitrile. The higher-melting insoluble isomer (A) melted at 163–164°, $[\alpha]^{25}_D$ +24.4 (*c*, 1.0 in water). *Anal.* Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.32; N, 16.08. Found: C, 64.39; H, 7.20; N, 16.01. The lower-melting soluble isomer (B) melted at 83–86°, $[\alpha]^{24}_D$ −14.6° (*c*, 1.0 in water). *Anal.* Found: C, 64.31; H, 7.34; N, 15.96. Hydrolysis of (A) in aqueous hydrochloric acid gave D-1-phenyl-2-propylhydrazine hydrochloride, m.p. 148–149°, $[\alpha]^{25}_D$ +13.8° (*c*, 1.0 in water). *Anal.* Calcd. for $C_9H_{15}ClN_2$: Cl, 18.99; N, 15.00. Found: Cl, 18.70; N, 14.81. Hydrolysis of (B) under similar conditions gave L-1-phenyl-2-propylhydrazine hydrochloride, m.p. 148–149°, $[\alpha]^{25}_D$ −14.0° (*c*, 1.0 in water).

To establish the configuration of the isomers relative to D-amphetamine, the D-isomer was reduced with palladium-on-charcoal as the catalyst. The amine thus obtained was benzoylated to yield D-N-(1-phenyl-2-propyl)-benzamide, m.p. 155–156°, $[\alpha]^{25}_D$ +71.6° (*c*, 1.1 in methanol). *Anal.* Calcd. for $C_{16}H_{17}NO$. N, 5.85. Found: N, 6.05. A sample of D-amphetamine also was benzoylated to yield an authentic sample of D-N-(1-phenyl-2-propyl)-benazmide, m.p. 155–156°, $[\alpha]^{25}_D$ +72° (*c*, 1.0 in methanol).[4] A mixture m.p. showed no depression. A similar reduction of the L-isomer with subsequent benzoylation yielded L-N-(1-phenyl-2-propyl)-benzamide, m.p. 155–156°, $[\alpha]^{25}_D$ −71.3° (*c*, 0.97 in methanol). A mixture m.p. with D-N-(1-phenyl-2-propyl)-benzamide was 130–131°.

Preliminary pharmacological tests indicate that D-1-phenyl-2-propylhydrazine hydrochloride is approximately twice as active as the racemate and four times as active as the L-isomer when screened *in vitro* as an inhibitor of monoamine oxidase of mouse brain. In an antireserpine test in mice,[5] the racemate appeared to be of the same order of activity as the D-isomer, which was approximately four times as active as the L-isomer. In normal mice, not reserpine treated, the racemate appeared to resemble closely the D-isomer in that both produced hyperactivity and hyperirritability during the first hour after treatment, a period of relative quiescency during the next hour, and then a second period of hyperactivity which lasted for several hours. The L-isomer, however, in normal mice manifested much less early hyperactivity although the delayed hyperactivity was observed.

(1) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuher, A. C. Conway and A. Horita, THIS JOURNAL, **81**, 2805 (1959).

(2) "Amine Oxidase Inhibitors," *Ann. N. Y. Acad. Sci.*, in press.

(3) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, THIS JOURNAL, **75**, 1933 (1953).

(4) W. Leithe, *Ber.*, **65B**, 660 (1932), reported a m.p. of 159–160°, $[\alpha]^{11}_D$ +72° (*c*, 1.14 in methanol).

(5) Drug administered to mice intraperitoneally four hours prior to the intraperitoneal administration of 10 mg./kg. of reserpine.

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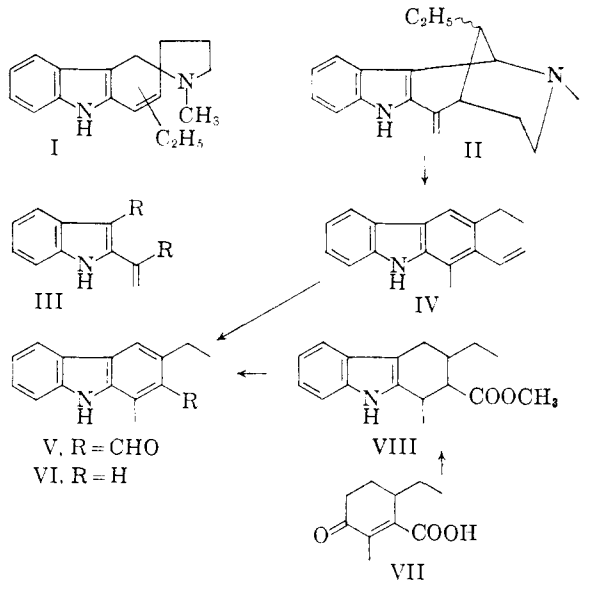
THE STRUCTURE OF ULEINE

Sir:

The alkaloid uleine, $C_{18}H_{22}N_2$, from *Aspidosperma ulei* Mgf., is remarkable for its C_{17} skeleton which contains two carbons less than most other indole alkaloids.[1] A previous investigation[1] led to the tentative proposal of structure I which we now wish to replace by II. The infrared spectrum of the alkaloid exhibited bands at 877, 1635 and 3030 $cm.^{-1}$ whilet he n.m.r. spectrum (all values for 60 mc. in $CDCl_3$) possessed peaks at 68, 86 (2 vinyl H); −134 (NH of indole); −73 to −38 c.p.s. (4 arom. H) relative to the benzene proton at 0 c.p.s. These findings, coupled with earlier ultraviolet evidence,[1] demand part structure III. In agreement with III the bands associated with the terminal methylene group were missing in the spectra of dihydrouleine. The optically inactive IV, available by two Hofmann degradations,[1] is a vinylcarbazole. Thus, osmylation of IV gave a diol which on cleavage with periodate was converted to formaldehyde and the yellow aldehyde

(1) J. Schmutz, F. Hunziker and R. Hirt, *Helv. Chim. Acta*, **40**, 1189 (1957); **41**, 288 (1958).

V, m.p. 152°, infrared bands at 2800, 1675 and 1625 cm.$^{-1}$ (arom. aldehyde), n.m.r. peaks at −258 (−CH=O); −112 to − 42 (carbazole NH, 5 arom. H); a quadruplet centered at 196 (CH_2 of ethyl); 218 (arom. methyl) and a triplet centered at 304 c.p.s. (CH_3 of ethyl); λ_{max}^{EtOH} 255 (40700); 324 (25000) and 378 mμ (ε 4350). The ultraviolet spectrum of V was very similar to that of 2-formylcarbazole, λ_{max}^{EtOH} 252 (34200), 321 (25300) and 372 mμ (ε 4350) but entirely different from the spectra of the three remaining formylcarbazoles[2] kindly provided by Mrs. Tomlinson, Oxford. It had been suggested previously[1] that uleine contains a N-methyl and a C-ethyl grouping and this was confirmed by its n.m.r. spectrum which contained the anticipated N-methyl peak at 249 and a multiplet corresponding to five hydrogens in the 300–350 c.p.s. region. Furthermore, a single hydrogen at 138 c.p.s. is split into two lines in the spectra of II and dihydrouleine indicating part structure β-indolyl-CH(–CH)–NCH_3 which explains the exceedingly facile first Hofmann degradation.



The facts presented are in agreement only with II which was confirmed by chemical evidence. Decarbonylation of V over Pd/C at 270° yielded VI, m.p. 101°, identical in m.p., mixed m.p., ultraviolet and infrared spectra with an authentic sample prepared as described. Ethyl α-ethoxalylbutyrate[3] was converted to VII, m.p. 95° (after sublimation), λ_{max}^{EtOH} 246 mμ (ε 9800) by a Robinson–Mannich synthesis.[4] Reduction with zinc and then treatment with phenylhydrazine, sulfuric acid and esterification gave VIII which was transformed to VI by dehydrogenation over Pd/C.

(2) P. H. Carter, S. G. C. Plant and M. Tomlinson, *J. Chem. Soc.*, 2210 (1957).

(3) F. Adickes and G. Andresen, *Ann.*, **555**, 41 (1943).

(4) V. Prelog, M. M. Wirth and L. Ruzicka, *Helv. Chim. Acta*, **29**, 1425 (1946).

Uleine (II) shows a clear structural relationship to U-alkaloid B (N-methyltetrahydroellipticine), a minor constituent of *A. ulei*,[1] whose structure and synthesis are outlined in an accompanying communication.[5] We are much indebted to Dr. J. Schmutz, Berne, for the uleine and friendly discussions and to Chas. Pfizer and Co., Inc., for financial aid.

(5) R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, THIS JOURNAL, **81**, 4434 (1959).

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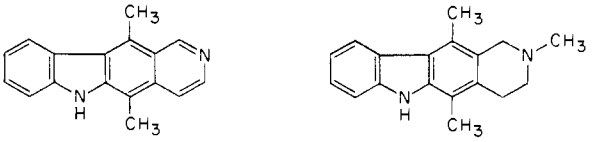
RECEIVED JULY 8, 1959

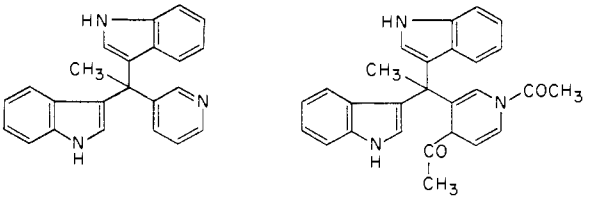
THE SYNTHESIS OF ELLIPTICINE

Sir:

It has been reported recently that *Ochrosia elliptica* Labill. and *Ochrosia sandwicensis* A.DC. contain a novel alkaloid, ellipticine,[1] and that the N-methyltetrahydroellipticine derived from the base by reduction of its methiodide with sodium borohydride is identical with alkaloid B from *Aspidosperma ulei* Mgf.[2] We have isolated both of these alkaloids from a Peruvian plant which bears the common name *quillo bordon*, and is believed to be *Aspidosperma subincanum* Mart.[3]; our structural studies have led us to the conclusion that ellipticine and N-methyltetrahydroellipticine are represented by the structures I and II. We now wish to record the synthesis of ellipticine.



Condensation of indole with 3-acetylpyridine in acetic acid in the presence of zinc chloride gave 1,1-bis-(3-indolyl)-1-(3-pyridyl)-ethane (III), m.p. 253° [dec.][calcd. for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.50; H, 5.59; N, 12.98], which was reduced by zinc and acetic anhydride at reflux to the N,γ-diacetyldihydropyridine derivative[4] (IV), m.p. 220–225° [dec.][infrared bands at 5.80 μ and 6.05μ]. Pyrolysis of



IV at 200° *in vacuo* [5×10^{-4} mm.] gave a distillate from which ellipticine (I) was separated readily in *ca.* 2% yield, in part by direct crystallization and

(1) S. Goodwin, A. F. Smith and E. C. Horning, THIS JOURNAL, **81**, 1903 (1959).

(2) J. Schmutz and F. Hunziker, *Helv. Chim. Acta*, **41**, 288 (1958).

(3) F. A. Hochstein, Anita M. Paradies and R. B. Woodward, paper in preparation.

(4) *Cf.* J. P. Wibaut and J. F Arens, *Rec. trav. chim.*, **60**, 120 (1941).