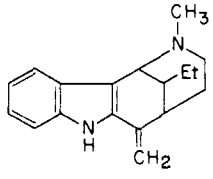
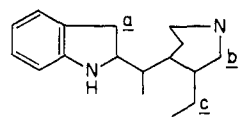
in part by chromatography on neutral alumina [activity I]. Recrystallized from methanol, the synthetic ellipticine separated in yellow prismatic needles, m.p. 312–314° [dec.] alone or in admixture with natural ellipticine. The chromatographic behavior, on neutral alumina or on paper,[1] and the infrared [KBr] and ultraviolet [MeOH] spectra [both unusually rich in detail] of the synthetic and natural bases were identical in all respects.

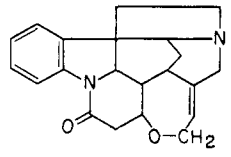
In an accompanying communication, Büchi and Warnhoff[5] present evidence which demonstrates that uleine, the major alkaloid of *Aspidosperma ulei* Mgf.[6] possesses the structure V. In view of the elaboration of N-methyltetrahydroellipticine (II) by the same plant,[1,2] it is of much interest that the two alkaloids possess closely related structures. The expression VI suggests a simple biogenetic relationship[7] between the two alkaloids [$a \rightarrow b$, uleine; $a \rightarrow c$, ellipticine] as well as



V



VI



VII

a natural connection with earlier known types [*cf.* strychnine (VII)].

We wish to express our appreciation to Professor George Büchi, who has kept us informed of the progress of his investigation of uleine, and to Dr. Sidney Goodwin and Professor Harold Conroy for stimulating discussions and exchanges of information. Our work has been generously supported by the Guggenheim Foundation and the National Institutes of Health.

(5) G. Büchi and E. W. Warnhoff, THIS JOURNAL, **81**, 4434 (1959).
(6) J. Schmutz, F. Hunziker and R. Hirt, *Helv. Chim. Acta*, **40**, 1189 (1957).
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RECEIVED JULY 8, 1959

THE MOLECULAR STRUCTURE OF $(Me_2N)_3(BH_2)_3$

Sir:

The compound previously reported[1] to be $(Me_2N)_3B_3H_4$ has been shown, by a three-dimensional X-ray diffraction study to be $(Me_2N)_3(BH_2)_3$, a cyclic trimer of Me_2NBH_2 with alternating B and N atoms in a chair configuration. Presumably this compound is closely related to the trimer of N-methylaminoborine.[2]

The symmetry is orthorhombic in the space group $Pn2_1a$, with four molecules in a unit cell having dimensions $a = 11.20$, $b = 13.17$ and $c = 8.07$ Å., in agreement with values obtained by J. Donohue.[3] Thus the symmetry is lower than that shown by the related compound[4] $(Me_2P)_3(BH_2)_3$. Refinement of the structure, still in progress, has reached values[5] of $R = 0.23$ and $r = 0.16$, with bonded distances of 1.61 ± 0.04 Å. for B—N and 1.55 ± 0.07 Å. for N—CH_3. Methyl hydrogen atoms have not yet been included in the refinement. Values of $R_{0kl} = 0.18$, $R_{h0l} = 0.25$ and $R_{hk0} = 0.16$ have been obtained for the three principal zones.

These results extend the inorganic-organic structural analogy of B–N compounds to include the cyclohexane type of ring, in the sense that BH_3NH_3 and C_2H_6, and $B_3N_3H_6$ and C_6H_6 are pairs of analogs.

Our structure proof agrees with a concurrent, and independent study[6] of the hydrogen hyperfine splitting of the B^{11} n.m.r. resonance showing a single 1:3:1 triplet strongly suggesting three equivalent BH_2 groups in the molecule.

We wish to thank the Office of Naval Research and the Office of Ordnance Research for support of this research. We are indebted to Professor A. B. Burg for the sample, and to Professor J. Donohue for his preliminary X-ray diffraction results.

(1) A. B. Burg, THIS JOURNAL, **79**, 2129 (1957).
(2) T. C. Bissot and R. W. Parry, *ibid.*, **77**, 3481 (1956).
(3) J. Donohue, private communication.
(4) W. C. Hamilton, *Acta Crystallographica*, **8**, 199 (1955).
(5) R. E. Dickerson, P. J. Wheatley, P. A. Howell and W. N. Lipscomb, *J. Chem. Phys.*, **27**, 200 (1957).
(6) G. W. Campbell and L. Johnson, THIS JOURNAL, to be published.

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RECEIVED JULY 6, 1959

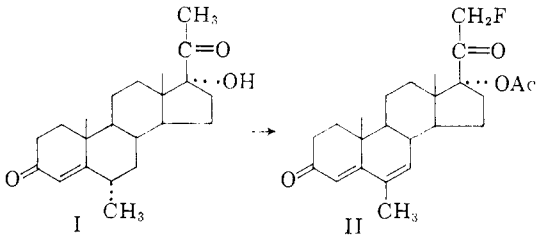
6-METHYL-17α-ACETOXY-21-FLUORO-4,6-PREGNADIENE-3,20-DIONE. A NEW ORALLY ACTIVE PROGESTIN

Sir:

Our recent discovery of the high oral progestational activity of 21-fluoro-17α-acyloxyprogesterones[1] coupled with the demonstrated utility of 6-methylated steroids[2] as progestational agents, led us to attempt the synthesis of a molecule containing both of these desirable features.

6α-Methyl-17α-hydroxyprogesterone (I)[2b] was iodinated according to the method of Ringold and Stork[3] using 2 moles of iodine and 9.2 moles of calcium oxide per mole of steroid. The resulting, crude iodo-compound [$\lambda_{max}^{methanol}$ 240 mμ, (ε 8,450), 291 mμ, (ε 10,500); I, 28.56%] was treated with silver fluoride[4] plus a small quantity of silver oxide in acetonitrile for 16 hours. The crude

(1) C. G. Bergstrom, P. B. Sollman, R. T. Nicholson and R. M. Dodson, unpublished data.
(2) (a) A. David, F. Hartley, D. R. Millson and V. Petrow, *J. Pharm. Pharmacol.*, IX, 929 (1957); (b) 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); (c) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).
(3) H. J. Ringold and G. Stork, THIS JOURNAL, **80**, 250 (1958).
(4) P. Tannhauser, R. J. Pratt, E. V. Jensen, *ibid.*, **78**, 2658 (1956).



I II

fluorine containing steroid was acetylated with acetic anhydride, *p*-toluenesulfonic acid,[5] then treated with methanol and hydrochloric acid to hydrolyze any enol acetate that may have formed. The resulting material was chromatographed on silica gel. By the rechromatography of the crystalline steroid eluted with 10% ethyl acetate in benzene, there was obtained 6-methyl-17α-acetoxy-21-fluoro-4,6-pregnadiene-3,20-dione (II)[6]; m.p. 222-223°; $[\alpha]_D$ −2.5° ($CHCl_3$); $\lambda_{max}^{methanol}$ 288 mμ, (ϵ 23,300); λ_{max}^{KBr} 5.73, 5.98, 6.13, 6.31, 7.88 and 8.05 μ; (found: C, 71.78; H, 7.91).

When tested orally in the Clauberg assay[7] at a level producing a +2 degree of glandular arborization, compound II was 17 times as potent as subcutaneous progesterone or 1700 times as potent as oral progesterone. It was three times as potent orally as 6α-methyl-17α-acetoxyprogesterone.[2b]

(5) R. B. Turner, THIS JOURNAL, **75**, 3489 (1953).

(6) A. Bowers and H. J. Ringold [*ibid.*, **80**, 3091 (1958)] have treated 11-oxo-6α-methyl-17α-hydroxyprogesterone with iodine (2.1 moles/mole of steroid) and calcium oxide (9.6 moles/mole of steroid) in tetrahydrofuran–methanol in practically the same way as we have treated 6α-methyl-17α-hydroxyprogesterone (I), but they have not reported the formation of any 6-methyl-6-dehydrosteroid. It should be noted that the 6,7-double bond probably was introduced during the iodination. The crude iodo-compound had a maximum in the ultraviolet at 291 mμ, (ϵ 10,500).

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

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THE FUNCTION OF CYTIDINE DIPHOSPHATE DIGLYCERIDE IN THE ENZYMATIC SYNTHESIS OF INOSITOL MONOPHOSPHATIDE[1]

Sir:

In previous studies of the enzymatic synthesis of inositol monophosphatide, Agranoff, Bradley and Brady[2] showed that tritiated CMP[3] could be enzymatically converted to a lipid compound, tentatively identified as CDP-diglyceride,[3] while Paulus and Kennedy[4] showed that the phosphorus moiety of inositol monophosphatide is derived from L-α-glycerophosphate and that CTP is specifically required for this reaction sequence. These findings are consistent with the occurrence of these enzymatic reactions, for which further evidence has now been obtained: (1) CTP + L-α-glycerophosphate + 2 RCO-S-CoA → → CDP-diglyceride; (2) CDP-diglyceride + inositol → inositol monophosphatide + CMP.

When Cyt-P^{32}-P-P + DL-α-glycerophosphate are incubated with an acylating system (ATP, CoA and oleic acid) in the presence of an enzyme preparation from guinea pig liver, an extensive conversion to a labeled ether-soluble nucleotide occurs (Table I). This compound does not accumulate if *myo*-inositol is added to the system, indicating the occurrence of reaction (2). The conversion of L-α-glycerophosphate to CDP-diglyceride presumably involves a series of steps, which have not yet been studied in detail, but which may involve either phosphatidic acid or CDP-glycerol as intermediates.

TABLE I

CONVERSION OF CYT-P^{32}-P-P TO CDP-DIGLYCERIDE

System: Cyt-P^{32}-P-P, 1.0 μmole (37,000 c.p.m.); DL-α-glycerophosphate, 1.0 μmole; CoA, 0.2 μmole; oleic acid, 0.1 μmole; ATP, 5 μmoles; $MnCl_2$, 3 μmoles; $MgCl_2$, 3 μmoles; 0.5 ml. of a dialyzed whole homogenate of guinea pig liver in 0.05 *M* phosphate buffer, *p*H 7.4. The final volume was 1.5 ml. Incubation was for 1 hour at 37°. The lipids were extracted with hot methanol, transferred to ether, and an aliquot of the washed ether phase was counted.

Additions	None	1 μmole *myo*-inositol
CDP-diglyceride, mμmoles	70	7

For the direct study of reaction (2) CDP-dipalmitin was synthesized from CMP and dipalmitoyl-DL-α-glycerophosphoric acid by a method essentially similar to that used for the synthesis of CDP-choline.[5] The CDP-dipalmitin was precipitated as the barium salt from aqueous solution, dissolved in chloroform–methanol by the addition of hydrogen chloride and chromatographed on silicic acid. It was eluted at about 20% methanol in chloroform, using gradient elution. The cytidine:phosphate:ester ratio was 1.00:1.93:2.03 and the purity was estimated at 93%. The yield was 6–7%.

TABLE II

REACTION OF CDP-DIPALMITIN WITH INOSITOL

Each tube contained washed and dialyzed chicken liver microsomes in 0.5 ml. of 0.05 *M* Tris buffer *p*H 7.5 and 2 μmoles $MnCl_2$ in a total volume of 1.0 ml. and was incubated at 40° for 1 hour. The CMP released was determined spectrophotometrically at 280 mμ in the supernatant after deproteinization with perchloric acid. The lipids were extracted with hot methanol, transferred to chloroform, and an aliquot of the washed chloroform layer counted in a windowless gas-flow counter with appropriate H^3-inositol standards.

	Additions	CMP released (mμmoles)	H^3-inositol incorp. (mμmole)
1	330 mμmoles CDP-dipalmitin	0	. .
2	2 μmoles H^3-inositol	. .	4
3	330 mμmoles CDP-dipalmitin + 2 μmoles H^3-inositol	73	79

The enzymatic reaction of synthetic CDP-diglyceride with inositol, with the formation of inositol monophosphatide and the release of CMP, is shown in Table II. Preparations of microsomes from chicken liver in which the exchange reaction[4] of inositol with inositol monophosphatide is low

(1) Supported by grants from the Nutrition Foundation, Inc., the Life Insurance Medical Research Fund and the National Institute for Neurological Diseases and Blindness (B 1199). Mr. Henry Paulus is a pre-doctoral Fellow of the National Science Foundation.

(2) B. W. Agranoff, R. M. Bradley and R. O. Brady, *J. Biol. Chem.*, **233**, 1072 (1958).

(3) Abbreviations: CDP-diglyceride = cytidine diphosphate diglyceride; CMP = cytidine-5′-phosphate; CTP = cytidine-5′-triphosphate; Tris = tris-(hydroxymethyl)-aminomethane.

(4) H. Paulus and E. P. Kennedy, THIS JOURNAL, **80**, 6689 (1958).

(5) E. P. Kennedy, *J. Biol. Chem.*, **222**, 185 (1956).