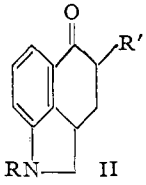
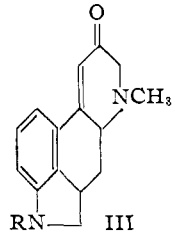
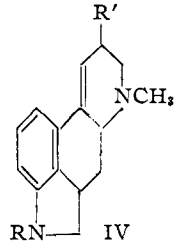


II



III

$-N(CH_3)CH_2C(CH_3)OCH_2CH_2O$) (m.p. 135–136°; calcd. for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.49; N, 6.95). Acid hydrolysis of the latter yielded the diketone (II, R = H, R′ = $-N(CH_3)CH_2COCH_3$) (m.p. 109–110°; calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 70.00; H, 7.41; N, 10.91), which on treatment with sodium methoxide was converted to the tetracyclic ketone (III, R = H) (m.p. 155–157°; calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.08; H, 6.95; N, 11.78). Acetylation of the ketone afforded (III, R = $-COCH_3$) (m.p. 169–170°; calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.61; H, 6.53; N, 9.75), which on reduction with sodium borohydride gave the alcohol (IV,



IV

R = $-COCH_3$, R′ = OH) (m.p. 187–188°). The *hydrochloride* (m.p. 245–246° (*dec.*); calcd. for $C_{17}H_{21}N_2O_2Cl$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.47; H, 6.81; N, 8.96) of the latter, when treated with thionyl chloride in liquid sulfur dioxide, furnished an amorphous *chloride hydrochloride*, which was converted by sodium cyanide in liquid hydrogen cyanide to the nitrile (IV, R = $-COCH_3$; R′ = —CN) (m.p. 181–182°; calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.41; H, 6.53; N, 14.17). Methanolysis of the nitrile gave the ester (IV, R = H, R′ = $-COOCH_3$) (m.p. 160–161°; calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.86; H, 7.19; N, 10.05). Alkaline hydrolysis of the latter, followed by catalytic dehydrogenation in water using a deactivated Raney nickel catalyst[2] gave *dl*-lysergic acid (I, R = —OH) (m.p. 241–242° (*dec.*); calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.32). The synthetic *dl*-lysergic acid was converted to the corresponding ester by means of diazomethane and thence with hydrazine to *dl*-isolysergic acid hydrazide (I, R = $-NHNH_2$) (m.p. 224–227° (*dec.*); calcd. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85. Found: C, 68.00; H, 6.44; N, 19.76). Both the acid and hydrazide were identical with the corresponding samples derived from natural ergot alkaloids[3,4] in melting point, mixture melting point, ultraviolet spectrum, infrared spectrum, paper chromatographic behavior and X-ray diffraction pattern.

Since *dl*-isolysergic acid hydrazide (I, R = $-NHNH_2$) has already been resolved and reconverted to ergonovine (I, R = $-NHCH(CH_3)CH_2OH$),[5] the present work constitutes also a total synthesis of this ergot alkaloid.

(2) E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, **18**, 455 (1948).

(3) S. Smith and G. M. Timmis, *J. Chem. Soc.*, 1440 (1936).

(4) A. Stoll and A. Hofmann, *Z. physiol. Chem.*, **250**, 7 (1937).

(5) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922, 944 (1943).

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RECEIVED SEPTEMBER 17, 1954

FORMATION OF BICYCLO(4.1.0)HEPTANE DERIVATIVES FROM EUCARVONE

Sir:

Reaction of eucarvone (I) with selenium dioxide in ethanol yields 40% of a crystalline hydroxy derivative, m.p. 85–86°, λ_{max} 229 mμ (log ε 4.06), ν_{max} 3610, 3408, 1659, 1641 cm.$^{-1}$ (*Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.46; 1 double bond (Pd–C catalyst)) to which, on the basis of these data and the following evidence, we assign the *bicyclic* structure II. The hydroxy ketone II is transformed by oxidation with manganese dioxide into the diketone III, m.p. 93–94°, λ_{max} 240 mμ (log ε 3.92), ν_{max} 1670, 1628 cm.$^{-1}$ (*Anal.* Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.19; H, 7.25. 1 double bond (Pd–C catalyst)). Oxidation of the diketone III with neutral permanganate produces the known *cis*-carconic acid,[1,2] m.p. 175.5–176.5°, ν_{max} 3180, 1725, 1685 cm.$^{-1}$ (*Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.22; H, 6.57), monomethyl ester, m.p. 107–109°, which establishes the presence of the *gem*-dimethylcyclopropyl unit in II and III.

Eucarvone is oximated by butyl nitrite–sodium ethoxide–ethanol to give a 72% yield of the *bicyclic* oximino ketone IV, m.p. 153–154°, λ_{max} 222,296 mμ (log ε 3.92, 4.00), ν_{max} 3585, 3275, 1648 cm.$^{-1}$ (*Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.30; N, 7.78). The same oximino ketone could be prepared by addition of the sodio derivative of I in dioxane to cold, ethereal butyl nitrite. The oximino ketone IV was correlated with the diketone III by conversion to the same dioxime V, m.p. 185–186°, λ_{max} 278 m (log 4.43), ν_{max} 3250, 3195, 1625(w) cm.$^{-1}$ (*Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.62; H, 7.00; N, 14.28).

In order to gain information regarding the possible courses for the formation of bicyclo[4.1.0]-heptane derivatives from eucarvone, we have studied the ethoxide-catalyzed hydrogen–deuterium

(1) W. H. Perkin and J. F. Thorpe, *J. Chem. Soc.*, **75**, 48 (1903).

(2) K. Hariharan, K. Menon and J. Simonsen, *ibid.*, 431 (1928).

exchange between eucarvone and deuteroethanol at room temperature (oximation conditions). Our findings indicate clearly that *three* hydrogens from eucarvone are replaceable by deuterium under these conditions.[3] Since eucarvone in the monocyclic form has only two readily replaceable hydrogens, and in view of the results mentioned above, the intervention of the bicyclic ketone VI and/or its anion seems probable.

If there is any of the bicyclic ketone VI normally in equilibrium with eucarvone, the amount is small (less than 1%) as determined from the ultraviolet spectrum of eucarvone, λ_{max} 302 mμ (log ϵ 3.82), only slight end absorption near 230 mμ.[4]

It seems likely that other transformation products of eucarvone (including some previously described) also possess the bicyclic nucleus. We are investigating some of these cases at present.

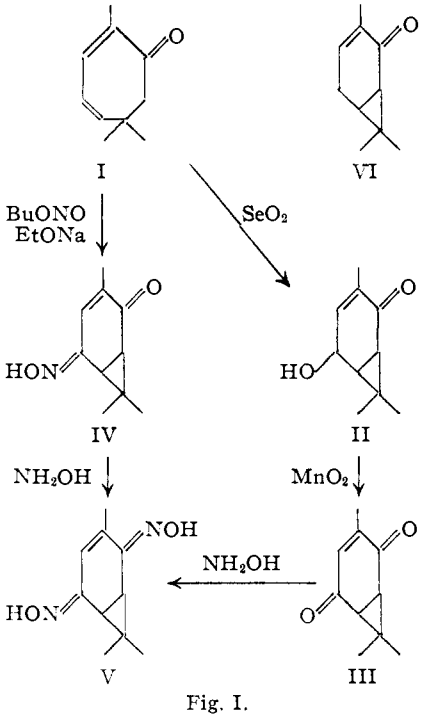

Fig. I.

(3) Determined by isolation of the eucarvone, combustion, and assay of the D_2O–H_2O mixture by the falling drop method: A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1942).

(4) All ultraviolet spectra were determined in 95% ethanol.

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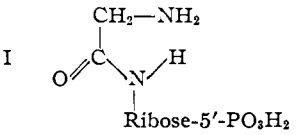
RECEIVED AUGUST 26, 1954

GLYCINE RIBOTIDE INTERMEDIATES IN THE *de novo* SYNTHESIS OF INOSINIC ACID[1]

Sir:

Pigeon liver extracts carry out the synthesis of two glycine-containing aliphatic ribotides which appear to be intermediates in the *de novo* synthesis of inosinic acid. Compound I has been tentatively assigned the following basic structure:



The second compound (II) appears to differ from I by the presence of a formyl group.

The synthesis of I by pigeon liver extracts, passed through a Dowex-1-chloride column and dialyzed, requires ATP[2], R-5-P, glycine and glutamine (Table I). This reaction is measured by the conversion of glycine-1-C^{14} to a radioactive compound which does not lose C^{14} when treated with ninhydrin. I is eluted from a Dowex-1-formate column with 0.05 *M* ammonium formate at *p*H 6.5.

TABLE I

REQUIREMENTS FOR THE SYNTHESIS OF I

Additions: 20 mg. of an extract of pigeon liver acetone powder treated with Dowex-1 chloride,[3] dialyzed *versus* 0.05 *M* K_2HPO_4 and lyophilized. 1.5 μM. ATP, 5 μM. Na phosphocreatine, 0.05 ml. 1:2 aqueous rabbit muscle extract dialyzed against water, 6.4 μM. $MgCl_2$, 5 μM. glycine-1-C^{14}, 5 μM. glutamine, 2.5 μM. K-ribose-5-phosphate, 30 μM. K_2HPO_4 (final quantity); vol. 0.67 ml.; time 20 min., 38°, air.

R-5-P		+	−	+	+
Glutamine		+	+	−	+
ATP[a]		+	+	+	−
μM. C^{14} glycine	Expt. 1	0.25	0.00	0.01	...
incorporated	Expt. 2	0.15	0.01	0.02	0.02

[a] Includes regenerating system of creatine phosphokinase (muscle extract) and phosphocreatine.

II is eluted from a Dowex-1-formate column with 0.05 *M* ammonium formate at *p*H 5.0. This compound possesses a characteristic acid-labile (0.1 *N* HCl, 100°, 15 min.) formyl group which allows its direct determination. II can be labeled by either C^{14} glycine or C^{14} formate, but not by $C^{14}O_2$. The requirements for the synthesis of II are: ATP, R-5-P, glycine, glutamine, formate and boiled extract of liver. The boiled extract can be completely replaced by leucovorin or by tetrahydrofolic acid.[3] Some of these requirements are shown in Table II.

TABLE II

REQUIREMENTS FOR THE SYNTHESIS OF II

Conditions as in Table I plus the following: 0.2 mg. Ca leucovorin or tetrahydrofolic acid (neutralized), 2.5 μM. C^{14} Na-formate and non-radioactive glycine; time 30 min.

Experiment	1			2			
FAH_4	+	−	−	−	−	−	−
CF	−	+	−	+	+	+	+
R-5-P	+	+	+	+	−	+	+
Glutamine	+	+	+	+	+	−	+
Glycine	+	+	+	+	+	+	−
Hydrolyzable C^{14}-formyl, μm.	0.35	0.37	0.016	0.49	0.12	0.08	0.04

Under conditions for synthesis of II, small quantities of I are found by chromatographic anal-

(1) This investigation was aided by grants from the U. S. Public Health Service, National Institutes of Health, The Elisabeth Severance Prentiss Foundation and Eli Lilly and Company.

(2) Abbreviations: adenosine triphosphate, ATP; D-ribose-5-phosphate, R-5-P; leucovorin (*dl* form of citrovorum factor), CF; tetrahydrofolic acid, FAH_4.

(3) G. R. Greenberg, THIS JOURNAL, **76**, 1458 (1954).