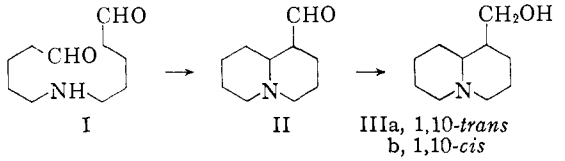
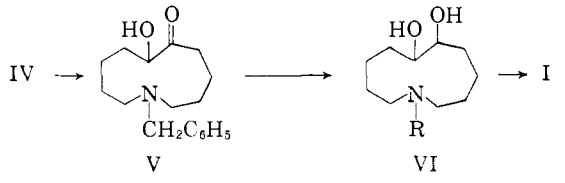


I II IIIa, 1,10-*trans* b, 1,10-*cis*

decarboxylative deamination, and coupling, of two molecules of lysine.[1] We wish to report the realization of this ring-closure in the laboratory, and the reduction of the product (II) to *dl*-epilupinine (IIIa).

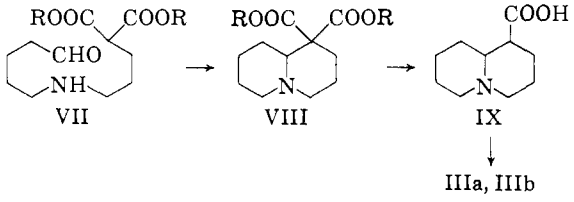
Acyloin ring-closure[2] of diethyl N-benzyl-N,N-bis-(ω-*n*-valerate) (IV) (b.p. 180–184° (0.6 mm.)) afforded N-benzyl-azacycloundecan-6-ol-7-one (V) (b.p. 172° (0.2 mm.)), which (without deliberate purification of intermediates) was reduced with lithium aluminum hydride to VI (R = benzyl), and then hydrogenolyzed catalytically to the



V VI

secondary amine (VI, R = H). The debenzylated diol was allowed to stand for one day at room temperature in dilute solution with periodic acid at *p*H 5. Under these conditions normal periodate cleavage to the dialdehyde I was followed by cyclization; lithium aluminum hydride reduction of unisolated II afforded *dl*-epilupinine (IIIa).[3]

Lupinine, the less stable epimer (IIIb), can be synthesized by a modification of the above approach. The amorphous quinolizidine-1,1-dicarboxylic acid (VIII, R = H) was prepared by three methods, each of which proceeds by way of VII, or an equivalent[4]: (a) selective two-mole hydrogena-



VII VIII IX

tion of the betaine X (dec. 130–135°), carried out in methanol over nickel in the presence of one equivalent of hydrochloric acid[5]; (b) mercuric acetate dehydrogenation of γ-piperidyl-*n*-propylmalonic ester XI (b.p. 134–135° (0.2 mm.), and then saponification of the resulting bicyclic ester VIII (R = C_2H_5) (b.p. 133–134° (1.0 mm.)); and (c) alkylation of Δ^1-piperideine trimer with γ-bromo-*n*-propylmalonic ester, and subsequent hydrolysis.

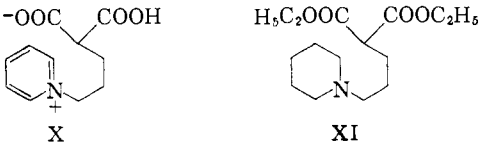
(1) (a) C. Schöpf, E. Schmidt and W. Braun, *Ber.*, **64**, 683 (1931); (b) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, 1955, p. 74.

(2) N. J. Leonard, R. C. Fox and M. Ōki, THIS JOURNAL, **76**, 5708 (1954).

(3) Identified by analysis, melting point, mixed melting point and infrared comparison.

(4) The corresponding, cyclic alkanolamine, enamine or iminium salt.

(5) *Cf.* C. Schöpf, G. Herbert, R. Rausch and G. Schröder, *Angew. Chem.*, **69**, 39 (1957).



X XI

Decarboxylation of crude VIII (R = H), when carried out in refluxing 20% hydrochloric acid, gave mono acid IX, which was converted to the ethyl ester (b.p. 154–155° (20 mm.)); hydride reduction of the latter afforded a mixture consisting of approximately 20% *dl*-lupinine[3] and 80% *dl*-epilupinine.[3] On the other hand, heating of the fused diacid at 165° induced formation of monoacid which was converted as above to a mixture composed of approximately 50% each of the two alkaloids in the racemic form.[6]

Discussion of the biogenetic and mechanistic aspects of these results will be presented subsequently.

Acknowledgment.—The authors are indebted to Professors C. Schöpf (Darmstadt) and V. Boekelheide (Rochester) for samples of *dl*-lupinine and epilupinine, and to the National Institutes of Health for financial support (Grant RG-3892).

(6) Where possible, and except as indicated, satisfactory analyses of substances reported herein have been secured.

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RECEIVED NOVEMBER 30, 1959

LABORATORY REALIZATION OF THE ROBINSON-SCHOPF SCHEME OF ALKALOID SYNTHESIS. THE PYRROLIZIDINE ALKALOIDS[1]

Sir:

The early suggestions of Robinson[2] as to possible reaction sequences which can lead to the formation of alkaloids have stimulated laboratory syntheses under mild conditions, examination of the applicability of the postulates to plant alkaloid biogenesis, and logical argumentation in structure elucidations.[3–7] A scheme for the biogenesis of lupinine has been proposed by Schöpf[8–10] and Robinson[3] based on the over-all sequence: 2 lysine → δ,δ'-imino-bis-valeraldehyde → 1-hydroxymethylquinolizidine, and for the biogenesis of the ring-homologous moiety of the *Senecio* alkaloids,[3,10] on the sequence: 2 ornithine →

(1) This investigation was supported in part by the Marsh Fund of the National Academy of Sciences and in part by a research grant (USPHS-RG5829) from the National Institutes of Health, Public Health Service.

(2) R. Robinson, *J. Chem. Soc.*, **111**, 876 (1917).

(3) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, 1955; see especially pp. 72–78.

(4) R. Robinson, *J. Roy. Soc. Arts*, **96**, 795 (1948).

(5) G. K. Hughes and E. Ritchie, *Revs. Pure and Appl. Chem. (Aust.)*, **2**, 125 (1952).

(6) C. Schöpf, *Angew. Chem.*, **50**, 779, 797 (1937).

(7) E. Leete, "The Use of Isotopes in the Study of Alkaloid Biogenesis," Chap. VIII in "The Biogenesis of Natural Substances," edited by M. Gates, Interscience Publishers, Inc., New York, in press. The authors are grateful to Dr. Leete for providing this chapter in manuscript form.

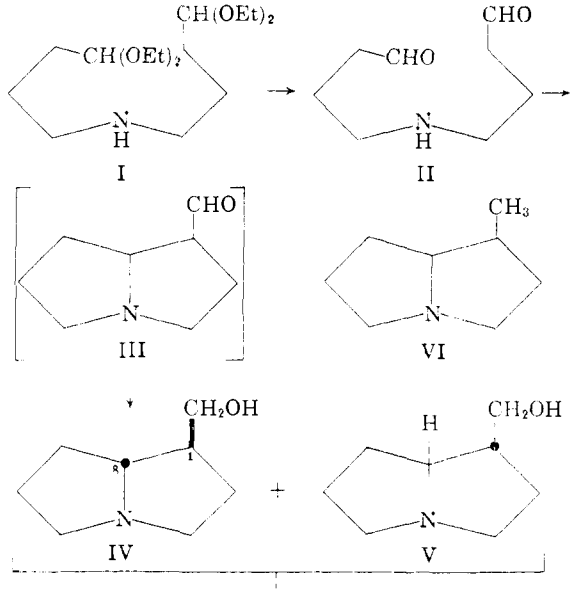
(8) C. Schöpf, E. Schmidt and W. Braun, *Ber.*, **64**, 683 (1931).

(9) C. Schöpf, *IX International Congress of Pure and Applied Chemistry (Madrid)*, **5**, 189 (1934).

(10) C. Schöpf, *Chimia Switz.*, **2**, 206, 240 (1948).

γ,γ'-imino-bis-butyraldehyde (II) → 1-hydroxymethylpyrrolizidine.[11]

We now report the double ring-closure of γ,γ'-imino-bis-butyraldehyde (II), liberated from the tetraethyl diacetal (I), to the pyrrolizidine ring system and the concordant synthesis of 1-hydroxymethylpyrrolizidine, mainly that racemate (C-1,8 hydrogens *trans*) consisting of *laburnine* (IV)[12] (1β-hydroxymethyl-(8β)-pyrrolizidine[13,14] plus *trachelanthamidine* (V)[15,16] (1α-hydroxymethyl-(8α)-pyrrolizidine).[13,14] By the reaction[17] of γ-aminobutyraldehyde diethyl acetal[18] with γ-chlorobutyraldehyde diethyl acetal[19] at 100° under nitrogen



during 24 hours, γ,γ'-imino-bis-butyraldehyde tetraethyl diacetal (I) was obtained in 60% yield, b.p. 130–132° (0.65 mm.) (some *dec.*), $n^{25}D$ 1.4369, d^{25}_4 0.935 (*Anal.* Calcd. for $C_{16}H_{35}NO_4$: N, 4.59; *MR*D, 86.27. Found: N, 4.82; *MR*D, 85.57). After liberation,[20] the imino-bis-aldehyde II (not isolated) was allowed to stand in aqueous phosphate buffer at *p*H 7 for 7 days. After the sequence of ether extraction, evaporation, reduction of the residue with sodium borohydride, and benzoylation, 1-benzoyloxymethylpyrrolizidine hydrochloride was isolated in 52% over-all yield, m.p. 185–185.5° dec. (*Anal.* Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.93; H, 7.15; N, 4.97. Found: C, 63.82; H, 7.44; N, 5.16).[21] The fact that the parent alkanolamine was mainly the racemate of 1-hydroxymethylpyrrolizidine with C-1,8 hydrogens *trans*, corresponding to the thermodynamically more stable form of the ring-closed aldehyde (III) and namable as either (±)-laburnine or (±)-trachelanthamidine,[24] was shown by conversion of IV-V to (±)-pseudoheliotridane (VI, C-1,8 hydrogens *trans*) by treatment with thionyl chloride followed by lithium aluminum hydride.[25] The picrate (over-all yield 50%), m.p. 231–232° (dec.) (*Anal.* Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.42; H, 5.03; N, 15.85), was identified by direct comparison (m.p., superposable infrared spectra in chloroform solution) with (±)-pseudoheliotridane picrate[24] and by contrast in properties with those of the diastereoisomeric racemate, (±)-heliotridane (VI, C-1,8 hydrogens *cis*) picrate.[24,26] Feasibility of the Robinson–Schöpf scheme for facile synthesis in the quinolizidine alkaloid series is also under test.

(11) The scheme of biogenesis based upon D-erythrose-4-phosphate could also generate the ring system (E. Wenkert, *Experientia*, **15**, 165 (1959)).

(12) F. Galinovsky, O. Vogl and H. Nesvadba, *Monatsh. Chem.*, **85**, 913 (1954).

(13) F. L. Warren and M. E. von Klemperer, *J. Chem. Soc.*, 4574 (1958).

(14) N. J. Leonard, "Senecio Alkaloids," Chap. 4 in "The Alkaloids," Vol. VI, edited by R. H. Manske, Academic Press, Inc., New York, N. Y., in press.

(15) G. P. Men'shikov and G. M. Borodina, *Zhur. Obshchei Khim.*, **15**, 225 (1945).

(16) G. P. Men'shikov, *ibid.*, **16**, 1311 (1946).

(17) C. Mannich and P. Horkheimer, *Arch. Pharm.*, **264**, 167 (1926).

(18) R. H. F. Manske, *Can. J. Research*, **5**, 592 (1931).

(19) R. B. Loftfield, THIS JOURNAL, **73**, 1365 (1951).

(20) E. F. L. J. Anet, G. K. Hughes and E. Ritchie, *Australian J. Sci. Research*, **3A**, 336 (1950).

(21) Assurance at this point that we were in the bicyclic series was obtained by a favorable infrared comparison of the product with the active diastereomer, benzoylisoretronecanol hydrochloride, m.p. 181–182°.[22] An active form of the racemate in hand (see continuing text), benzoyltrachelanthamidine hydrochloride, m.p. 204–206°,[23] was not available for comparison. In this series the diastereoisomers have very similar spectra, so that the comparison cited serves as a structural guide.

(22) R. Adams and K. E. Hamlin, Jr., THIS JOURNAL, **64**, 2597 (1942).

(23) E. L. Gurevich and G. P. Men'shikov, *Zhur. Obshchei Khim.*, **17**, 1714 (1947).

(24) N. J. Leonard and D. L. Felley, THIS JOURNAL, **72**, 2537 (1950).

(25) W. C. Wildman and H. M. Fales, *ibid.*, **80**, 6465 (1958).

(26) ADDED IN PROOF.—The synthesis of (±)-1-hydroxymethylpyrrolizidine by K. Babor, I. Ježo, V. Kaláč and M. Karvaš, *Chem. zvesti*, **13**, 163 (1959), has been noted. The acid *p*H is actually less favorable for the condensation, and the stereochemistry of the product was not delineated.

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RECEIVED NOVEMBER 23, 1959

A NOVEL SYNTHESIS OF 16-SUBSTITUTED STEROIDS

Sir:

The effects on corticoid activity brought about by substitution of certain groups in the C-16 position of cortisol derivatives have received considerable study in other laboratories.[1] In an attempt to extend this series, our attention centered on the search for an intermediate which could be used for introducing a variety of new 16-substituents and still contain structural features which permit ready conversion to potentially active corticoids. We wish to report the preparation of uch an intermediate and some of its reactions.

Mild acidic hydrolysis of 16β-bromocortexolone 21-acetate[2] and then treatment in benzene–hexane with acidic aqueous formaldehyde[3] gave

(1) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., pp. 682–699, for a recent summary of the pertinent literature.

(2) P. L. Julian, *et al.*, THIS JOURNAL, **72**, 5145 (1950). (Nomenclature as proposed in ref. 1, p. 602.)

(3) R. E. Beyler, R. M. Moriarty, F. Hoffman and L. H. Sarett, *ibid.*, **80**, 1517 (1958).