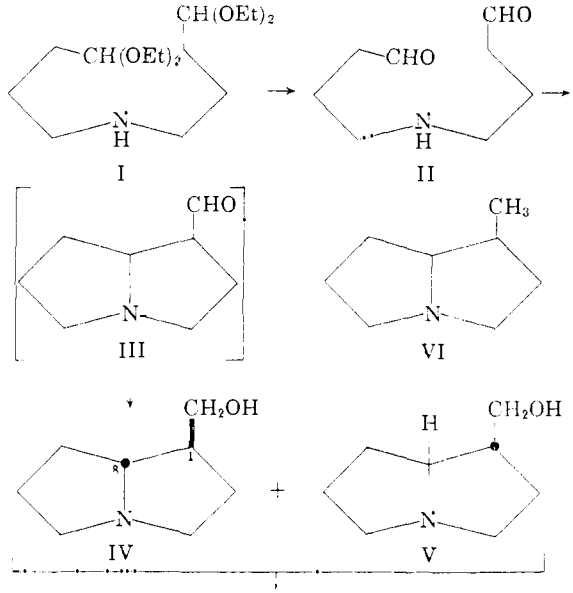
γ,γ'-imino-bis-butyraldehyde (II) → 1-hydroxymethylpyrrolizidine.[11]

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.

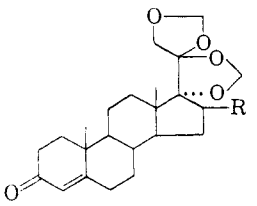
Mild acidic hydrolysis of 16β-bromocortexolone 21-acetate[2] and then treatment in benzene–hexane with acidic aqueous formaldehyde[3] gave

(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).

the 16β-bromo-17α,20:20,21-bismethylenedioxy-Δ^4-pregnene-3-one (I, 16β-bromocortexolone BMD), m.p. 208–209° dec., $[\alpha]^{27}D$ − 45° (*c* 2.0).[4]



I, R = Br
II, R = $OCOCH_3$
III, R = OH
IV, R = OCH_3
V, R = $OCH(CH_3)_2$
VI, R = F

Excess silver acetate in refluxing glacial acetic acid in the presence of sodium acetate smoothly converted I to 16β-acetoxycortexolone BMD (II), m.p. 197–198°, $[\alpha]^{26}D$ + 4.5° (*c* 3.6).[4] Similarly, silver perchlorate in aqueous acetone gave the 16β-hydroxy derivative (III), m.p. 231–233.8°, $[\alpha]^{26}D$ − 12.5° (*c* 3.8).[4] Anhydrous methanolic silver perchlorate analogously formed 16β-methoxycortexolone BMD (IV), m.p. 173–175, 184–187.6°, $[\alpha]^{26}D$ + 5.9° (*c* 1.0).[4] Treatment of I with silver fluoride in 2-propanol gave, in addition to a minor amount of the isopropoxy compound (V), m.p. 149–152°, $[\alpha]^{26}D$ + 5.9° (*c* 1.0),[4] a 75% yield of 16β-fluorocortexolone BMD (VI), m.p. 228–229°, $[\alpha]^{26}D$ + 5.9° (*c* 1.0).[4]

Brief treatment of the acetate II with refluxing 60% formic acid[3] and then by methanolic sulfuric acid to cleave residual formates and acetylation of the resulting mono-acetate gave a major product which was identical in all respects with an authentic sample of 16β-hydroxycortexolone 16,21-diacetate.[5,6,7] The alcohol III could be converted to the acetate II with acetic anhydride in pyridine at room temperature; similarly, methylation of the alcohol III gave the methyl ether IV. Thus unequivocal evidence is provided for the structures of II, III and IV and, in view of the similarity in preparation, it is assumed that V and VI are analogous. It had been anticipated that the β-orientation of the leaving bromine coupled with the general tendency for attacking species to approach the rear of the steroid molecule[8] would strongly favor inversion of configuration at C-16 leading to 16α-substituents. These results clearly show that this was not the case and that the displacements occurred predominantly with *net retention of configuration*, possibly as a result of interaction between one of the ether oxygens in the side-chain and C-16.

Using the conditions for removal of the side-chain protection noted above for II, IV was converted to 16β-methoxycortexolone, m.p. 149.4–150°, $[\alpha]^{26}D$ + 111° (*c* 3.1),[4] and VII to 16β-fluorocortexolone, m.p. 178–179°, $[\alpha]^{27}D$ +89°, (*c* 1.0).[4]

Additional reactions of some of these products including the preparation of 16β-fluoro and 16β-methoxy derivatives related to cortisol will be the subject of forthcoming publications.

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RECEIVED NOVEMBER 21, 1959

(4) Satisfactory analyses have been obtained for all compounds herein described. Rotations are in dioxane. The infrared spectra (KBr) for I-VI are all characterized by absorption near 5.98, 6.16, 9.15, 10.10, 10.67 and 11.58 μ; infrared and ultraviolet absorption for all compounds is consistent with structures assigned.

(5) K. Heusler and A. Wettstein, *Chem. Ber.*, **87**, 1301 (1954); *cf.* B. Ellis, F. Hartley, V. Petrow and D. Wedlake, *J. Chem. Soc.*, 4383 (1955); J. Romo and A. R. De Vivar, *J. Org. Chem.*, **21**, 902 (1956).

(6) We are indebted to Dr. Seymour Bernstein for samples of 16α- and 16β-hydroxycortexolone 16,21-diacetates and 16α-hydroxycortexolone.

(7) 16α-Hydroxycortexolone 16,21-diacetate was unchanged when subjected to the same sequence of reactions.

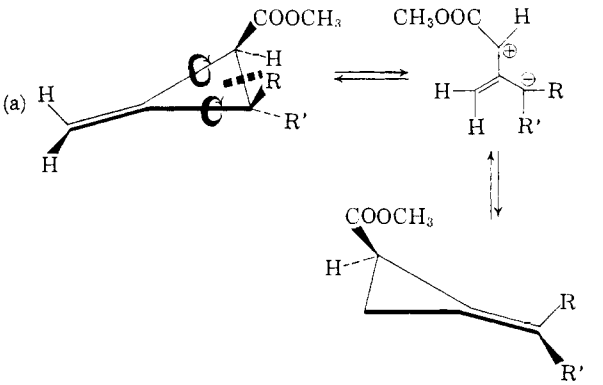
(8) Ref. 1, p. 14.

THERMAL REARRANGEMENT OF FEIST'S ESTER. A NEW TYPE OF INTERMEDIATE

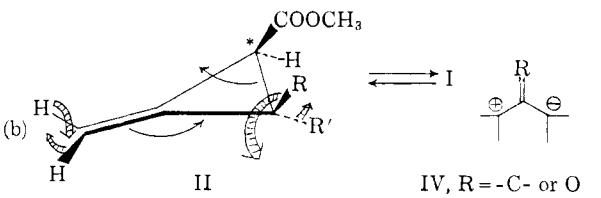
Sir:

The recent structure proof[1] of the pyrolysis product I of Feist's ester (IIa) has brought into question the mechanism of this remarkable rearrangement. Two routes appear possible: *viz.*, (a) rotation of both ester-bearing carbons with scission of their common bond to give the resonance-stabilized "zwitterion" III, and then a related transformation of III to product, or (b) a "valence-tautomerization" involving simultaneous cleavage and reformation of the ring bonds with concomitant rotation of one ester-bearing carbon and the terminal methylene to give I directly.

IIa, R = H; R′ = $COOCH_3$ IIIa, R = H; R′ = COOCH
IIb, R = $COOCH_3$; R′ = H IIIb, R = COOCH; R′ = H



Ia, R = H; R′ = $COOCH_3$
Ib, R = $COOCH_3$; R′ = H



II IV, R = -C- or O

Pathway a is of particular interest in view of LCAO-MO calculations suggesting considerable resonance stabilization in the related intermediates IV.[2] Evidence supporting intermediate III in the pyrolysis reaction is given.

It is seen that rearrangement of optically active *trans*-ester IIa *via* the planar intermediate (path a) would lead to racemic product, while rearrange-

(1) E. F. Ullman, THIS JOURNAL, **81**, 5386 (1959).

(2) J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).