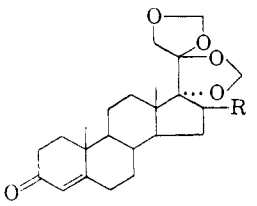
the 16β-bromo-17α,20:20,21-bismethylenedioxy-Δ^4-pregnene-3-one (I, 16β-bromocortexolone BMD), m.p. 208–209° dec., $[\alpha]^{27}D$ − 45° (*c* 2.0).[4]



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.

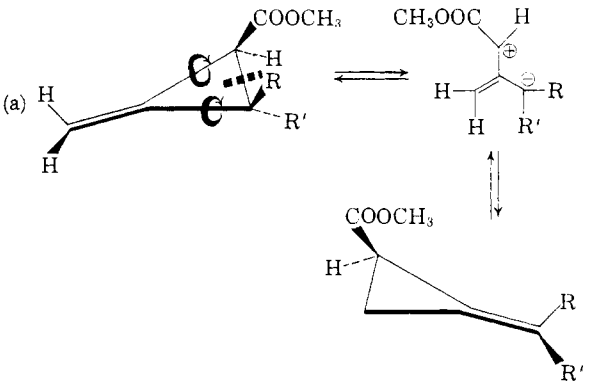
(8) Ref. 1, p. 14.

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

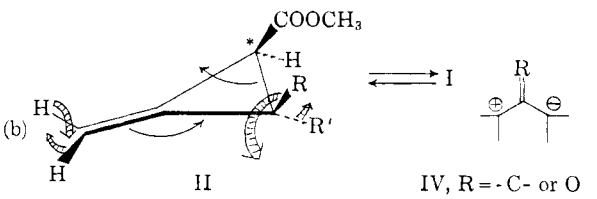
Sir:

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



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).

ment through path b should lead to retention of configuration (IIa, starred atom). Accordingly, pyrolyses of Feist's ester (IIa), $[\alpha]^{25}D$ $-119°$,[3] were carried to roughly 25 and 50% completion. The chromatographically separated products were Ia,[4] $[\alpha]^{25}D$ $+28°$, $+10°$[5]; Ib[4], $[\alpha]^{25}D$ $+18°$, $+6°$; and IIa, $[\alpha]^{25}D$ $-93°$, $-34°$, respectively. No *cis*-Feist's ester (IIb) was detected.

The isolation of active product provides convincing evidence for the "valence-tautomerization" pathway (b), but the observed racemization of starting material requires additional comment. Two racemization mechanisms not involving the "zwitterion" III appear possible. (1) The *trans*-ester (IIa) might equilibrate rapidly with product which has partially racemized either by equilibration with the internally-compensated *cis*-ester (IIb) or by some other unspecified route. (2) The *trans*-ester might equilibrate directly with its *cis*-isomer.

The first alternative is untenable because the experimental conditions effectively inhibit reconversion of product to IIa or IIb by virtue of the demonstrably favorable equilibria between the product and these esters.[6] The second was tested by partial pyrolysis of the *cis*-ester[7] (IIb) using conditions under which the *trans*-isomer was substantially unaffected.[3] The resulting mixture was shown by n.m.r. to be pyrolysis product (I), *trans*-ester (IIa) and *cis*-ester (IIb) in the approximate ratios 75:10:15. Thus the *cis*-ester (IIb) rearranges about 7.5 times faster than it isomerizes to the *trans*-ester (IIa) and, contrary to fact, racemization of IIa *via* IIb could occur only less than 1/7.5 times the rate of product appearance.

It is thus concluded that racemization must occur by reversible equilibration of *trans*-ester with the "zwitterion" IIIa (and/or IIIb) and that rearrangement proceeds competitively by both mechanisms a and b.

The author thanks W. von E. Doering and A. S. Kende for helpful suggestions and J. E. Lancaster for the n.m.r. spectra.

(3) Pyrolyses were carried out in 2% benzene solutions in a bomb partially immersed in a 210° bath for intervals of 30 and 45 minutes for IIa and 23 minutes for IIb.

(4) Stereochemistry not implied.

(5) The +10° sample was contaminated with Ib.

(6) An equilibrium ratio of IIa:IIb:1 was found by n.m.r. analysis to be 6:<0.5:94 (*cf.* ref. 1).

(7) *Cf.* M. G. Ettlinger and F. Kennedy, *Chemistry & Industry*, 891 (1957).

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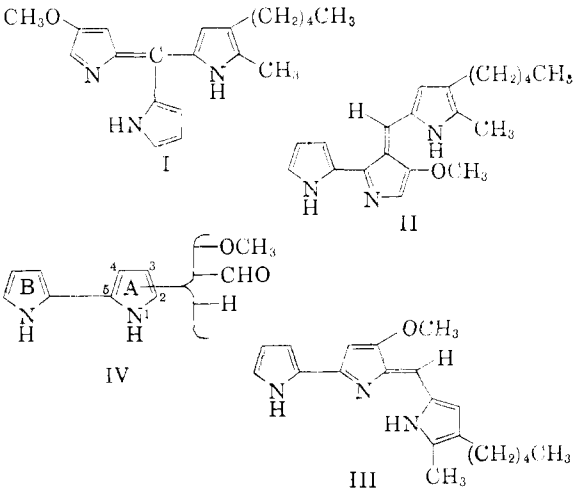
RECEIVED DECEMBER 3, 1959

PRODIGIOSIN. STRUCTURE AND PARTIAL SYNTHESIS[1]

Sir:

Prodigiosin, the blood-red pigment[2] of *Serratia marcescens*, assigned the tripyrrylmethene structure I by Wrede,[3] has attracted recent interest because of the possible relationship of I to the tripyrrylmethane type of intermediate in the biosynthesis of porphyrin.[4] We now present new evidence which makes I untenable, and which shows that prodigiosin is II, or III.



Wrede isolated 2-methyl-3-amylpyrrole, $C_{10}H_{17}N$, (A) from prodigiosin,[3] while Santer and Vogel[5] showed recently that a mutant strain (9–3–3) of *Serratia* accumulated a $C_{10}H_{10}O_2N_2$ precursor (B) which could be converted to prodigiosin by another mutant (W-1).[6] In a formal way, the condensation of these two C-10 fragments leads to prodigiosin, $C_{10}H_{17}N + C_{10}H_{10}O_2N_2 \rightarrow C_{20}H_{25}ON_3 + H_2O$. We have now, in fact, shown that pure A and B react readily under conditions of dipyrrylmethene synthesis to form prodigiosin, indistinguishable (infrared spectra of zinc salt and hydrochloride) from the natural material.

The n.m.r. spectrum of B (60 m.c. in dimethyl sulfoxide) contains two broad peaks at $\tau = -1.35$ and -1.52 (two pyrrolic NH protons) and a sharp singlet at $\tau = 0.57$ (aldehyde hydrogen). The α,α'-linkage of the pyrrole rings is shown by the isolation of pyrrolecarboxamide from the alkaline-peroxide oxidation of both B and prodigiosin.

The above evidence, and other properties of B[5] (one OCH_3, ultraviolet absorption at $\lambda_{max}^{CHCl_3}$ 254 mμ, ϵ 13000; 363 mμ, ϵ 35000), now can be accommodated by expression IV. This can be refined further: (i) the strong ultraviolet absorption requires conjugation of both pyrrole rings with the formyl group and excludes any structure with $-CHO$ at C-3. (ii) In view of the isolation of methoxymaleimide from prodigiosin[7] the methoxyl must be at C-3 or C-4. (iii) In the n.m.r. spectrum of B, the doublet at $\tau = 3.69$, which changes to a singlet in base, corresponds to the lone C–H proton on ring A (IV). Were this proton located at C-3, adjacent to CHO at C-2, it would be expected to show resonance closer to $\tau = 2.7$–2.9, as in 2-pyrrolealdehyde. B thus contains OCH_3 at C-3, and CHO

(1) This investigation was supported by Grants P-64 and P-64A from the American Cancer Society.

(2) E. N. Morgan and E. M. Tanner, *J. Chem. Soc.*, 3305 (1955).

(3) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **226**, 95 (1934).

(4) D. Shemin, C. S. Russel and T. Abramsky, *J. Biol. Chem.*, **215**, 613 (1955).

(5) U. V. Santer and H. J. Vogel, *Biochim. Biophys. Acta*, **19**, 578 (1956).

(6) M. T. M. Rizki, *Proc. Natl. Acad. Sci.*, **40**, 1057 (1954).

(7) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **215**, 67 (1933).