result of an increase in the acidity constant of the important 11β-hydroxyl group (or the degree of polarization of the 11-keto group) brought about by the inductive (−I) effect of the neighboring 9α-substituent. Such a thesis would receive support if 12α-substituted corticoids could be shown to possess activities similar to those of their 9α-congeners. It is the purpose of the present communication to demonstrate that this is indeed true in the case of the 12α-halo-11β-hydroxyprogesterones.

11-Dehydroprogesterone[4] on treatment with N-bromoacetamide and perchloric acid in dioxane furnished 12α-bromo-11β-hydroxyprogesterone (I),[5] m. p. 220–222° (dec.); $[\alpha]^{23}D$ +128° (*c* 0.39 in $CHCl_3$); λ_{max}^{alc} 239 mμ (ϵ = 16,000); λ_{max}^{Nujol} 2.97, 5.96, 6.18 μ; *Anal.* Calcd. for $C_{21}H_{29}O_3Br$: C, 61.62; H, 7.14. Found: C, 61.99; H, 7.06. The latter on treatment with potassium acetate in alcohol yielded 11β,12β-oxidoprogesterone (II), m. p. 169–170°; $[\alpha]^{23}D$ +203° (*c* 0.81 in $CHCl_3$); λ_{max}^{alc} 238 mμ (16,300); λ_{max}^{Nujol} 5.90, 6.01, 6.21 μ; *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.70, H, 8.74, which with aqueous hydrochloric acid in dioxane was transformed into 12α-chloro-11β-hydroxyprogesterone (III),[6] m. p. 233–234°; $[\alpha]^{23}D$ +162° (*c* 0.60 in $CHCl_3$); λ_{max}^{alc} 239 mμ (17,000); λ_{max}^{Nujol} 2.98, 5.97, 6.17 μ; *Anal.* Calcd. for $C_{21}H_{29}O_3Cl$: C, 69.12; H, 8.01. Found: C, 69.26; H, 7.97.

Alternatively, III was prepared as follows: treatment of 12α-bromopregnane-11β-ol-3,20-dione,[5] m. p. 251–252° (dec.); $[\alpha]^{23}D$ +76° (*c* 0.37 in dioxane) with potassium carbonate in methanol yielded 11β,-12β-oxidopregnane-3,20-dione, m. p. 139–140°; $[\alpha]^{23}D$ +89° (*c* 0.38 in $CHCl_3$); λ_{max}^{Nujol} 5.86, 5.88 μ; *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.15; H, 8.90, which with HCl in dioxane was converted into 12α-chloropregnane-11β-ol-3,20-dione, m. p. 241–244°; $[\alpha]^{23}D$ +80° (*c* 0.31 in $CHCl_3$); λ_{max}^{Nujol} 2.96, 5.83, 5.95 μ. Calcd. for $C_{21}H_{31}O_3Cl$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 69.16, H, 8.50; Cl, 9.36. The latter with bromine in acetic acid afforded 12α-chloro-4β-bromopregnane-11β-ol-3,20-dione, m. p. 184–186° (dec.); $[\alpha]^{24}D$ +100° (*c* 0.50 in $CHCl_3$); λ_{max}^{Nujol} 2.95, 5.78, 5.92 μ, which was dehydrobrominated to III by means of lithium chloride in dimethylformamide.[7]

12α-Fluoro-11β-hydroxyprogesterone IV, m. p. 182–183°; $[\alpha]^{23}D$ +193° (*c* 0.47 in $CHCl_3$); λ_{max}^{alc} 239 mμ (18,000); λ_{max}^{Nujol} 3.00, 5.89, 6.05, 6.20 μ. *Anal.* Calcd. for $C_{21}H_{29}O_3F$: C, 72.29; H, 8.39; F, 5.45. Found: C, 72.41; H, 8.32; F, 5.49, was prepared from II with hydrogen fluoride in chloroform containing 5% alcohol at 0°. Oxidation of IV with chromic acid in acetic acid furnished 12α-fluoro-11-ketoprogesterone, m. p. 147–148°; $[\alpha]^{23}D$ +271° (*c* 0.35 in $CHCl_3$); λ_{max}^{alc} 236 mμ (16,500); λ_{max}^{Nujol} 5.81, 5.86, 6.00, 6.20 μ.

We are indebted to F. M. Singer, W. B. Kessler and A. Borman of our laboratories for the bioassay data shown below. The activities of the 12α-halo derivatives in the rat liver glycogen assay[8] are listed in Table I and compared (cortisone acetate = 1) with those previously obtained for the corresponding 9α-halo derivatives.[2b] The sodium-retaining activity of 9α- and 12α-fluoro-11β-hydroxyprogesterone was found[8] to be approximately equal to that of desoxycorticosterone. Recently Huggins and Jensen[9] have shown that 9α-fluorinated Δ^4-pregnene derivatives are powerful inhibitors of estrogen and androgen-induced uterine growth in the rat. IV was found to inhibit estradiol in the mouse at dose levels approximately equal to those of 9α-fluoro-11β-hydroxyprogesterone.[10]

TABLE I

GLUCOCORTICOID ACTIVITIES OF 12α- AND 9α-HALO-11β-HYDROXYPROGESTERONES

	12α	9α
Bromo-11β-hydroxyprogesterone (I)	0.25–0.35	0.1–0.2
Chloro-11β-hydroxyprogesterone (III)	0.5–0.6	0.35
Fluoro-11β-hydroxyprogesterone (IV)	0.6–0.9	0.85

(4) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 715 (1943).

(5) The addition of the elements of HOBr to the 11,12 double bond in the pregnane series has been shown to proceed in the direction indicated; *cf.* P. Hegner and T. Reichstein, *ibid.*, **26**, 721 (1943).

(6) The opening of 11β,12β-oxides with hydrogen halides has been shown to lead to the all-axial 12α-halo-11β-ols; *cf.* J. Schmidlin and A. Wettstein, *ibid.*, **36**, 1241 (1953); J. W. Cornforth, J. M. Osbond and G. H. Phillipps, *J. Chem. Soc.*, 907 (1954).

(7) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

(8) F. M. Singer and A. Borman, to be published.

(9) Charles Huggins and E. V. Jensen, *J. Exp. Med.*, **102**, 347 (1955).

(10) W. B. Kessler and A. Borman, to be published.

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RECEIVED MARCH 26, 1956

ON THE RATE EQUATION FOR THE PERSULFATE OXIDATION OF ISOPROPYL ALCOHOL

Sir:

We wish to point out that the procedure followed in the development of the rate equation in our recent article[1] on the kinetics of the persulfate oxidation of isopropyl alcohol is not valid.[2] In Eq. 12 it is not permissible to substitute the quantity $[SO_4] - [X]$ for $[SO_4]$, since $[SO_4]$ itself already represents the concentration of free sulfur tetroxide remaining after formation of a certain quantity of complex, [X].

Unless certain questionable assumptions are made about the magnitude of some of the rate constants and the concentration of the proposed intermediates, it does not appear that a rate equation of the required form, predicting a limiting rate at higher initial alcohol concentrations, can be derived from the proposed mechanism. Furthermore, newer kinetic data recently obtained in this laboratory[3] indicate that a limiting rate also is attained at higher initial concentrations of persulfate when the initial alcohol concentration is kept constant. Any correct theory of the mechanism of these oxidations must therefore take this fact into account, along with other recently observed anom-

(1) L. S. Levitt and E. R. Malinowski, THIS JOURNAL, **77**, 4517 (1955).

(2) As a result of discussions initiated by Dr. K. B. Wiberg, this error has come to our attention.

(3) L. S. Levitt and E. R. Malinowski, unpublished experiments.

alous effects which will be reported in detail at a later date.

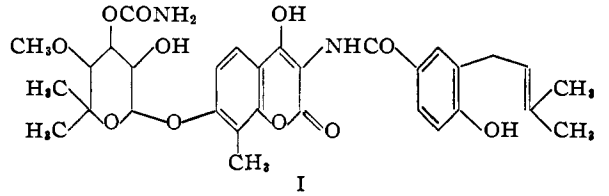
DEPARTMENT OF CHEMISTRY
STEVENS INST. OF TECHNOLOGY L. S. LEVITT
HOBOKEN, N. J. E. R. MALINOWSKI

RECEIVED JANUARY 19, 1956

NOVOBIOCIN.[1] III. THE STRUCTURE OF NOVOBIOCIN

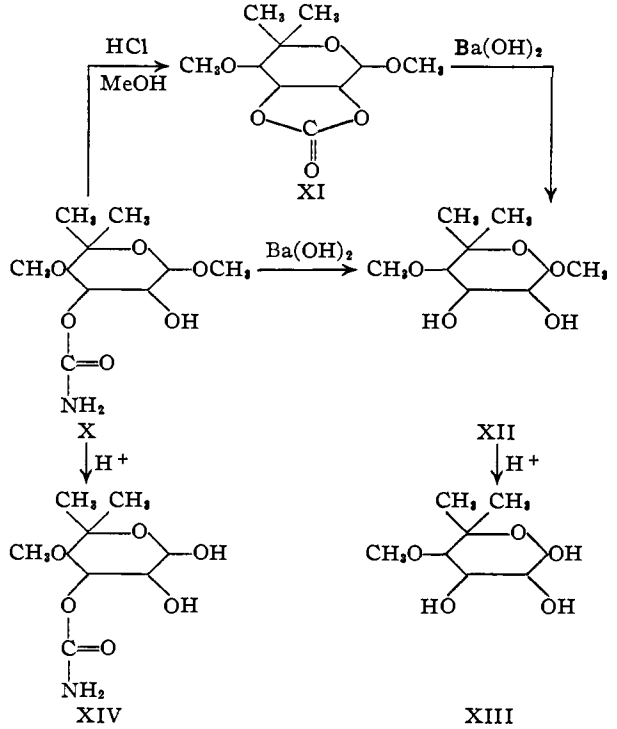
Sir:

A partial structure of the antibiotic novobiocin was proposed in the previous communication[2] in this series. The present studies deal with the structure of the sugar moiety, noviose (XII). The following results, considered with the previous findings,[2-3] permit the assignment of structure I to novobiocin.



I

The structural relationships between the methyl glycoside (X), the carbonate ester (XI), and the dihydroxy compound (XII) of the previous communication[2] are



XI

XIV XIII

Reaction of X with aqueous barium hydroxide at room temperature gives XII (m.p. 65–70°) in 96% yield with evolution of ammonia, and precipitation of the theoretical amount of barium carbonate (*Anal.* for XII. Calcd. for $C_9H_{18}O_5$: C, 52.41; H, 8.80; OCH_3, 30.1; C-CH_3, 14.5. Found: C, 52.67; H, 8.88; OCH_3, 26.8; C-CH_3, 2.17). Chromic acid oxidation of XII gives acetone, isolated in 46% yield as the dinitrophenylhydrazone. This confirms the presence of *gem*-dimethyl groups indicated previously[2] by infrared absorption and low C-CH_3 analyses. Compound XII, Benedict-negative, consumes one mole of periodate rapidly with the formation of a dialdehyde, which upon warming with an acid ethanol solution of 2,4-dinitrophenylhydrazine yields the dinitrophenylosazone of glyoxal in quantitative amounts and a partially characterized canary-yellow derivative, m.p. 105–106° (*Anal.* found: C, 46.66; H, 4.79). Oxidation of the dialdehyde with bromine in the presence of strontium carbonate gives a 77% yield of the expected optically active strontium salt (Calcd. for $C_9H_{14}O_7Sr \cdot 1.5H_2O$: C, 31.00; H, 4.91; OCH_3, 17.39; Sr, 25.12. Found: C, 31.18; H, 5.07; OCH_3, 19.65; Sr, 25.68).

Hydrolysis of XII in 0.5 *N* sulfuric acid at 80° for 30–45 minutes removes the glycosidic methyl group to form Benedict-positive noviose (XIII), m.p. 128–130° (Calcd. for $C_8H_{16}O_5$: C, 49.99; H, 8.39; OCH_3, 16.15; C-CH_3, 15.6. Found: C, 49.71; H, 8.50; OCH_3, 16.23; C-CH_3, 1.88). Noviose (XIII) consumes two moles of periodate with the formation of two moles of formic acid which was isolated and identified as the strontium salt. These findings establish the structures XI, XII and XIII.

Hydrolysis of X with 0.5 *N* sulfuric acid at 80° for *ca.* one hour removes the glycosidic methyl group without appreciable hydrolysis of the carbamate to give 3-(O)-carbamylnoviose (XIV), m.p. 124–126° (Calcd. for $C_9H_{17}NO_6$: C, 45.95; H, 7.29; N, 5.96. Found: C, 45.95; H, 7.66; N, 5.92). The purity of XIV was established by a 340-transfer countercurrent distribution analysis using 1-butanol and water as the solvent system. While pure X does not react with periodate according to the Fleury and Lange procedure,[4] XIV consumes one mole within 30 minutes with the formation of one mole of formic acid. Excluding the possibility of carbamate migration, which appears unlikely in view of the excellent yields and clean-cut periodate results, the carbamate is assigned to carbon no. 3 of XIV. This permits the identification of novobiocin as 7-[4-(carbamoyloxy)-tetrahydro-3-hydroxy-5-methoxy-6,6-dimethylpyran-2-yloxy]-4-hydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylcoumarin[5] (I).

Although carbamate occurrence in nature appears to be rare, recent studies indicate the role of the carbamyl group in the biochemical synthesis of citrulline from ornithine.[6,7] The isolation of O-carbamyl-D-serine from the culture medium of a new *Streptomyces* species has been reported.[8]

(1) The Upjohn Company Registered Trade Mark for novobiocin is Albamycin.

(2) J. W. Hinman, H. Hoeksema, E. L. Caron and W. G. Jackson, THIS JOURNAL, **78**, 1072 (1956).

(3) H. Hoeksema, J. L. Johnson and J. W. Hinman, *ibid.*, **77**, 6710 (1955).

(4) P. F. Fleury and J. Lange, *J. Pharm. Chim.*, **17**, 107, 196 (1933).

(5) We are indebted to W. Russell Stemen, Associate Editor of Chemical Abstracts, for this name.

(6) S. Grisolia and P. P. Cohen, *J. Biol. Chem.*, **198**, 561 (1952); **204**, 753 (1953).

(7) M. E. Jones, L. Spector and F. Lipmann, *Fed. Proc.*, **14**, 232 (1955).

(8) G. Hagemann, L. Pénasse and J. Teillon, *Biochim. et Biophys. Acta*, **17**, 240 (1955).