acidity of boric acid to the marked degree characteristic of 1,8-naphthalenediols.[4]

Lithium aluminum hydride reduction of pentamethyldecarboxamidoterrinolide consumes 0.5 mole of hydride and yields no hydrogen; the reaction product is a dialcohol (IV), m.p. 114–115°, *anal.* Calcd. for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.09; H, 6.69, which is readily dehydrated in dilute mineral acid to an ether, m.p. 141–142°. *Anal.* Calcd. for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.06; H, 6.06. That the lactone structure shown by this reduction is a phthalide is indicated by the extreme resistance of decarboxamidoterrinolide to hydrolysis. This assignment is in agreement with the carbonyl band at 5.73 $\mu$ (dioxane) in the infrared absorption spectra of I and II. The marked similarity of the ultraviolet spectra of I, II and 1,8-dihydroxynaphthalene-2-carboxylic acid[3] determines the orientation of the phthalide ring on the naphthalenediol system. Further, the acidity of terrinolide, $pK_{a_1} = 4.5$, is in good agreement with the acidity of 1,8-dihydroxy-2-naphthaldehyde, $pK_a = 4.5$ (dimethylformamide–water).

The presence of five phenolic hydroxyl groups in I and II is shown by the formation of pentamethyl and pentaacetyl derivatives. The stability of II in strong acid, and the marked susceptibility of I and II to air oxidation suggest that the $C_6H_5O_3$ moiety not accounted for by the dihydroxybenzophthalide system is a trihydroxybenzene. Comparison of the ultraviolet spectrum of the dialcohol (IV) to the composite curves derived from 3-hydroxymethyl-4-methyl-1,8-naphthalenediol[3] and the three isomeric trihydroxybenzenes indicates that the $C_6H_5O_3$ group is hydroxyhydroquinone.

The presence in terrinolide of a carboxamide group which is lost by hydrolysis in sulfuric acid is supported by the infrared absorption spectra of I, II and their derivatives. The second acid constant of I, $pK_{a_2} = 7.5$ (compare $pK_{a_1} = 10.2$ for II) requires that the carboxamide group in terrinolide (I) be attached to the hydroxyhydroquinone ring between two phenolic groups.

(4) J. Böeseken, J. de Bruin and W. van Rijswijk de Jong, *Rec. trav. chim.*, **58**, 3 (1939).

RESEARCH LABORATORIES F. A. HOCHSTEIN
CHAS. PFIZER AND CO., INC. P. P. REGNA
BROOKLYN 6, N. Y. K. J. BRUNINGS
CONVERSE LABORATORY
HARVARD UNIVERSITY R. B. WOODWARD
CAMBRIDGE, MASSACHUSETTS

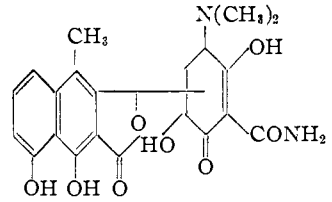
RECEIVED JUNE 25, 1952

## TERRAMYCIN. VI. THE STRUCTURE OF α- AND β-APOTERRAMYCIN, ACID REARRANGEMENT PRODUCTS OF TERRAMYCIN

*Sir:*

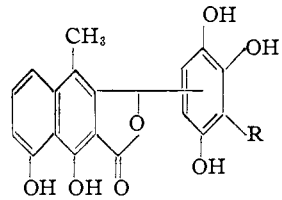
In 1.5 *N* aqueous hydrochloric acid at 60°, terramycin[1] loses a molecule of water and rearranges to form two closely related optically active compounds: α-Apoterramycin hydrochloride (I), $[\alpha]^{25}D$ +123° (*c* 1% in ethanol), $pK_{a_1} = 4.0$, $pK_{a_2} = 5.1$, $pK_{a_3} = 8.4$ (dimethylformamide–water). *Anal.* Calcd. for $C_{22}H_{22}N_2O_8 \cdot HCl$: C, 55.17; H, 4.84; N, 5.85; Cl, 7.40. Found: C, 54.85; H, 5.13; N, 5.97; Cl, 7.19. β-Apoterramycin hydrochloride (I)[2], $[\alpha]^{25}D$ −28° (*c*, 1% in ethanol), $pK_{a_1} = 3.6$, $pK_{a_2} = 5.2$, $pK_{a_3} = 7.8$ (dimethylformamide–water). *Anal.* Calcd. for $C_{22}H_{22}N_2O_8 \cdot HCl \cdot H_2O$: C, 53.17; H, 5.07; N, 5.64; Cl, 7.14. Found: C, 52.90; H, 4.76; N, 5.65; Cl, 6.90.

We consider α- and β-apoterramycin to be stereoisomers of structure I. The two compounds are interconvertible in acid and alkaline solution, and their ultraviolet spectra are virtually identical.




I

Alkali fusion of the apoterramycins yields 1,8-dihydroxy-4-methylnaphthalene-3-carboxylic acid[3] and 2,5-dihydroxybenzoquinone. Both isomers lose carbon dioxide, ammonia and dimethylamine in hot concentrated hydrochloric acid, and are converted to decarboxamidoterrinolide (II).[4] Pentamethylterrinolide is formed by treatment of α-apoterramycin with methyl iodide and potassium carbonate in acetone. The presence of the dihydroxybenzophthalide system in the apoterramycins and terrinolide (III) is evident since the absorption spectra of these compounds are practically superimposable in the 330–420 mμ region of the ultraviolet spectrum, and all three compounds show the strong enhancement of the acidity of boric acid characteristic of 1,8-naphthalenediols.[5] Thus, the apoterramycins differ from terrinolide (III) only in the structure of the isolated six-membered ring.




II, R = H
III, R = $CONH_2$

The isolation of 2,5-dihydroxybenzoquinone from α-apoterramycin suggests the relative positions of two carbonyl groups, a hydroxyl and a dimethylamine group in the isolated ring. The stability of the apoterramycins under the conditions of their formation from terramycin excludes α- or γ-diketone structures within the carbocyclic ring since

(1) P. P. Regna, I. A. Solomons, K. Murai, A. E. Timreck, K. J. Brunings and W. A. Lazier, THIS JOURNAL, **73**, 4211 (1951).

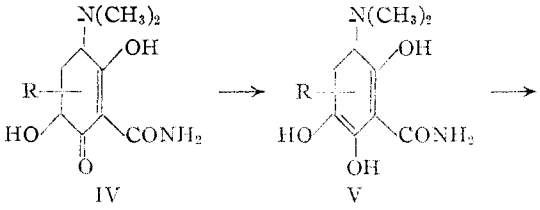
(2) This compound was described by R. Pasternack, P. P. Regna, R. L. Wagner, A. Bavley, F. A. Hochstein, P. N. Gordon and K. J. Brunings, *ibid.*, **73**, 2400 (1951), as $C_{22}H_{24}N_2O_8 \cdot HCl$. It has since been found that Karl Fischer reagent shows the presence of one molecule of water, and that recrystallization from methanol displaces the water with a molecule of methanol.

(3) F. A. Hochstein, *et al.*, to be published.

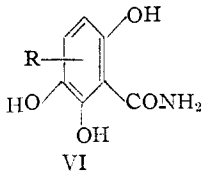
(4) F. A. Hochstein, P. P. Regna, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **74**, 3706 (1952).

(5) J. Böeseken, J. de Bruin and W. van Rijswijk de Jong, *Rec. trav. chim.*, **58**, 3 (1939).

such systems necessitate the attachment of either a hydroxylic or a dimethylamino function $\beta$ to the carbonyl group. The $\beta$-diketone structure (I) expresses the stability of the hydroaromatic ring except under conditions which bring about enolization of both carbonyl functions, thus permitting ready elimination of the dimethylamino group and the formation of a hydroxyhydroquinone ring, as, for example in IV → V → VI.



IV V



VI

RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC.
BROOKLYN 6, N. Y.

F. A. HOCHSTEIN
C. R. STEPHENS
P. N. GORDON
P. P. REGNA
F. J. PILGRIM
K. J. BRUNINGS

CONVERSE LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS

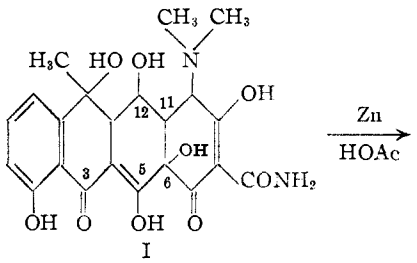
R. B. WOODWARD

RECEIVED JUNE 25, 1952

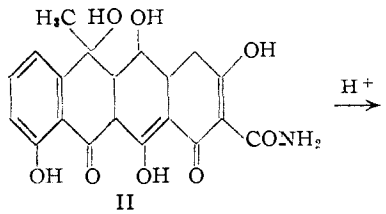
## TERRAMYCIN. VII. THE STRUCTURE OF TERRAMYCIN

*Sir:*

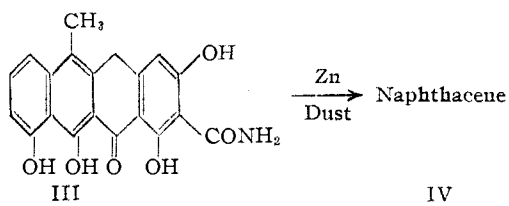
Terramycin[1] has been assigned the structure I.



I



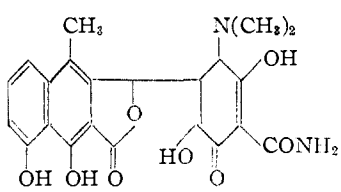
II



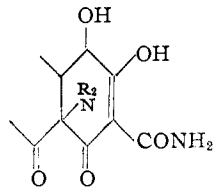
III IV

The naphthacene carbon skeleton is demonstrated by the reaction sequence I → IV. Terramycin is reduced with zinc and acetic acid at room temperature to form desoxydesdimethylaminoterramycin (II)[2]: *Anal.* Calcd. for $C_{20}H_{19}NO_8 \cdot {}^1/_2CH_3COCH_3$: C, 59.99; H, 5.15; N, 3.26. Found: C, 59.99; H, 5.17; N, 3.29. In methanolic hydrochloric acid, II is readily converted to the orange-red crystalline compound (III) or a tautomer: *Anal.* Calcd. for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83. Found: C, 65.74; H, 4.29; N, 4.15. Zinc dust distillation of III yields naphthacene.

Structure I is consistent with the dehydration and rearrangement of terramycin in acid media to form the dihydroxybenzophthalide structure known to be present in $\alpha$- and $\beta$-apoterramycin,[3] to which we now assign structure V.



V



VI

The phthalide carbonyl in the apoterramycins must be derived from a highly conjugated or enolized carbonyl group, since the infrared absorption spectrum of terramycin shows no absorption between 5 and 6 $\mu$. In order to permit ready cleavage to form the apoterramycins, this carbonyl must be incorporated in an actual or potential $\beta$-dicarbonyl system. With this limitation, only two formulas (I and VI) can be written for terramycin. The alternative VI is excluded, *inter alia*, by the acidity relationships of terramycin and its transformation products. For example, the *p*Ka (8.0 in dimethylformamide–water) of the dimethylamino group in terramycin does not change markedly in the conversion to the apoterramycins.

Structure I is also consistent with the formation of terracinoic acid,[4] 7-hydroxy-3-methylindanone-2-acetic acid,[5] 7-hydroxy-3-methylphthalide,[6] 6-acetylsalicylic acid,[7] and 3-hydroxymethyl-4-methyl-1,8-naphthalenediol,[5] in the alkaline degradation of terramycin, which involves cleavages at the 3–4, 5–6, and 11–12 positions. The indanone ring of terracinoic acid is presumed to form through the intermediate VII by aldehyde condensation in the position para to the phenolic group, while 7-hydroxy-3-methylindanone-2-acetic acid is formed through condensation in the ortho position with loss of the carboxyl group.

(1) P. P. Regna, I. A. Solomons, K. Murai, A. E. Timreck, K. J. Brunings and W. A. Lazier, THIS JOURNAL, **73**, 4211 (1951).

(2) R. Pasternack, P. P. Regna, R. L. Wagner, A. Bavley, F. A. Hochstein, P. N. Gordon and K. J. Brunings, *ibid.*, **73**, 2400 (1951). In this paper II was assigned the formula $C_{28}H_{21}NO_8$.

(3) F. A. Hochstein, C. R. Stephens, P. N. Gordon, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **74**, 3707 (1952).

(4) R. Pasternack, L. H. Conover, A. Bavley, F. A. Hochstein, G. B. Hess and K. J. Brunings, *ibid.*, **74**, 1928 (1952).

(5) F. A. Hochstein, to be published.

(6) F. A. Hochstein and R. Pasternack, THIS JOURNAL, **73**, 5008 (1951).

(7) R. Kuhn and K. Dury, *Ber.*, **84**, 848 (1951).