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The Structure of Terramycin[1,2]

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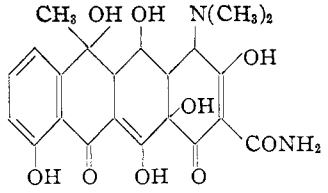
The antibiotic Terramycin has been shown to have the structure I.

Among the products of the metabolism of the actinomycete *Streptomyces rimosus* is Terramycin,[3,4] a yellow crystalline amphoteric substance of the composition $C_{22}H_{24}N_2O_9$. The structure of Terramycin is of special interest in view of the marked activity of the metabolite against both gram-positive and gram-negative bacteria. In this communication, it is shown that Terramycin possesses the structure I.



I

General Considerations

The ultraviolet and infrared spectra of Terramycin (Figs. 1 and 2) demonstrated no features which were positively definitive of special groups or functions in the early stages of the structural work. On the other hand, the absence of bands in the infrared below 6 μ was of great value in that it excluded the presence within the molecule of simple unconjugated aldehyde, ketone, carboxylic acid, ester and lactone functions.

Terramycin is an amphoteric substance; it forms well-defined salts with acids or bases. Titration of the hydrochloride in aqueous solution gives pK_a values of 3.5, 7.6 and 9.2. Two of these constants represent acid functions of Terramycin, and were further defined by the formation of a *dimethyl derivative*, $C_{22}H_{22}N_2O_9(CH_3)_2$ (hydrochloride, pK_a 7.7), by the action of diazomethane on neutral Terramycin. Since the spectrographic evidence precluded the presence of simple carboxyl functions,

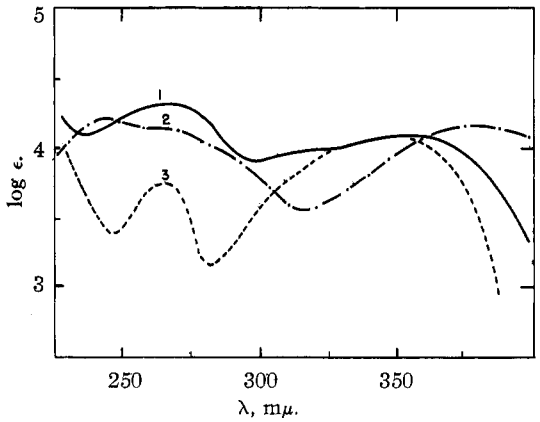


Fig. 1.—Ultraviolet spectra: 1, Terramycin in acid–ethanol; 2, Terramycin in alkaline ethanol; 3, 2-acetyl-8-hydroxytetralone (XXIV) in acid–ethanol.

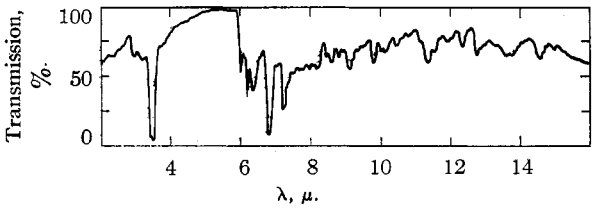


Fig. 2.—Infrared spectrum of Terramycin mulled in mineral oil.

(1) Terramycin. X. The investigations which form the subject of this paper were first outlined in a series of preliminary communications (THIS JOURNAL, **74**, 3706, 3707, 3708 (1952)).

(2) Terramycin is a registered trade name of Charles Pfizer and Co. for the antibiotic whose generic name is oxytetracycline.

(3) A. C. Finlay, G. L. Hobby, S. Y. Plan, P. P. Regna, J. B. Routien, D. B. Seeley, G. M. Shull, B. A. Sobin, I. A. Solomons, J. W. Vinson and J. H. Kane, *Science*, **111**, 85 (1950).

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

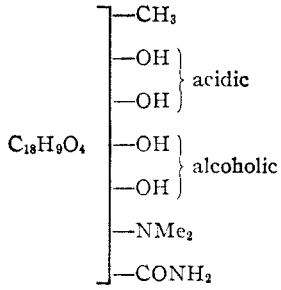
it seemed probable that one or more of the titrable groups was phenolic or enolic. This possibility was supported by the positive ferric reaction given by Terramycin.

Since Terramycin was found to possess *eight* active hydrogen atoms, no more than two of which could be identified as titrable groups, it was clear that a number of alcoholic functions must be present. Two such groups could be identified through the formation of a *diacetyl derivative*, $C_{22}H_{22}N_2O_7(OCOCH_3)_2$, which still possessed two acidic groups (pK_a 6.75 and 8.85).

The nitrogen atoms of Terramycin were readily placed as components of a dimethylamino and a carboxamide group. Alkaline treatment of the antibiotic led smoothly to the liberation of one mole each of dimethylamine and ammonia.[5] Further, Terramycin was converted, by benzenesulfonyl chloride in pyridine, into a *benzenesulfonyl nitrile*, $C_{21}H_{21}N_2O_8(SO_2C_6H_5)(CN)$, whose cyano group was detected through the appearance of a new and distinctive infrared band at 4.5 μ.

One further function, a methyl group attached to carbon, was detected by analytical means in the course of the preliminary studies on characterization.

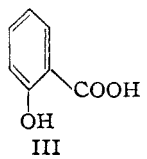
Thus, at the outset of degradation studies, the structural position could be summarized in the expression II.



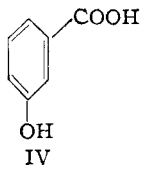
II

Alkaline Degradation

The characterization studies just described revealed little about the skeletal structure of Terramycin, beyond the tenuous suggestion that a phenolic grouping might be present. This hypothesis received immediate support at the outset of the degradation studies, when the antibiotic was subjected to fusion with alkali; in addition to acetic and succinic acids, salicylic acid (III) and *m*-hydroxybenzoic acid (IV) were produced.[5] The

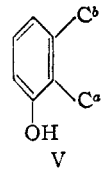


III



IV

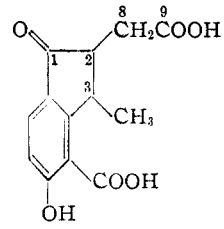
formation of these substances led to the tentative[6] proposal of the part structure V for Terramycin.



V

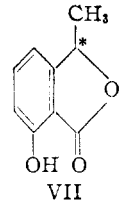
The ready loss of biological activity when Terramycin was treated with warm alkali, and the mildness of the alkaline conditions necessary for the liberation of all of the nitrogen of the molecule as ammonia and dimethylamine,[5] led to the search for the products of mild alkaline degradation.

The major product of the action of aqueous alkalies on Terramycin was found to be a well-defined crystalline acid, *terracinoic acid*, $C_{13}H_{12}O_6$, the determination of whose structure VI has been described previously.[7] The isolation of this sub-



VI

stance, under relatively mild conditions, suggested the elaboration of the structural hypothesis V in several directions: (a) the carbon atom *a* could now reasonably be assumed to be an actual[8] or potential carboxyl group; (b) the C-methyl group known to be present in Terramycin could very probably be attached at C-*b;* (c) the phenolic ring appeared to be fused to a five-membered carbocyclic ring, bearing a two-carbon chain terminating in a potential carboxyl group. The first two of these presumptions received strong support when the phenolic lactone VII was found among the products



VII

of the action of alkali on Terramycin under mild conditions in the presence of the reducing agent, metallic zinc.[9] On the other hand, the presence in Terramycin itself of the five-membered ring of terracinoic acid was subject, from the first, to grave suspicion, for three main reasons. First, *terracinoic acid, as isolated from the degradation of Terramycin, was racemic.* Although one of the asymmetric

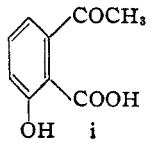
(5) R. Pasternack, A. Bavley, R. L. Wagner, F. A. Hochstein, P. P. Regna and K. J. Brunings, THIS JOURNAL, **74**, 1926 (1952).

(6) In view of the drastic nature of the fusion process, it was not possible at this stage to define the functional character of the atoms attached to the aromatic ring, to exclude the attachment of further groups at other ring positions, or indeed to be certain that the aromatic ring in the observed products had not been derived from a hydroaromatic precursor in Terramycin itself.

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

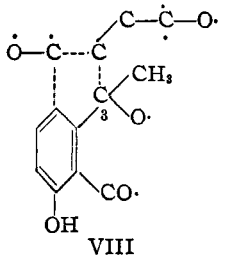
(8) It will be noted that the absence of infrared absorption by Terramycin in the region immediately below 6 μ did not exclude a carboxyl group of the salicylic acid type, whose carbonyl vibration, in consequence of strong hydrogen bonding by the adjacent hydroxyl group, appears at 6.03 μ.

(9) F. A. Hochstein and R. Pasternack, THIS JOURNAL, **74**, 3905 (1952). The isolation of the closely related 6-acetylsalicylic acid (i) from low temperature alkaline fusion of Terramycin was first described by R. Kuhn and K. Dury (*Ber.*, **84**, 848 (1951)).



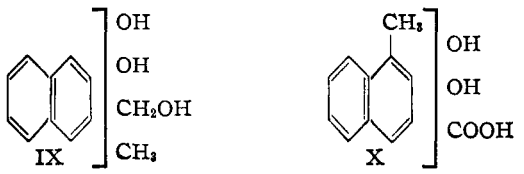
i

centers present in terracinoic acid is adjacent to a carbonyl group, and consequently invertible, the second (C-3) is not one at which the ready inversion necessary for formation of a racemic product could be envisaged. It therefore seemed likely that C-3 of terracinoic acid had at some stage in the formation of the degradation product been non-asymmetric. Second, the striking fact was noted that C-3 of terracinoic acid is saturated and does not bear oxygen, while by contrast, the corresponding atom[10] (starred) in the phthalide VII, *formed under reducing conditions*, is attached to an oxygen atom. It was necessary to conclude that the atom in Terramycin from which C-3 of terracinoic acid is derived, is oxygenated, and that its reduced state in terracinoic acid is achieved at the expense of oxidation of another function elsewhere in the Terramycin molecule. Third, it was clear from the infrared spectrum of Terramycin that the antibiotic could not contain, as does terracinoic acid, a carbonyl group in a five-membered ring. All of these facts indicated that the changes leading from Terramycin to terracinoic acid must necessarily be complicated, quite possibly to the extent of involving formation of a new ring in the degradation product where none had existed before.[11] In these circumstances, it was felt that the information available at this stage justified no more than the structural hypothesis VIII, in which C-3 represents a potential carbonyl group, and any of the dotted bonds, though perhaps actually present in Terramycin, could have been created during the course of the alkaline treatment.



VIII

A great step forward was made possible through the study of a further product, found in small quantity in those alkaline degradations in which zinc was present. This weakly acidic substance, $C_{12}H_{12}O_3$, was named *terranaphthol*, since the presence in it of a naphthalene nucleus was readily evident from its empirical formula, phenolic properties and ultraviolet spectrum. Terranaphthol was found to contain one methyl group bound to carbon. It was smoothly transformable to a *triacetyl derivative*, $C_{12}H_9(OCOCH_3)_3$, and was converted into a monocarboxylic acid, *terranaphthoic acid*, $C_{12}H_{10}O_4$, when fused with alkali. These reactions permitted the formulation of the phenol as IX. The attachment of the methyl group in an α-position of the naphthalene nucleus was demonstrated



by the formation of α-methylnaphthalene when terranaphthoic acid (X) was distilled with zinc dust. The orientation of the phenolic hydroxyl groups in peri positions, which was suspected from ultraviolet studies (*cf.* Fig. 3),[12] was simply and conclusively established through the dramatic effect of terranaphthol in increasing the acidity of boric acid solutions. This phenomenon is exhibited generally by substances containing two hydroxyl groups so disposed in space as to permit formation

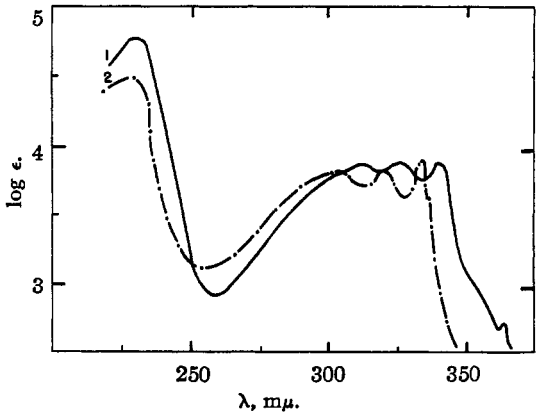
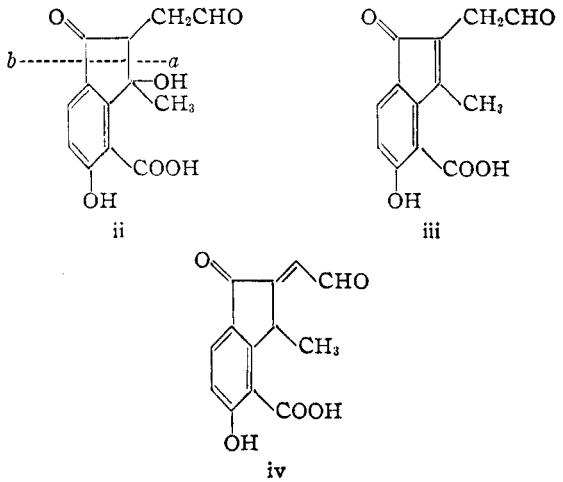


Fig. 3.—Ultraviolet spectra: 1, terranaphthol in ethanol; 2, 1,8-naphthalenediol in ethanol.

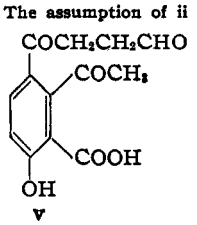
(10) The correspondence of these atoms follows from the fact that each bears the single C-methyl group of Terramycin.

(11) To exemplify: suppose that a stage in the alkaline degradation of Terramycin might be represented by (ii), which could be transformed by the further action of base, through the stages ii → iii → iv → VI into *racemic* terracinoic acid.



ii iii iv

Alternatively, by de-aldolization, with cleavage at *a*, and scission at *b*, 6-acetylsalicylic acid (i, footnote 9) and in the presence of zinc, the phenolic lactone (VII) could be formed. The assumption of ii as an intermediate thus accommodates the unusual facts outlined above. But, it follows further that ii might have been produced, either from a Terramycin structure which contained an actual five-membered carbocyclic ring, or alternatively, *by aldolization within an open chain precursor such as v in which the bond at a (in ii) did not exist.* All of the schemes considered for the rationalization of the racemic nature of terracinoic acid, and the contrast between the state of oxidation at C-3 in VI and VII, involved a similar pair of alternatives, in one of which in each case the five-membered ring appears as an artifact.



v

(12) The spectrum alone did not distinguish between a 1,5- and 1,8-diol system.

of 5- or 6-membered cyclic borate complexes,[13] but *the magnitude of the effect in the case of terranaphthol finds a parallel only with 1,8-dihydroxynaphthalene* (*cf.* Table I). It was now possible to

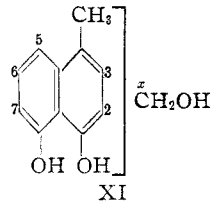
TABLE I

EFFECT OF DIOLS ON ACIDITY OF BORIC ACID[a]

Compound	ΔpH
Sorbitol	0.7
Catechol	1.0
o-Hydroxybenzyl alcohol	0.7
o-Hydroxyacetophenone	.1
Terramycin	.6
1,8-Dihydroxynaphthalene	2.8
Terranaphthol	2.8
1,5-Dihydroxynaphthalene	0.5
β-Apoterramycin	3.2[b]
Terrinolide	3.0[b]

[a] One mole of compound in 12.5 moles of 0.36 *M* aqueous alcoholic boric acid. [b] These two results extrapolated from measurements in dimethylformamide–aqueous boric acid.

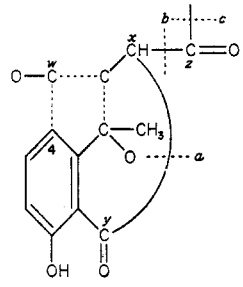
assign to terranaphthol the structure XI.



XI

At this point, we assumed that *terracinoic acid (VI) and terranaphthol (XI) were the end-products of alternative modes of decomposition of the same portion of the Terramycin structure.* The empirical compositions alone of the two substances required that at least five carbon atoms of each be derived from a common source. But beyond that, each of them contains the one C-methyl group known to be present in Terramycin, and that function in each molecule is attached through a single carbon atom to the *m*-position of a phenolic ring. Further, in both substances, the ring bears in the *o*-position to the hydroxyl group an equivalent oxygenated carbon atom. These common features account for all except three carbon atoms of terranaphthol (XI), *viz.*, C-2, C-3 and C-*x*, and it was a consequence of our assumption of common origin that these atoms in Terramycin be co-extensive with three of those which form the chain C-1–C-2–C-8–C-9 of terracinoic acid (VI).

We could now elaborate our earlier structural hypothesis VIII to the new expression XII, through the expansion of C-*z* to a carbonyl group, and the construction of the new bond C-*y*–C-*x*, to complete the six-membered ring which appears in terranaphthol.[14] It may be noted that the reality of this latter bond in Terramycin could scarcely be

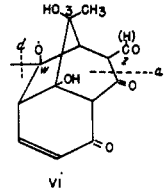


XII

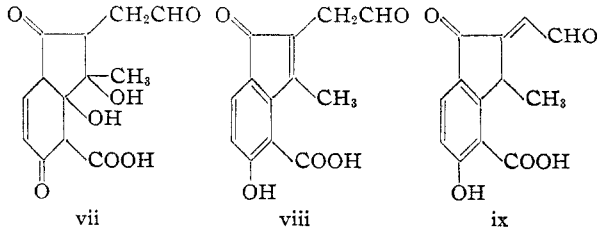
questioned, since the formation in aqueous alkaline media of a β-dicarbonyl system is substantially without precedent. The new developments accommodate further the necessity for two alternative modes of degradation. The first, involving cleavage of the β-dicarbonyl system at *b* permits retention of the second carbocyclic ring of terranaphthol (XI). Alternatively, cleavage at *a*, coupled with a further scission at *c*, gives rise to the aromatic carboxyl group and the acetic acid side chain of terracinoic acid (VI).

It was now necessary to consider further the circumstances surrounding the appearance of a five-membered carbocyclic ring in terracinoic acid. We have described already the grounds for suspecting strongly the absence of this ring in Terramycin itself. Which, then, of the dotted bonds in XII were actually present in Terramycin?[15] The simplest assumption was that C-*w*–C-4 was absent and that C-*w* was of such nature in Terramycin that alkaline treatment of the antibiotic generated an aldehyde function[16] at that site. These expansions of XII lead directly to the expression XIII, which was an eminently satisfactory vehicle for the interpretation of the formation of both terracinoic acid (VI) and terranaphthol (XI). Thus, cleavages at *b* and *d* (de-aldolization, or an equivalent)

(15) We considered the possibility that *all* of the bonds of XII were in fact present in Terramycin. In this case, for steric reasons, it was necessary to replace the aromatic ring of XII by a hydroaromatic equivalent, as in vi. In such a tricyclic unit, C-*w* must be convertible to a ketonic carbonyl group, in order to permit loss of the hydroxyl group at C-3 by alkali-catalyzed dehydration; further, C-*z* must be equivalent to an aldehyde function, to accommodate the internal oxidation–reduction necessary in the formation of terracinoic acid. These points may be illustrated by the reaction sequence, vi (cleavage at *a* and *d*) → vii → viii → ix → VI. But in the products of the acid catalyzed reactions suffered by Terramycin,



vi



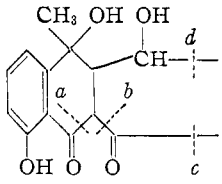
C-w was found to be bound to hydrogen, while C-*z* enjoyed the oxidation state of a *carboxyl* function. No reasonable rationalization of these facts could be constructed on the basis of the tricyclic formula; this and the isolation and formulation of isodecarboxyterracinoic acid (*vide infra*) dealt this interesting possibility the final *coup de grace.*

(16) An aldehyde function as such at C-*w* in Terramycin was of course excluded by the absence of normal carbonyl absorption in the infrared.

(13) *Inter al.*, J. Böeseken, "Advances in Carbohydrate Chemistry," Vol. 4, Academic Press, Inc., New York, N. Y., pp. 189–210. The unusual magnitude of this effect with 1,8-naphthalenediol has been reported by J. Böeseken, J. A. de Bruin and W. E. van Rijswijk de Jong, *Rec. trav. chim.*, **58**, 3 (1939).

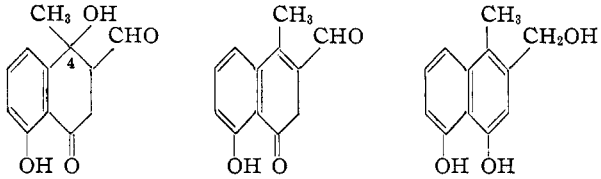
(14) The *a priori* alternative of constructing a bond from C-*y* to C-*w* was excluded through consideration of the states of oxygenation of C-2 and C-*x* in terranaphthol (XI): C-2 bears no oxygen, while C-*x* does. A precursor with a C-*y*–C-*w* bond would lead to precisely the opposite state of affairs.

give XIV. With the liberation of the aldehyde carbonyl function, the β-hydroxyl group at C-4 is susceptible to base-catalyzed elimination. Aroma-



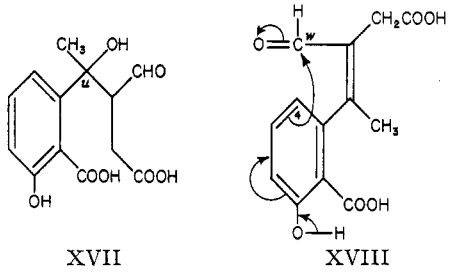
XIII

tization of the resulting molecule XV, and reduction of the aldehyde group by zinc, leads to terranaphthol (XVI ≡ XI). If, on the other hand, the initial



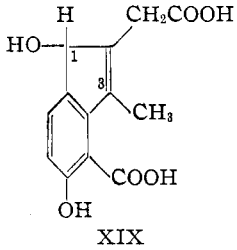
XIV XV XVI

alkaline cleavages occur at *a*, *c* and *d*, the intermediate XVII will be produced; as in XIV, the hydroxyl group at C-*u* will now be lost, with generation of XVIII. Formation of a new bond between



XVII XVIII

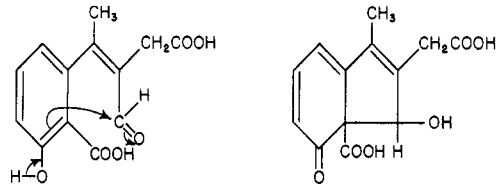
the anionoid C-4 and the cationoid C-*w* (XVIII, *arrows*) will give XIX, from which by simple base-catalyzed prototropic changes,[17] terracinoic acid



XIX

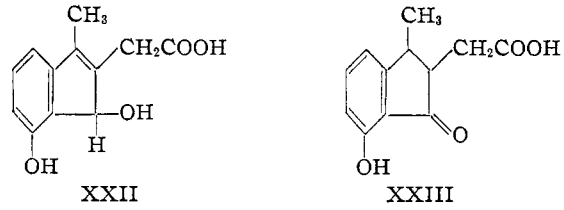
(VI) is produced. The last of these changes accounts simply and elegantly for all of the striking facts about terracinoic acid which were early noted, *viz.*, its racemic nature, the necessity for an internal oxidation–reduction reaction involving C-3, and the requirement that a carbonyl group be generated at C-1 where none existed in Terramycin itself.

The presence in Terramycin of the part structure XIII, and the mode of formation of terracinoic acid just outlined now received remarkable confirmation from a new quarter. Consideration of the intermediate XVIII ≡ XX, and its cyclization to XIX, suggested the possibility of an alternative reaction-path (XX, *arrows*), leading through XXI,



XX XXI

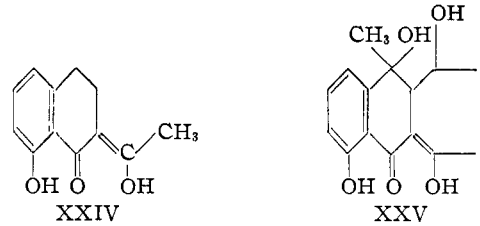
with decarboxylation, to XXII and thence to XXIII. In point of fact, careful search of the alkaline degradation media had led to the isolation



XXII XXIII

in small yield of a further acidic substance, $C_{12}H_{12}O_4$. *This degradation product, isodecarboxyterracinoic acid, was now shown to have the structure XXIII.* Thus, the ultraviolet spectrum of the acid was found to be substantially identical with that of 7-hydroxyindanone. The structure XXIII is consonant with the observed acid constants, pK_{a_1} 5.5, pK_{a_2} 9.6, and with the infrared carbonyl absorption (5.88 μ, 6.00 μ) of isodecarboxyterracinoic acid. Like terracinoic acid, isodecarboxyterracinoic acid gives *m*-ethylphenol on alkaline fusion, and its monobromo derivative suffers concerted dehydrobromination–decarboxylation on treatment with alkali. Finally, the structure XXIII was confirmed by synthesis.[18]

Further verification of the presence in Terramycin of the part structure XIII was obtained when it was shown, through study of the model compound XXIV,[19] that the major features of the



XXIV XXV

ultraviolet absorption spectrum of the antibiotic (Fig. 1) are attributable to the conjugated chromophore of XXV ≡ XIII.[20,21]

(17) The high prototropic mobility of indene is well-known (*cf.* C. K. Ingold and N. A. Piggott, *J. Chem. Soc.*, **123**, 1469 (1923); C. F. Koelsch and R. A. Schiederbauer, THIS JOURNAL, **65**, 2311 (1943)).

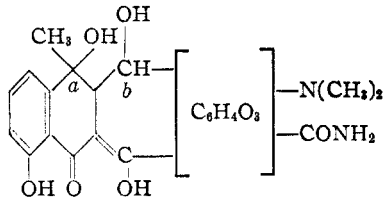
(18) L. H. Conover, *ibid.*, **75**, 4017 (1953).

(19) This model was prepared by the direct condensation of 8-hydroxy-α-tetralone with ethyl acetate under strongly basic conditions (*cf.* G. Wittig, *Ann.*, **446**, 169 (1926) for an analogous preparation of *o*-hydroxybenzoylacetone.)

(20) Hitherto, for simplicity in explication, the β-dicarbonyl system of XIII has been written in the un-enolized form. Actually, it would be expected that the system would be stable in an enolic modification, and in any event it is known that Terramycin cannot contain an un-enolized, unconjugated carbonyl group. In the sequel, an enolic representation (as in XXV) will be used except where it obscures interpretation.

(21) The differences between the spectra of Terramycin and the model were rightly ascribed to the presence elsewhere in the molecule of a chromophore exhibiting absorption of moderate strength in the intermediate wave length region (250–300 mμ).

The conclusions from the study of the degradation of Terramycin by alkali could thus be summarized in the expression XXVI.[22] As yet, no



XXVI

information had been forthcoming about the disposition of six of the carbon atoms of the antibiotic. In order to throw light upon this still obscure area of the molecule, as well as to obtain final confirmation of the part structure XXVI, it was now necessary to turn to the results of acid degradation.

Acid Degradation

The degradation of Terramycin in acidic media differed markedly from alkaline degradation in that acidic treatment did not bring about extensive fragmentation of the molecule. Through the use of successively more strongly acidic conditions, it was possible to establish a consecutive degradation series (Fig. 4), each member of which was related simply to its precursor.

ACID DEGRADATION SERIES

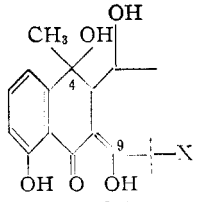
Terramycin $C_{22}H_{24}N_2O_9$ ⟶ anhydroterramycin $C_{22}H_{22}N_2O_8$ ⟶

α- and β-apoterramycins $C_{22}H_{22}N_2O_8$ ⟶

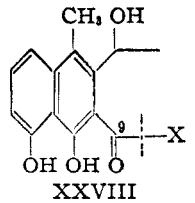
terrinolide $C_{20}H_{15}NO_8$ ⟶ decarboxamidoterrinolide $C_{19}H_{14}O_7$

Fig. 4.

From the structural point of view, the first fruits of the study of the course of the degradation of the Terramycin molecule by acid lay in a simple and powerful verification of the presence of the part structure XIII ≡ XXVII, which had been deduced from the alkaline degradation studies. Thus, it was clear that the *tertiary* hydroxyl group at C-4, placed



XXVII



XXVIII

as it is α to a phenyl group, should be readily susceptible to acid-catalyzed dehydration, and that the product of such a change would contain the moiety XXVIII. In point of fact, the presence in anhydroterramycin, the proximate product of the action of acidic reagents on Terramycin in nonaqueous media, of the system XXVIII was clearly

(22) Strictly speaking, the argument presented so far only identifies the atoms attached at *a* and *b* as electronegative. Thus, it is possible that either of the hydroxyl groups shown might be replaced by the $-NMe_2$ group, or by an ether function whose other bond extends to the C_8 unit. Such possibilities involve considerably more complicated schemes for the interpretation of the alkaline degradation.

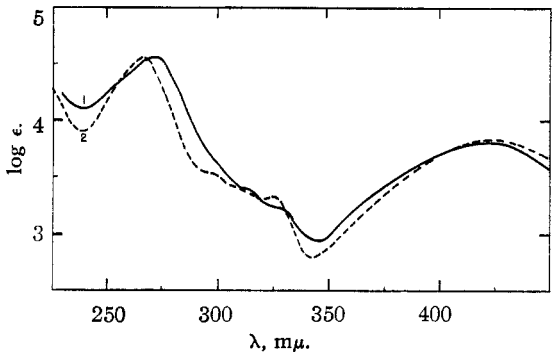
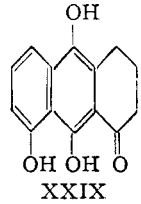


Fig. 5.—Ultraviolet spectra in acid–ethanol: 1, anhydroterramycin; 2, 8,9,10-trihydroxy-1-keto-1,2,3,4-tetrahydroanthracene.

evident from comparison (Fig. 5) of the characteristic ultraviolet spectrum of the transformation product with that of the model compound XXIX.[23]

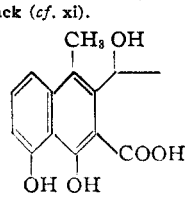


XXIX

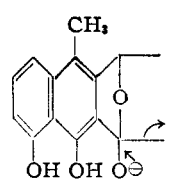
Further, it was found that anhydroterramycin was an exceptionally labile substance, which was isomerized very readily in hydroxylic media, in the presence either of acids or bases, to a mixture of two very similar compounds, the α- and β-apoterramycins; not surprisingly, these substances represented the first transformation products isolated after the action of acids on Terramycin itself under mild conditions in hydroxylic media. The most striking characteristic of the apoterramycins was the presence in their infrared spectra of a new band at 5.75 μ, suggestive of a lactone function. In the light of the presence in the precursors of the systems XXVII and XXVIII, and of the necessity, from the results of the alkaline degradation studies, that the bond C-9–X be labile, it followed that the apoterramycins should contain the 1,8-dihydroxybenzophthalide system (XXX).[24] This view received ready confirmation from several quarters: (i) The apoterramycins increased the acidity of boric acid under standard conditions

(23) The published ultraviolet absorption for 2-acetyl-1,5,8-trihydroxynaphthalene (C. J. P. Spruitt, *Rec. trav. chim.*, **68**, 321 (1949)) with peaks at 265, 337 (w) and 420 mμ shows the major features of the spectrum of anhydroterramycin. We prepared XXIX by catalytic hydrogenation of 1,8-dihydroxyanthraquinone and were gratified to note the remarkable similarity in ultraviolet spectra evident in Fig. 5.

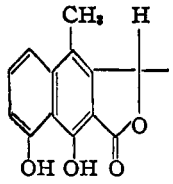
(24) In a formal sense, transformation of XXVIII into XXX would involve hydrolytic cleavage of C-9–X, to give *x*, followed by constitution of the very stable phthalide system (*cf.* footnote 28). On the other hand, it is very likely that the reaction in fact involves internal attack (*cf.* xi).



x



xi



XXX

(*vide supra*, Table I) by 3.2 *p*H units. (ii) The ultraviolet spectra of the apoterramycins corresponded closely (Fig. 6) to that of the model sub-

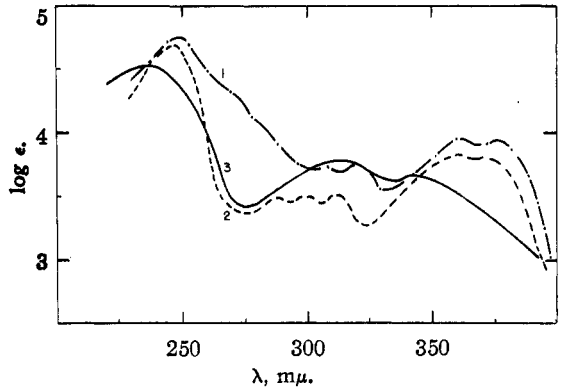
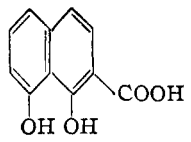
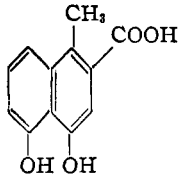


Fig. 6.—Ultraviolet spectra in acid–ethanol: 1, β-apoterramycin; 2, 1,8-dihydroxy-2-naphthoic acid (XXXI); 3, terranaphthoic acid (XXXII).

stance XXXI. (iii) Alkali fusion of the apoterramycins gave terranaphthoic acid (XXXII).



XXXI



XXXII

The survival in the subsequent members of the acid degradation series of the 1,8-dihydroxybenzophthalide system (XXX) of the apoterramycins was established through the observation that the ultraviolet (Fig. 7) and infrared spectra of terrinolide and decarboxamidoterrinolide exhibited in detail the features which had been found characteristic of the system XXX (Fig. 6); further, the strong acidifying effect on boric acid of the two remaining members of the series, and the persistence of a first dissociation constant, $pK_a \sim 4.5$, were interpretable only in terms of the continued presence

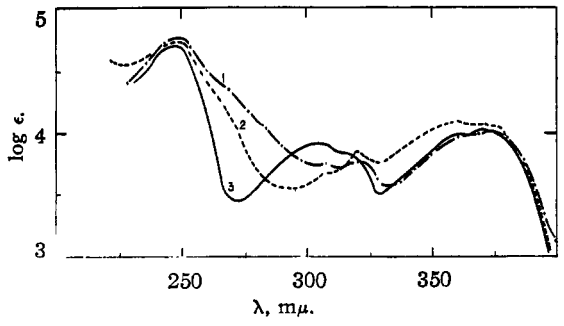
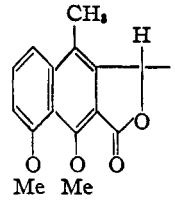
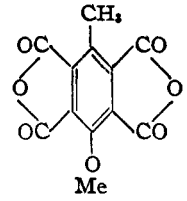


Fig. 7.—Ultraviolet spectra in acid–ethanol: 1, β-apoterramycin; 2, terrinolide; 3, decarboxamidoterrinolide.

of XXX. Moreover, the presence in the fully methylated derivatives (*vide infra*) of terrinolide and decarboxamidoterrinolide of the grouping XXXIII was confirmed through nitric acid oxida-



XXXIII



XXXIV

tion of the latter to a compound, $C_{12}H_6O_7$. This substance was found to contain one C-methyl group, one methoxyl group, and to consume four molecules of alkali on titration. Its infrared spectrum was clearly indicative of anhydride carbonyl groups (four bands at 5.35 to 5.60 μ), and comparison of its ultraviolet spectrum with that of dimethoxypyromellitic anhydride[25] (Fig. 8)

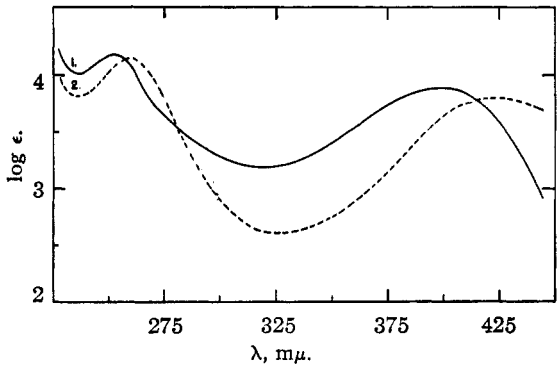
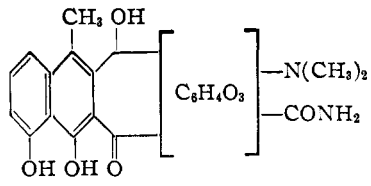


Fig. 8.—Ultraviolet spectra in concentrated sulfuric acid: 1, 3-methoxy-6-methylpyromellitic anhydride; 2, dimethoxypyromellitic anhydride, replotted from reference 25.

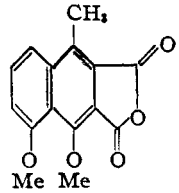
left no doubt that the oxidation product must be formulated as XXXIV.[26] It was now possible to formulate the acid degradation series in terms of the expressions XXXV–XXXVIII.



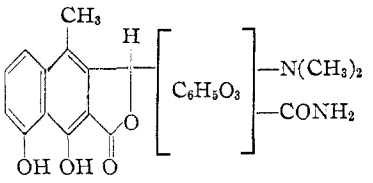
XXXV, anhydroterramycin

(25) H. Schmidt, A. Ebnother and Th. M. Meijer, *Helv. Chim. Acta*, **33**, 1751 (1950).

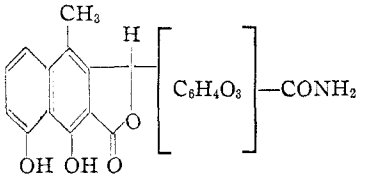
(26) When a *partially* methylated terrinolide was subjected to permanganate oxidation, a *substance*, $C_{13}H_{12}O_8$, was produced, which is formulable only as xii. Thus, its infrared spectrum shows characteristic anhydride absorption and no hydroxyl bands. The ultraviolet spectrum is clearly naphthalenoid.



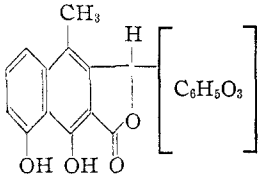
xii



XXXVI, α- and β-apoterramycin

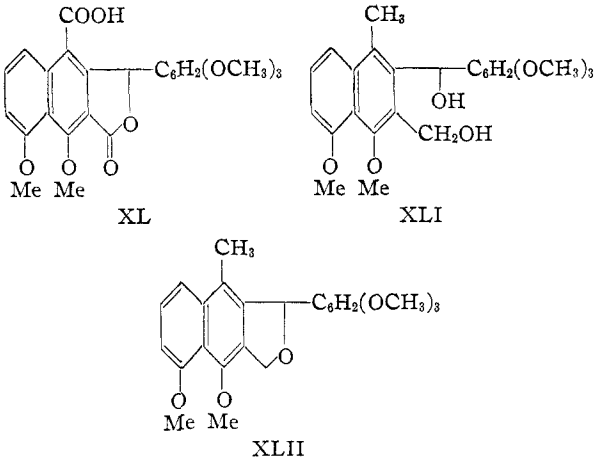


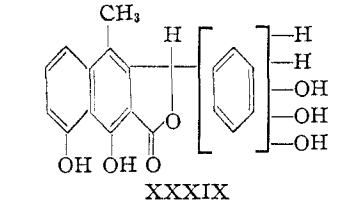
XXXVII, terrinolide



XXXVIII, decarboxamidoterrinolide

We could now, for the first time, come to grips with the problem of the disposition of the six carbon atoms of Terramycin about which no structural information had been available hitherto. In decarboxamidoterrinolide (XXXVIII), the ultimate product of the acid degradation series, the structurally undefined residue ($C_6H_5O_3$) was clearly suggestive of a polyhydric phenolic system, as in XXXIX. This possibility was established through the preparation from decarboxamidoterrinolide of well-characterized crystalline *pentamethyl, pentaacetyl* and *pentatoluenesulfonyl* derivatives. Moreover, the stability of the C_6 grouping was demonstrated, and final verification in detail of the 1,8-dihydroxybenzophthalide system was found, when O-pentamethyldecarboxamidoterrinolide was oxidized to a monocarboxylic acid, $C_{24}H_{22}O_9$, clearly XL, and reduced by lithium aluminum hydride to a *glycol*, $C_{24}H_{28}O_7$ (XLI), which was dehydrated by acidic treatment to a *cyclic ether*, $C_{24}H_{26}O_6$ (XLII). It remained to ascertain the orientation of the four groups attached to the benzenoid ring. The disposition of the hydroxyl groups was first inferred in the following way: Since the two chromophores of the glycol XLI are insulated, the ultraviolet spectrum of the compound must be the simple sum of the separate absorptions of the 1,8-dimethoxynaphthalene and the *x,y,z*-trimethoxybenzene systems. Consequently, additive curves for the naphthalene chromophore plus, alternately, the 1,2,3-, 1,2,4- and 1,3,5-trimethoxybenzene chromophores were constructed. *Only in the case of the addition spectrum involving 1,2,4-trimethoxybenzene was satisfactory agreement with the observed spectrum of XLI obtained* (Fig. 9).[27] It was now possible to expand the structure of decarboxamidoterrinolide to XLIII; it should be emphasized at this point that this initial assignment of the hydroxyl positions received independent confirmation from subsequent studies of the other members of the acid degradation series (*vide infra*).





XXXIX

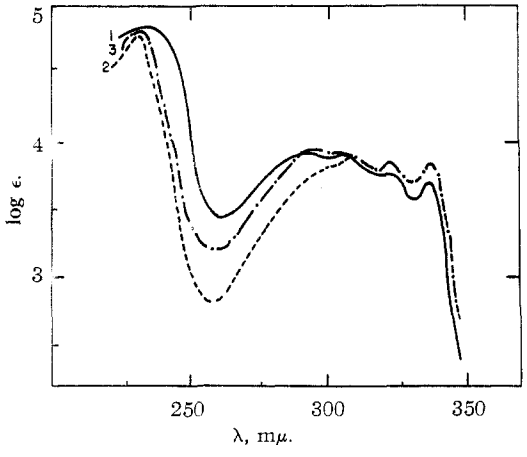
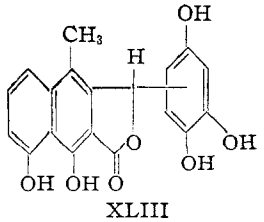


Fig. 9.—Ultraviolet spectra in ethanol: 1, the glycol XLI; 2, terranaphthol; 3, terranaphthol + 1,2,4-trimethoxybenzene.

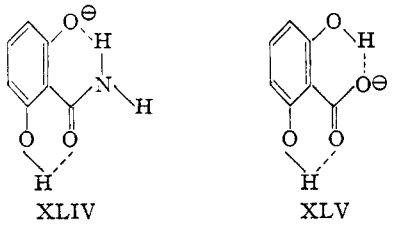


XLIII

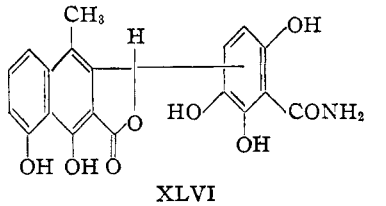
We turn now to a consideration of the circumstances which permitted the ready further expansion of the part structure XXXVII of terrinolide. The empirical changes accompanying the

(27) 1,2,4-Trimethoxybenzene shows its peak absorption at 285 mμ and gives the composite curve shown. 1,2,3- and 1,3,5-trimethoxybenzenes both show their peak absorption near 260 mμ and give a much less satisfactory composite curve. The lateral displacement of the composite curve to shorter wave lengths is a direct consequence of the lower degree of substitution of the naphthalenediol in the composite. A fully methylated terranaphthol was not available, so terranaphthol itself, whose ultraviolet absorption is identical with that of monomethylterranaphthol, was used as the base compound.

transformation of this substance into decarboxamidoterrinolide, and the liberation of carbon dioxide and ammonia in the course of the reaction proved that the change $RCONH_2 \rightarrow RH$ was involved. Now decarboxamidoterrinolide, in addition to an acid constant (pK_a 4.7) associated with the 1,8-dihydroxybenzophthalide system (XXX), was found to possess a second titrable group, pK_a 10.2, which could be attributed to a simple phenolic grouping in the C_6 unit.[28] In sharp contrast, terrinolide, while possessing a substantially identical strong acid constant (pK_a 4.6), exhibited a second group of pK_a 7.5. This acidifying effect of the carboxamido group (ΔpK_a 2.7) is remarkably strong, and it was recognized that it must be associated with a unique structural environment. Thus, the introduction of a carboxamido group into the *o*- or *p*-position of phenol (pK_a 10.6) is associated with the relatively small ΔpK_a values of 1 unit. On the other hand, there was reason to believe that the interpolation of an amide group *between two hydroxyl groups* should result in a marked increase in acidity, since the corresponding anion is one in which an exceptional opportunity exists for stable multiple hydrogen bonding (*cf.* XLIV). The situation is not dissimilar from that which makes 2,6-dihydroxybenzoic acid an unusually strong acid (pK_a 1.3)[29] (*cf.* XLV). These views were confirmed when it was found that 2,4,6-trihydroxybenzamide[30] has pK_a 8.2, and terrinolide could thus be formulated as XLVI with confidence.

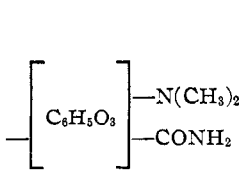


XLIV XLV

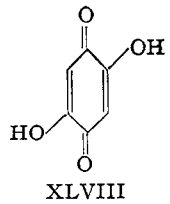


XLVI

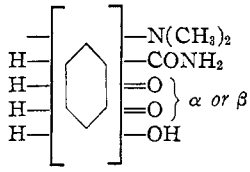
It was now possible to consider the structure of the group XLVII in the α- and β-apoterramycins. The empirical change in the transformation of this array into the 2,3,6-trihydroxybenzamide grouping of terrinolide (XLVI) corresponds to the simple loss of the elements of dimethylamine; this relationship alone suggested strongly that XLVII represented a hydroaromatic system. Nevertheless, the *a priori* possibility had to be considered that the aromatic system of terrinolide had its genesis in a more complicated reaction, for example, a cyclization of an open chain unit, until it was found that *2,5-dihydroxybenzoquinone XLVIII was produced from the apo compounds on alkali fusion.* Since none of the carbon–carbon bonds of XLVIII is so situated that the possibility of its formation under alkaline fusion conditions could be entertained seriously, we could be confident of the presence of a six-membered carbocyclic ring in the unit XLVII.[31] Now the apoterramycin hydrochlorides possess three titrable groups (α-apoterramycin, pK_a 4.0, 5.1 and 8.4; β-apoterramycin, pK_a 3.6, 5.2 and 7.8). One of these constants was attributable to the dimethylamino group, and another to the 1,8-dihydroxybenzophthalide unit (XXX). It was clear that the third must be associated with the C_6 unit (XLVII), and, consequently, that *at least two carbonyl groups, either in the α- or the β-relationship, must be present in XLVII.*[32] On simple empirical grounds, it followed then that the remaining oxygen atom must be incorporated as a hydroxyl group, and the expansion of XLVII to XLIX could be made. Of the two possibilities, α- or β-, for the relationship of the carbonyl groups, the first was unequivocally excluded through consideration of the details of the transformation of the apoterramycins into terrinolide (XLVI). Thus: (i) Any system (L, X *or* Y = OH *or* NMe_2) must necessarily be transformed on



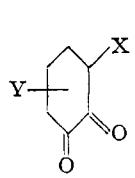
XLVII



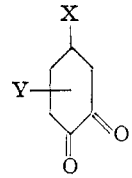
XLVIII



XLIX



L



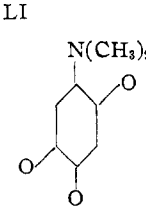
LI

(28) It should be noted that neither acid constant is associated with cleavage of the lactone function, which shows the characteristic stability of 3-arylphthalides (*cf.* A. Tasman, *Rec. trav. chim.*, **46**, 653 and 922 (1927)).

(29) *Cf.* W. Baker, *Nature*, **137**, 236 (1936).

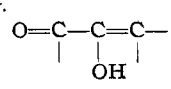
(30) We are much indebted to Dr. V. M. Clark for generously providing us with a sample of 2,4,6-trihydroxybenzamide, prepared by the method of W. Borsche and J. Niemann, *Ber.*, **62**, 1745 (1929).

(31) It may be noted that the disposition of oxygen atoms in the quinone XLVIII was confirmatory of the arrangement of hydroxyl groups deduced for the C_6 unit of terrinolide (XLVI), and suggested further the placing of the dimethylamino group of XLVII in a particular relationship to the oxygen atoms (*cf.* xiii), the more so since the quinone could *not* be obtained by alkaline fusion of terrinolide on repeated attempts.

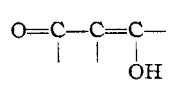


xiii

(32) Since, in the absence of a carboxyl function, only an enolized α- (xiv) or β-dicarbonyl (xv) system could give rise to the requisite acidity.

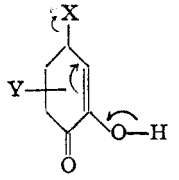


xiv



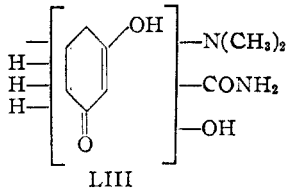
xv

aromatization into a 1,2,3-trihydroxybenzene group rather than the 1,2,4-trihydroxybenzene group observed; (ii) if on the other hand, the group X (= OH *or* NMe_2) were in the β-position with respect to a carbonyl group, as in LI, *very ready elimination*, with consequent aromatization, would be observed (*cf.* LII, *arrows*). In point of fact, the transformation of the apoterramycins into terrino-

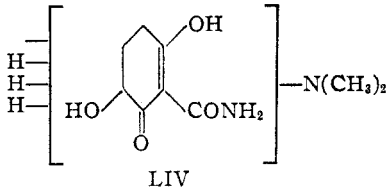


LII

lide takes place only with remarkable difficulty. With rigorous exclusion of oxygen,[33] either α- or β-apoterramycin largely survived when heated to 60° with 0.5 *N* hydrochloric acid for six weeks. To bring about the change to decarboxamidoterrinolide, it was necessary to use 12 *N* acid at its boiling point for 24 hours; racemic terrinolide was produced in rather low yield by heating to 100° in 0.1 *N* hydrochloric acid for ten days. In these circumstances, it was necessary to place the two carbonyl groups of XLIX in the β-relationship, as in LIII; this fact taken with the appearance in terrinolide (XLVI) of a 2,3,6-trihydroxybenzamide grouping, required the expansion of the C_6 unit of the apo-

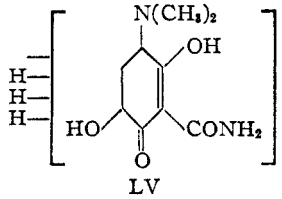


LIII



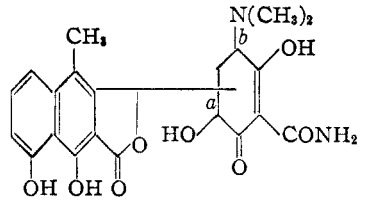
LIV

terramycins to LIV. The placing of the dimethylamino group in the remaining available position α to a carbonyl group, as in LV, had already been sug-



LV

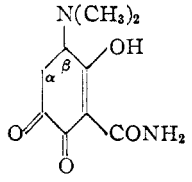
gested by the formation of 2,5-dihydroxybenzoquinone from the apoterramycins on alkaline fusion.[31] This tentative assignment was now considered established by the familiar argument (*vide supra*) that a β-relationship of dimethylamino and carbonyl groups was incompatible with the necessity for very vigorous conditions in bringing about the aromatization of the apo compounds.[34] Except for the point of attachment of the C_{13} unit (XXX),[35] the development of the C_6 unit (XLVII) was now complete,



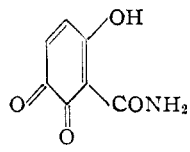
LVI

(33) The effect of catalytic amounts of oxygen or other oxidizing agents in facilitating the aromatization is discussed in the sequel (*cf.* footnote 34).

(34) In the presence of small amounts of air (more than traces leads to widespread oxidative destruction) or ferric chloride, the aromatization reaction is greatly facilitated. This phenomenon is interpretable on the basis of the presence of LV in the apo compounds in the following way: The oxidation of a trace of LV gives xvi. In xvi, the dimethylamino group is β to a carbonyl function, and



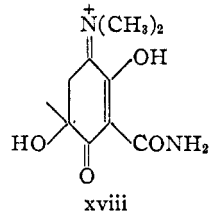
xvi



xvii

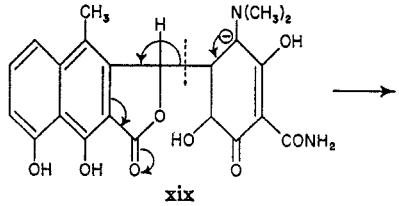
is readily eliminated, giving xvii. Now xvii oxidizes LV, giving xvi, to carry on the chain, while it is itself reduced to the observed 2,3,6-trihydroxybenzamide system of terrinolide.

It may be mentioned that these considerations do not permit the further particularization of groups within LV, *e.g.*, definite incorporation of -CHOH, since schemes equivalent to the above can be couched *mutatis mutandis* in terms of an intermediate such as xviii.

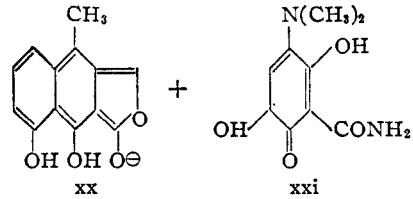


xviii

(35) At this stage, no definitive information was available which permitted a conclusion about the manner of attachment of the C_{13} and the C_6 units of the apoterramycins. It may be noted, however, that the formation of 2,5-dihydroxybenzoquinone (XLVIII) was clearly suggestive of the mode of coupling later shown to be correct. Thus, assuming the structure xix, the key step in the degradation could be construed as a reverse Michael reaction (xix, *arrows*) of a type recog-



xix

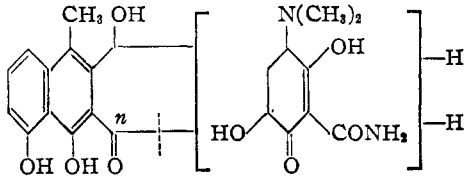


xx xxi

nized as of wide occurrence in alkali fusions (*cf.* R. B. Woodward, F. J. Brutschy and H. Baer, THIS JOURNAL, **70**, 4216 (1948)). The formation of the observed products XXXII and XLVIII from the initial fragments, xx and xxi, does not require explication.

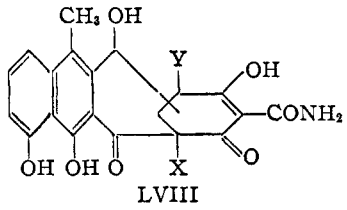
and the apoterramycins could be formulated as LVI.[36]

The elaboration of the structure LVI for the apo compounds permitted the expansion of the formula XXXV for anhydroterramycin, the proximate product of the action of acidic reagents on Terramycin, to LVII. Beyond that, the very ready cleavage

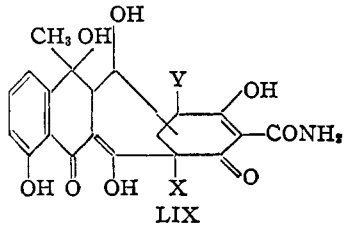


LVII

(LVII, dotted line) attendant upon the change of anhydroterramycin into the apo compounds required that C-*n* be incorporated in a β-dicarbonyl system. The resulting expression for anhydroterramycin (LVIII: X *or* Y = OH *or* NMe_2) corresponds to four full structures for Terramycin itself (LIX: X *or* Y = OH *or* NMe_2). This latter



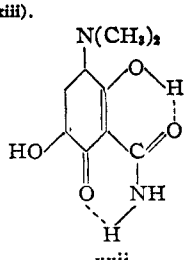
LVIII



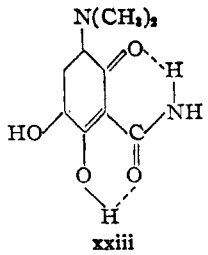
LIX

expression represented the limit to which the interpretation of the degradation of Terramycin by acids and bases could be rigorously brought. In order to distinguish among the remaining possibilities, it was now necessary to advert to a new method of attack—reductive degradation.

(36) Hitherto, the relationship between the isomeric α- and β-apoterramycins has not been considered explicitly, since the great chemical similarity between the two substances justified their treatment together in the development of the structural argument. Thus, the isomers have substantially identical ultraviolet spectra (*cf.* Fig. 12), behave similarly on titration, are transformed under similar conditions into terrinolide, etc. (*vide supra*). Further, they are formed simultaneously from anhydroterramycin, and are interconvertible in the presence of acidic or basic catalysts. Clearly, both substances have the same gross structure (LVI). They must be stereoisomers differing in configuration at C-*a* or C-*b* or, just possibly, in the orientation of the enolized β-dicarbonyl system and the attached amide group (xxii *vs.* xxiii).



xxii



xxiii

Reductive Degradation

When Terramycin was subjected to the prolonged action of zinc and glacial acetic acid, dimethylamine was cleaved from the molecule, one oxygen atom was lost, and *desoxydesdimethylaminoterramycin*, $C_{20}H_{19}NO_8$, was produced. The ultraviolet spectrum (Fig. 10) of the reduction product is markedly different from that of Terramycin. It

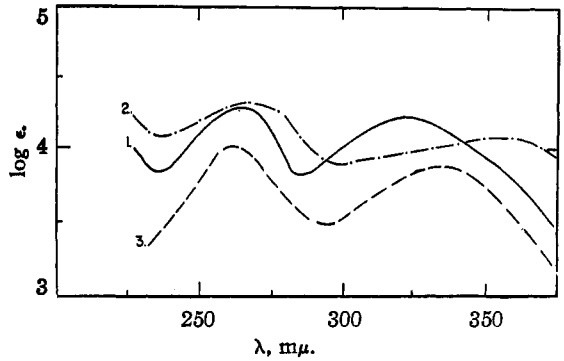
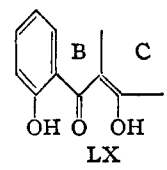
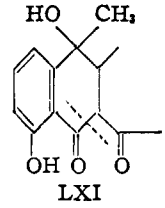


Fig. 10.—Ultraviolet spectra: 1, desoxydesdimethylaminoterramycin in acid–ethanol; 2, Terramycin in acid–ethanol; 3, 8-hydroxy-1-tetralone in acid–ethanol + 3,6-dihydroxy-4-keto-2,5-cholestadiene (xxvi) in chloroform (latter calculated from Windaus and Kuhr, ref. 37.)

was clear that the system LX, to which the long wave length absorption of Terramycin is attributable (*vide supra*, XXIV) could not be present as such in the desoxy compound. *Nevertheless, the*

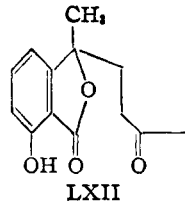


LX



LXI

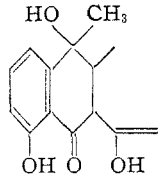
chemical properties of desoxydesdimethylaminoterramycin showed beyond question that the β-dicarbonyl system (LXI) was still potentially present. In particular, the reduction product was smoothly isomerized by alkali to a new substance, $C_{20}H_{19}NO_8$, in whose molecule the presence of the hydroxyphthalide system of LXII was shown conclusively. Thus, isodesoxydesdimethylaminoterramycin pos-



LXII

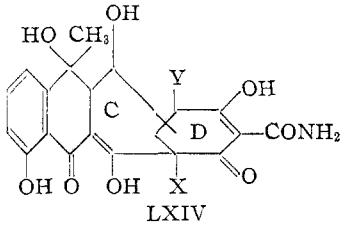
sesses a second acidity constant pK_a 9.2, its infrared spectrum exhibits the very characteristic hydroxyphthalide carbonyl band at 5.75 μ, and it yields 7-hydroxy-3-methylphthalide (VII) on pyrolysis. It was thus clear that the carbonyl group of ring C of Terramycin, which in the latter is enolized in the direction of ring B (as in LX), must in the desoxy compound be otherwise involved. The absence of a carbonyl band in the infrared below 6 μ excluded the possibility that a simple un-

enolized carbonyl function is present (as in LXI). Consequently, it was necessary to conclude that *the ring C carbonyl group of desoxydesdimethylaminoterramycin is enolized in the alternative sense* (LXIII).

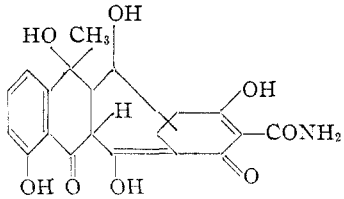


LXIII

Thus, in Terramycin (LXIV), the presence of the group X (= OH *or* NMe_2) at the C/D ring junction prevents enolization toward the junction, but removal of the blocking group on reduction permits the establishment of the more stable system of LXV.[37]

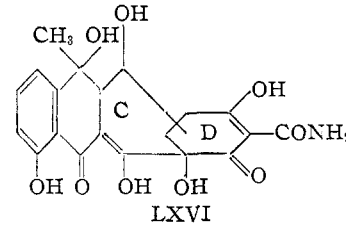


LXIV

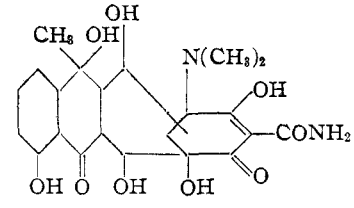


LXV

It was next possible to demonstrate that *the blocking group X of Terramycin (LXIV) must be an hydroxyl group.* When Terramycin was treated with zinc and acetic acid under very mild conditions, reduction proceeded only as far as *desdimethylaminoterramycin*, $C_{20}H_{19}NO_9$. This substance could be converted by the further action of zinc and acid to desoxydesdimethylaminoterramycin. In sharp contrast to the latter, desdimethylaminoterramycin resembled Terramycin very closely in its absorption properties (Fig. 11). Clearly, the removal of the dimethylamino group alone did not permit the establishment of the new enolic system LXIII; this change occurs only after removal of an oxygen atom, and the latter, therefore, must be situated at the C/D ring junction. Thus, desdimethylaminoterramycin is LXVI and Terramycin becomes LXVII.

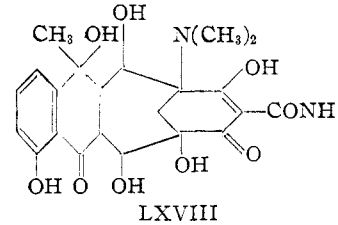


LXVI

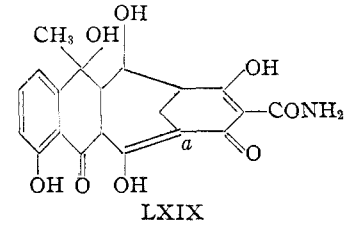


LXVII

The expression LXVII for Terramycin was susceptible of further elaboration in two ways only. Of these, one, leading to the complete structure LXVIII, was simply and conclusively excluded through consideration of the corresponding expression LXIX (*cf.* LXV) for desoxydesdimethylaminoterramycin; since LXIX contains (at *a*)

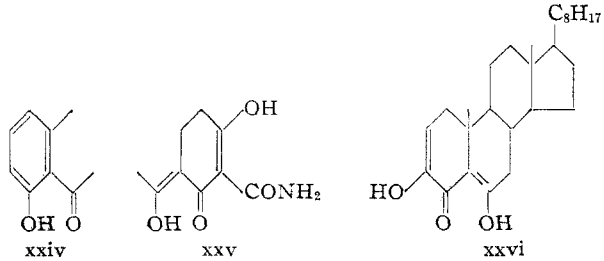


LXVIII



LXIX

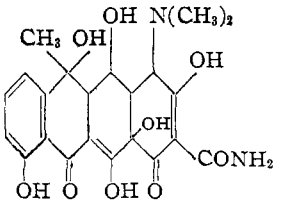
a double bond in a sterically very highly strained situation,[38] spontaneous enolization in the required sense could not seriously be entertained. By contrast, the sole remaining structure (LXX) for Terramycin led to an entirely acceptable complete formula (LXXI) for the desoxydesdimethylamino compound and, beyond that, received positive confirmation through the study of the further transformations of the desoxydesdimethylamino and the desdimethylamino compounds. Thus, while the latter, like Terramycin itself, was converted by acids into a simple orange *anhydro com-*



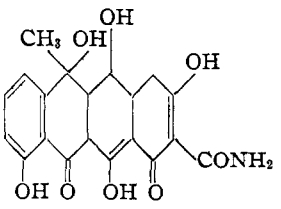
xxiv xxv xxvi

(37) These views received confirmation from a detailed consideration of the ultraviolet spectrum (Fig. 10) of desoxydesdimethylaminoterramycin. On the basis of the structure LXV, this spectrum must represent the simple sum of the absorptions of the *isolated* chromophores (xxiv) and (xxv). Unfortunately, no precise model for xxv is accessible. Nevertheless, the summation of the spectra of 8-hydroxy-1-tetralone and 3,6-dihydroxy-4-keto-$\Delta^{3,5}$-cholestadiene (xxvi) (A. Windaus and E. Kuhr, *Ann.*, **532**, 52 (1937)), a very rough surrogate for xxv, reproduces the salient details of the characteristic spectrum of the desoxydesdimethylamino compound very satisfactorily; the appearance of the requisite unusual feature of high intensity *in the long wave length band* is particularly noteworthy (Fig. 10).

(38) An unstrained double bond at a bridgehead position of a (1,3, *n*)-bicyclic system is only possible when $n \geqslant 5$ (*cf.* V. Prelog, L. Ruzicka, P. Barman and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948); V. Prelog, P. Barman and M. Zimmermann, *ibid.*, **32**, 1284 (1949)).

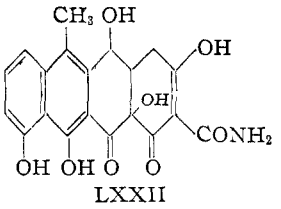


LXX

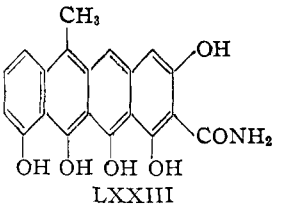


LXXI

pound, $C_{20}H_{17}NO_8$ (LXXII), desoxydesdimethylaminoterramycin (LXXI) under similar conditions smoothly lost *two* molecules of water, with the formation of a crystalline *red substance*, $C_{20}H_{15}NO_6$, clearly formulable as one of the possible tautomers of the fully aromatic naphthacene derivative

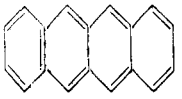


LXXII



LXXIII

(LXXIII).[39] When this red compound was distilled from zinc dust, the parent hydrocarbon



LXXIV

naphthacene (LXXIV) was produced.[40]

The structure LXX for Terramycin was now uniquely defined by all of the available degradative evidence.[41]

Experimental

Melting points, unless otherwise stated, were determined in Pyrex capillary tubes, and are corrected. Many of the compounds described here show no sharp melting or decomposition points; in some of these instances, no melting point data are reported. Infrared spectra were determined on a Baird double beam recording spectrophotometer, equipped with a sodium chloride prism. Ultraviolet absorption spectra were usually determined in 95% ethanol; acid and alkali, when present, were at a concentration of 0.01 *N*. Acid constants, unless otherwise indicated, refer to apparent values derived with a glass-electrode system in 1:1 dimethylformamide–water as solvent. Optical rotations were measured at 1% concentrations throughout. Terramycin and many of its transformation products, particularly those of the acid series, form solvates of unusual stability with a wide range of solvents. In many cases, special measures were necessary to prepare solvent-free samples.

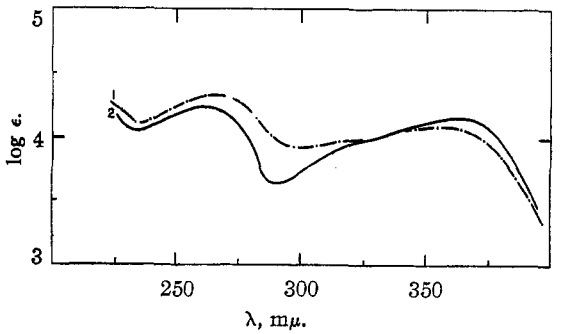


Fig. 11.—Ultraviolet spectra in acid–ethanol: 1, Terramycin; 2, desdimethylaminoterramycin.

Terramycin[42] **(4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide) (I).**—Anhydrous Terramycin, prepared by an earlier procedure, was further purified by recrystallization from anhydrous toluene.[43] For the third and final recrystallization, 1.8 g. of Terramycin was dissolved in 2 l. of dried toluene, and all traces of water removed by refluxing the toluene through a Soxhlet extractor charged with calcium hydride for 2 hours. The hot solution was filtered and cooled to yield 1.4 g. of pale yellow crystals which were dried to constant weight at 100° (0.1 mm.), m.p. 184.5–185.5° dec. when placed in a bath at 175°, heated at 2° per minute; $[\alpha]^{25}D$ −197°, at equilibrium (0.1 *N* hydrochloric acid).

Anal. Calcd. for $C_{22}H_{24}N_2O_9$: C, 57.39; H, 5.25; N, 6.09; C-methyl (1), 3.26. Found: C, 57.52; H, 5.33; N, 6.08; C-methyl, 3.06, amide-nitrogen,[44] 3.50.

Terramycin gives positive ferric chloride, Pauly, Friedel-Crafts, Fehling and Molisch tests. Zerewitinoff's method shows 7.8 moles of active hydrogen per mole. The ultraviolet absorption spectrum of Terramycin (Fig. 1) in hydrochloric acid–ethanol shows λ_{max} 267 mμ, log ε 4.32 and λ_{max} 357 mμ, log ε 4.10. In ethanol–sodium hydroxide, the absorption is shifted to λ_{max} 245 mμ, log ε 4.20, λ_{max} 266 mμ, log ε 4.14 and λ_{max} 380 mμ, log ε 4.16. The infrared spectrum in Nujol mull is shown in Fig. 2. The acid constants of Terramycin hydrochloride in aqueous solution[4] are 3.49, 7.55 and 9.24. In 1:1 dimethylformamide–water, the apparent pK_a values of amphoteric Terramycin shift to 8.0 and 9.8.

Oxidation of Terramycin.—The permanganate oxidation of Terramycin in acetone or aqueous solution required several moles of permanganate, but yielded no readily identified products other than dimethylamine and ammonia. An aqueous solution of Terramycin hydrochloride consumed 8 equivalents of periodate within 2 hours at 25°. No aldehydes were isolated from the reaction products. The hypoiodite oxidation of Terramycin yielded 1.75 equivalents of iodoform, but no other readily identified products.

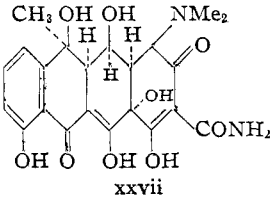
The oxidation of Terramycin in hot 15% nitric acid yielded 1.3 equivalents of oxalic acid, and smaller amounts of an unidentified nitrated phenolic acid, m.p. 217.5–218.5°.

Dimethylterramycin was prepared by the addition of a solution of 6 g. of diazomethane (0.14 mole) in 300 ml. of anhydrous ether to a solution of 18.6 g. (0.041 mole) of an-

(39) Following the isolation of this substance, it was found that Terramycin itself on treatment with strong cold mineral acid yielded small amounts of a crystalline red substance, terrarubein, $C_{22}H_{20}N_2O_8$. Terrarubein, which must be a dimethylamino-substituted LXXIII, also yields naphthacene on zinc dust distillation.

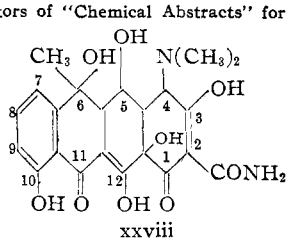
(40) Zinc dust distillation of Terramycin itself had been tried at the outset of the problem; the trace of hydrocarbon mixture produced was uninformative. Desdimethylaminoterrarubein (LXXIII) was the first compound containing the total carbon skeleton of Terramycin to yield an identifiable hydrocarbon by this procedure.

(41) Evidence has been accumulated which permits a tentative solution (xxvii) to the stereochemical problem presented by the Terramycin molecule. These investigations will form the subject of future communications.



xxvii

(42) We are indebted to the editors of "Chemical Abstracts" for suggesting this systematic name, and the accompanying numbering system, xxviii, for Terramycin, and for the nomenclature of certain other compounds in this paper. In view of the complexity of the systematic nomenclature, we have for the greater part used trivial names throughout the paper.



xxviii

(43) We are indebted to Dr. T. M. Vial for suggesting this procedure.

(44) R. H. Plummer, *J. Chem. Soc.*, **127**, 2651 (1925).

hydrous Terramycin in 400 ml. of dried dioxane at 10°. The solution was allowed to warm to room temperature. After 1.5 hours, nitrogen evolution had virtually ceased and the product, which had partially separated, was precipitated by the addition of 1400 ml. of commercial hexane. The amorphous product was dried *in vacuo* (16.9 g.) and then stirred with 100 ml. of methanol for 30 minutes. The crystalline insoluble precipitate (4.0 g.) which formed was further purified by recrystallization from 50% aqueous methanol to yield 2.0 g. (10% yield) of dimethylterramycin. This product decomposes without melting at about 225°. It is insoluble in water, pyridine and the common organic solvents.

Anal. Calcd. for $C_{24}H_{28}N_2O_9$: C, 59.00; H, 5.77; N, 5.73; OCH_3 (2), 12.69. Found: C, 59.23; H, 5.90; N, 5.69; OCH_3, 12.81.

The ultraviolet absorption spectrum is similar to that of Terramycin, λ_{max} 272 mμ, log ε 4.40 and λ_{max} 352 mμ, log ε 4.0.

The hydrochloride of dimethylterramycin was prepared by dissolution of the base in methanolic hydrogen chloride, precipitation with ether, and careful recrystallization from ethyl acetate–methanol containing hydrogen chloride; yellow hexagonal plates. The product decomposes without melting at 175° and has $[\alpha]^{28}D$ −110° (methanol). Titration in aqueous dimethylformamide showed pK_a 7.7, equivalent weight 540 (calcd. 525).

Along with the dimethylterramycin, there is obtained as the principal product (70% yield) an amorphous, unstable material which evolves trimethylamine on mild alkali treatment.

Diacetylterramycin (5,12a-Diacetoxy-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12-tetrahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide).[45]—Ten grams of anhydrous Terramycin was dissolved in 200 ml. of anhydrous dioxane, and the solution made up to 1 l. with acetic anhydride. After 14 days at 25–30°, the solution was concentrated to dryness *in vacuo*, below 35°, and the crystalline product twice recrystallized from toluene to yield 8.8 g. (75%) of pure diacetylterramycin.

Anal. Calcd. for $C_{28}H_{28}N_2O_{11}$: C, 57.35; H, 5.18; N, 5.15; acetyl (2), 15.81; mol. wt., 544.5. Found: C, 57.59; H, 5.23; N, 5.11; acetyl, 15.69; equiv. wt., 546.

This product melts with decomposition at 208–213° and has $[\alpha]^{25}D$ +211° (acetone). Titration in dimethylformamide–water shows pK_a 6.75 and 8.85. Terramycin can be regenerated from this product by the action of 1 *N* aqueous sodium hydroxide at 25° for 5 minutes.

Benzenesulfonylterramycinonitrile (10-Benzenesulfonoxy-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,12,-12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenenitrile).[46]—Benzenesulfonyl chloride, 3.6 g., was added to a solution of 2.5 g. of Terramycin hydrochloride in 7 ml. of pyridine at 5° and held at 5° overnight. The solution was poured into 50 ml. of ether and the gummy solid stirred for 1 hour with 25 ml. of water to yield 2.6 g. of a light tan crystalline product which was purified by two recrystallizations from dimethylformamide, washed with acetone and dried *in vacuo* at 100° for 3 hours. This product, m.p. 210–211°, contains a molecule of dimethylformamide of crystallization.

Anal. Calcd. for $C_{28}H_{26}N_2O_{10}S \cdot C_3H_7NO$: C, 56.78; H, 5.07; N, 6.41; S, 4.89; mol. wt., 655.7. Found: C, 57.33; H, 5.32; N, 6.13; S, 5.44.

Titration shows an equivalent weight of 680, pK_a 6.95 $[\alpha]^{25}D$ −378° (dimethylformamide). The ultraviolet absorption spectrum is similar in shape to that of Terramycin, λ_{max} 275 mμ, log ε 4.23, and λ_{max} 342 mμ, log ε 4.06 in acid methanol. The infrared spectrum shows the characteristic nitrile absorption band at 4.5 μ and carboxamide absorption at 6.05 μ, due to dimethylformamide. The crystalline monohydrate of benzenesulfonylterramycinonitrile, prepared by suspending the dimethylformamide solvate in water, no longer shows strong absorption at 6.05 μ.

On acetylation in acetic anhydride–pyridine, this compound yields a **triacetate** which was recrystallized from ethanol and dried *in vacuo* at 100° for 5 hours; $[\alpha]^{25}D$ +8° (dimethylformamide), pK_a 5.3.

Anal. Calcd. for $C_{34}H_{32}N_2O_{13}S \cdot {}^1/_2H_2O \cdot {}^1/_3CH_3CH_2OH$: C, 56.75; H, 4.90; N, 3.78; acetyl, 17.43; ethoxyl, 3.04; water, 1.21; mol. wt., 740.7. Found: C, 56.90; H, 4.71; N, 4.10; acetyl, 17.12; ethoxyl, 2.84; water (Karl Fischer), 0.8; equiv. wt. (titration), 765.

Terranaphthol (3-Hydroxymethyl-4-methyl-1,8-naphthalenediol) (XVI).[47]—The isolation of this compound has been described.[5] Purification through the triacetate, m.p. 148.7–149.4°, yielded XVI as the pure compound, m.p. 172.4–173.0°. XVI gives a green color with alcoholic or aqueous ferric chloride and a red precipitate with aminoantipyrine.[48] Titration showed an equivalent weight of 207 (calcd. 204), pK_a 7.5. A Kuhn–Roth C-methyl determination showed 6.2% C-methyl (calcd. for 1 C-methyl, 7.35%).

The ultraviolet absorption spectrum shows a major peak, λ_{max} 232 mμ, log ε 4.79 and a weaker group of peaks, λ_{max} 312–341 mμ, log ε 3.89 (Fig. 3).

The oxidation of terranaphthol with peroxide, nitric acid or potassium dichromate in acetic acid yielded intractable tars. An attempt to oxidize terranaphthol with a suspension of silver oxide in ether yielded only unchanged starting material.

Terranaphthol Monomethyl Ether.—When a dioxane solution of terranaphthol was added to 5 moles of diazomethane in ether solution and held at 25° overnight, a monomethyl ether[49] could be isolated by distillation at 160° (0.05 mm.). This oil crystallized slowly from benzene–ligroin and from ether–ligroin to yield a product, m.p. 88–91°, in 25% yield. The infrared absorption spectrum in dioxane solution shows a single OH absorption band at 2.90 μ, in contrast to the two OH bands observed for terranaphthol. The ultraviolet absorption spectrum is virtually identical with that of the free phenol.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.45; methoxyl, 14.21. Found: C, 71.68; H, 6.69; methoxyl, 14.38.

Effect of Terranaphthol on the Acidity of Boric Acid.—A solution of 40.8 mg. (0.2 mmole) of terranaphthol in 2 ml. of absolute ethanol was added to 5 ml. of 0.5 molar aqueous boric acid. The *p*H, as measured with a glass electrode instrument, was 2.20, while that of a blank prepared from 5 ml. of boric acid and 2 ml. of ethanol was 5.00. The observed *p*H change was, therefore, 2.8 *p*H units. This result, together with others obtained in a similar manner, is reported in Table I. It should be noted that the change in *p*H is due in part to the natural acidity of the added organic compound.

Terranaphthoic Acid (1,8-Dihydroxy-4-methyl-3-naphthoic Acid) (XXXII).—Two-tenths gram of terranaphthol was ground in a mortar with 2 g. of sodium hydroxide and 2 g. of potassium hydroxide, placed in a nickel crucible and immersed in a metal bath preheated to 260–270°. After 15 minutes, when the evolution of gas had nearly ceased, the brown melt was cooled, dissolved in 15 ml. of water, and quickly acidified with cooling to *p*H 1 using 4 *N* sulfuric

(45) The assignment of this structure is based on (i) the existence of two acid constants for this compound, (ii) the observation that it yields an anhydro compound analogous to anhydroterramycin chloroform–hydrogen chloride.

(46) (a) Consideration of the absorption spectra, the acid constants and chemical properties of this compound and its degradation products have led us to assign the benzene-sulfonyl group to the 10 position; (b) the conversion of amides to nitriles by the action of acid halides in pyridine has precedent, *cf.* Q. E. Thompson, THIS JOURNAL, **73**, 5841 (1951), and J. Mitchell Jr., and C. Ashby, *ibid.*, **67**, 161 (1945).

(47) The experiments on terranaphthol *per se* did not conclusively distinguish between XVI, and an alternative containing a $-CH_2OH$ at C-6. Thus, the group could not be placed at C-2 or C-7 for these reasons: (i) the acidity of terranaphthoic acid and its ultraviolet spectrum differ markedly from those of 1,8-dihydroxy-2-naphthoic acid; (ii) the carbonyl absorption of terranaphthoic acid occurs at 5.85 μ, as contrasted with that (6.05 μ) of 1,8-dihydroxy-2-naphthoic acid (salicylic acid type). Further, the positive aminoantipyrine test (*cf.* footnote 48) of both terranaphthol and terranaphthoic acid, and the relative difficulty of decarboxylation of the latter, as compared with 1,8-dihydroxy-4-naphthoic acid, exclude attachment at C-5. Of the remaining positions, C-3 and C-6, the former must be chosen, on the basis of the oxidations of methylated derivatives of terrinolide (XXXVII) and decarboxamidoterrinolide (XXXVIII) to xii and XXXIV.

(48) E. Emerson, H. Beacham and L. Beigle, *J. Org. Chem.*, **8**, 417 (1943).

(49) 1,8-Naphthalenediol, prepared by alkali fusion of 1-naphthol-8-sulfonic acid, likewise yields a monomethyl ether with diazomethane. See J. Böeseken and L. G. Smitt, *Rec. trav. chim.*, **58**, 125 (1939).

acid. After diluting to 30 ml. to dissolve precipitated alkali sulfates, the insoluble crystals and tar were removed by filtration and dried. After three recrystallizations from hot water (charcoal), and one from water–methanol, which proceeded very slowly, 0.06 g. of yellow-tan crystals was obtained, m.p. 233–235° with some decomposition above 220° when placed in a bath at 200°, whose temperature was rising at 2° per minute.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.85; H, 4.62.

Titration showed apparent pK_a values of 5.5 and 7.8, equivalent weight 222 (calcd. 218). The infrared absorption spectrum in dioxane solution shows a broad hydroxyl absorption band centered at 3.2 μ and carbonyl absorption at 5.85 μ. This acid gives a red aminoantipyrine test[48] and a green color with alcoholic or aqueous ferric chloride. The ultraviolet absorption spectrum (Fig. 6) shows λ_{max} 236 mμ, log ϵ 4.60, λ_{max} 310 mμ, log ϵ 3.76, and λ_{max} 343 mμ, log ϵ 3.71. Decarboxylation in boiling quinoline with copper bronze catalyst yielded 0.35 mole of carbon dioxide; no other product was identified.

Terranaphthoic acid methyl ether methyl ester was prepared by adding a solution of 0.05 g. of diazomethane in 10 ml. of ether to 0.05 g. of terranaphthoic acid dissolved in 0.5 ml. of dioxane and 0.5 ml. of ether at 0°; the solution was left at room temperature overnight. The oily product was sublimed and crystallized three times from methanol. The pale yellow needles, m.p. 101–102°, were dried at 80° (0.1 mm.) for 2 hours for analysis.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.74; methoxyl (2), 25.20. Found: C, 67.99; H, 5.72; methoxyl, 24.99.

This bicarbonate-insoluble product gives no color with ferric chloride. The infrared absorption spectrum in dioxane solution shows OH absorption at 3.0 μ, but no evidence of carboxyl OH. Carbonyl absorption occurs at 5.83 μ.

1,8-Dihydroxy-2-naphthaldehyde was prepared by a Gatterman synthesis following the procedure of Morgan and Vining.[50] The product was separated from the isomeric 4,5-dihydroxy-1-naphthaldehyde by extraction with cyclohexane in a Soxhlet apparatus. After recrystallization from cyclohexane, the bright yellow crystalline product was sublimed at 135° (0.1 mm.), and then melted at 137.8–138.5° (reported[50] 134–135°), yield 6%.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.21; H, 4.28; mol. wt., 188.2. Found: C, 69.95; H, 4.29; equiv. wt., 187.

1,8-Dihydroxy-2-naphthaldehyde is a strong acid, pK_a 4.5. The infrared spectrum in dioxane solution shows hydroxyl absorption at 2.9 μ, and carbonyl absorption at the unusually long wave length of 6.15 μ. The ultraviolet spectrum shows λ_{max} 265 mμ, log ϵ 4.53, λ_{max} 324 mμ, log ϵ 3.50 and λ_{max} 420 mμ, log ϵ 4.00.

1,8-Dihydroxy-2-naphthoic acid[51] was prepared by the fusion of 0.15 g. of 1,8-dihydroxy-2-naphthaldehyde with 0.7 g. of sodium hydroxide and 0.7 g. of potassium hydroxide at 220° for 3 minutes. The melt was dissolved in water, cooled, acidified and the amorphous product separated by filtration. The product was purified by one crystallization from aqueous ethanol (very unsatisfactory) followed by two recrystallizations from toluene to yield 40 mg. of colorless crystals, m.p. 170.5–171.5° (vigorous gassing).

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.72; H, 3.93; mol. wt., 204.2. Found: C, 64.52; H, 4.18.

Titration showed an equivalent weight of 211, pK_a 3.2 and > 12. The infrared spectrum in dioxane solution shows carbonyl absorption at 6.05 μ. The ultraviolet absorption spectrum in acid–ethanol (Fig. 6) shows λ_{max} 245 mμ, log ϵ 4.72, λ_{max} 314 mμ, log ϵ 3.67, λ_{max} 360 mμ, log ϵ 3.94 and λ_{max} 372 mμ, log ϵ 3.91.

When heated to 125° (0.05 mm.), this acid undergoes rapid decarboxylation and yields 1,8-naphthalenediol in excellent yield.

1,8-Dihydroxy-4-naphthoic acid, m.p. 58–60° dec., was prepared by alkali fusion of 4,5-dihydroxy-1-naphthaldehyde.[50] The titration curve is similar to that of terranaphthoic acid and shows two breaks at pK_a 5.6 and 8.2. Like the isomeric 1,8-dihydroxy-2-naphthoic acid, and unlike terranaphthoic acid, it undergoes ready decarboxylation at 130° *in vacuo*.

The infrared spectrum in dioxane solution shows carbonyl absorption at 5.89 μ. The ultraviolet spectrum in acid–ethanol is somewhat similar to that of terranaphthoic acid, with λ_{max} 220 mμ, log ϵ 4.44 and λ_{max} 335 mμ, log ϵ 4.00.

1,3-Dimethylnaphthalene from Terranaphthol.[52]—The zinc dust used in this experiment was obtained from an unidentified source. It was purified by washing first in 0.1 *N* hydrochloric acid, then in ethanol, and drying at 25° *in vacuo*. The dry product was then heated to about 300° in a slow stream of hydrogen for 15 minutes, and cooled in a hydrogen atmosphere. In a later experiment, Merck zinc dust (95%) which was purified in an identical manner gave a substantially lower yield of hydrocarbon.

One hundred mg. of terranaphthol was thoroughly mixed in a mortar with 5 g. of purified zinc dust, and the mixture packed between asbestos plugs in a 9 × 300 mm. Pyrex tube. The tube was flushed with hydrogen and the contents heated in a slow stream of hydrogen to near the softening point of the tube. The alkali-insoluble viscous green oil, which collected in the cooler part of the tube, was distilled at 80° (0.1 mm.), to yield 7.8 mg. (10%) of 1,3-dimethylnaphthalene, m.p. −10 to −8° (reported[53] −6 to −5°).

A portion was converted to a picrate, m.p. 116.5–118.5°, on a Kofler block (reported 116.5°), and a second portion to the styphnate, m.p. 118–120°, on a Kofler block (reported 116–117°). A separate preparation was converted to the trinitrobenzene adduct, m.p. 134–136°, on a Kofler block (reported 135°).

α-Methylnaphthalene from Terranaphthoic Acid.—Seventy-five mg. of terranaphthoic acid was thoroughly mixed with 7.5 g. of purified Merck zinc dust in a mortar and the mixture heated in a hydrogen stream as described for terranaphthol. The crude product (18 mg.) was dissolved in 0.5 ml. of carbon disulfide, washed with 10% sodium hydroxide to remove traces of phenolic components and distilled *in vacuo* to yield a mixture containing about 70% α-methylnaphthalene and lesser quantities of β-methylnaphthalene and naphthalene. The α- and β-methylnaphthalenes were identified through their mixed picrate, m.p. 123–124°.[54] Naphthalene was identified through its characteristic infrared absorption band at 12.8 μ, while the estimation of the ratios of the three compounds was based on the intensity of this absorption, and of the characteristic bands of α-methylnaphthalene at 12.68 and 12.93 μ and of β-methylnaphthalene at 11.8, 12.34 and 13.50 μ.

When subjected to our conditions for zinc dust distillation, α-methylnaphthalene yielded small amounts of β-methylnaphthalene and naphthalene, while β-methylnaphthalene yielded traces of naphthalene, but *no* detectable quantities of the α-isomer.[55]

Isodecarboxyterracinoic Acid (7-Hydroxy-3-methylindanone-2-acetic Acid) (XXIII).—The isolation of a crude concentrate of this product from the sodium hydroxide–zinc degradation products of Terramycin has been described.[5] The "bicarbonate-soluble fraction" from 100 g. of Terramycin was distilled at 220–224° (0.05 mm.), to yield 1.8 g. of viscous oil. After nine recrystallizations from cyclohexane, the product crystallized as colorless plates, m.p. 111.5–112.5°, yield 1 g. (2%).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.50; C-CH_3 (one), 6.82. Found: C, 65.73; H, 5.58; C-CH_3, 4.90; oxime no.,[56] 1.04.

Titration in aqueous alcohol showed equivalent weights of 110, 221 (calcd. 110, 220), pK_a 5.5 and 9.7. The ultraviolet absorption spectrum is virtually identical with that

(50) This compound was first prepared by G. T. Morgan and D. C. Vining, *J. Chem. Soc.*, **119**, 183 (1921). They did not analyze their preparation.

(51) This acid is presumably the compound, m.p. 170–173° dec., obtained by F. von Heyden, German Patent 55,414 (1891), through the carbonation of 1,8-naphthalenediol.

(52) The isolation of this hydrocarbon could well result from isomerization of 1,2-dimethylnaphthalene, or a rearrangement at an earlier stage.

(53) A. S. Bailey, K. C. Bryant, R. A. Hancock, S. H. Morrell and J. C. Smith, *J. Inst. Petroleum*, **33**, 503 (1947).

(54) M. D. Soffer and R. A. Stewart, THIS JOURNAL, **74**, 567 (1952)

(55) Similar thermal isomerizations of methylnaphthalenes have been reported by others. *Cf.* F. Mayer and R. Schiffner, *Ber.*, **67**, 67 (1934) and C. C. Hall, *J. Soc. Chem. Ind.*, **54**, 208 (1935).

(56) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 16.

of 7-hydroxyindanone,[7] λ_{max} 225 mμ, log ε 4.04, λ_{max} 319 mμ, log ε 3.56 in ethanol–hydrochloric acid. In ethanol–sodium hydroxide, it shows λ_{max} 237 mμ, log ε 4.34, λ_{max} 262 mμ, log ε 3.94 and λ_{max} 363 mμ, log ε 3.96. The infrared spectrum shows carbonyl absorption at 5.88 and 5.99 μ in chloroform solution. Isodecarboxyterracinoic acid gives a purple color with alcoholic ferric chloride.

The monomethyl ester was isolated from the reaction of 150 mg. of isodecarboxyterracinoic acid with 75 mg. (2 equivalents) of diazomethane in 20 ml. of ether at 0–20° for 2 hours. The bicarbonate insoluble oil, 100 mg., isolated by distillation gave a purple ferric chloride test and had $n^{25}D$ 1.5470.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02; CH_3O, 13.25. Found: C, 66.91; H, 6.13; CH_3O, 12.53.

Isodecarboxyterracinoic acid reacts readily with 2 atoms of bromine in glacial acetic acid to yield hydrogen bromide, and an oily product which is believed to be 2-bromo-7-hydroxy-3-methylindanone-2-acetic acid, since it gives a rapid test with alcoholic silver nitrate. The oily product was heated under reflux in 1 *N* alkali and rapidly yielded a crystalline bromine-free solid which gives a violet ferric chloride test and which, from its insolubility in sodium bicarbonate, must have lost the carboxyl group. This behavior parallels that of 2-bromoterracinoic acid which undergoes dehydrobromination and decarboxylation in alkali, and yields 4-carboxy-2,3-dimethyl-5-hydroxyindanone.[7]

***m*-Ethylphenol** was isolated from the fusion of 140 mg. of isodecarboxyterracinoic acid with 2 g. of sodium hydroxide and 2 g. of potassium hydroxide at 325° for 8 minutes. The melt was dissolved in water, acidified, extracted with ether and the ether extract distilled to yield 30 mg. of solid acids which were not investigated and 10 mg. of *m*-ethylphenol, identified through its characteristic infrared absorption spectrum.

8-Hydroxy-1-tetralone.[57]—Six grams of Raney nickel catalyst was added to a solution of 18 g. of freshly sublimed 1,8-naphthalenediol in 75 ml. of absolute ethanol, and the mixture hydrogenated at 60° at 50 p.s.i. When the pressure drop corresponded to the consumption of 1 equivalent of hydrogen, the reaction was stopped, the catalyst separated by filtration and the solvent removed *in vacuo*. Fractional distillation of the oily residue yielded 10.9 g. of colorless 8-hydroxy-1-tetralone, b.p. 82° at 0.07 mm., $n^{20}D$ 1.5871.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.19; H, 6.49.

The ultraviolet absorption spectrum in acid ethanol shows peaks at λ_{max} 260 mμ, log ε 3.97, and λ_{max} 335 mμ, log ε 3.49. The infrared spectrum in chloroform shows carbonyl absorption at 6.1 μ.

2-Acetyl-8-hydroxy-1-tetralone.—Freshly sliced sodium (4.2 g.) was added to a solution of 13 g. of 8-hydroxy-1-tetralone in 35 ml. of ethyl acetate, and the mixture heated to reflux and stirred under an atmosphere of dry nitrogen for 4 hours. The reaction mixture was cooled, made acid with 5% acetic acid and crushed ice, and extracted with seven 100-ml. portions of ether. The ether extract was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated to an oil. Addition of a saturated solution of cupric acetate in methanol yielded 7.8 g. of the deep green crystalline **copper salt** of 2-acetyl-8-hydroxy-1-tetralone. After 3 recrystallizations from benzene, it melted at 254–255° dec.

Anal. Calcd. for $C_{24}H_{22}O_6Cu$: C, 61.33; H, 4.72; Cu, 13.53. Found: C, 61.35; H, 4.75; Cu, 13.37.

A portion of this copper complex was decomposed by treatment with 10% sulfuric acid and the β-diketone extracted with ether. The ether extract was washed with bicarbonate, dried and distilled evaporatively at 150° (0.05 mm.), to yield 2-acetyl-8-hydroxy-1-tetralone.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.75; H, 5.96.

The ultraviolet absorption spectrum in acid–ethanol (Fig. 1) has λ_{max} 267 mμ, log ε 3.74, and λ_{max} 348 mμ, log ε 4.09. The infrared spectrum shows weak absorption at 5.87 μ and a strong doublet at 6.25–6.35 μ in chloroform solution.

(57) This compound has been prepared by the hydrogenation of 1,8-naphthalenediol over nickel-on-kieselguhr by G. Schroeter, German Patent 352,720, *C. A.*, **17**, 1245 (1923). This author reports neither physical constants, nor any analysis.

Anhydroterramycin (4-Dimethylamino-1,4,4a,5,12,12a-hexahydro-3,5,10,11-12a-pentahydroxy-6-methyl-1,12-dioxo-2-naphthacenecarboxamide).—A solution of 15.2 g. of anhydrous hydrogen chloride in 600 ml. of anhydrous acetone was cooled to −5° and poured over 15 g. of Terramycin hydrochloride. The temperature rose to 5° within 10 minutes, and the resulting solution was held at this temperature for 11 hours, at which time the rotation became constant, $[\alpha]^{20}D$ −300°. Anhydrous ether, 700 ml., was added to precipitate 12.9 g. of yellow product. Recrystallization from 250 ml. of anhydrous 1:2 butanol–dioxane yielded 9.4 g. (50%) of pure acetonylanhydroterramycin hydrochloride,[58] $[\alpha]^{20}D$ −455° (methanol). This compound decomposes at about 225° without melting.

Anal. Calcd. for $C_{25}H_{28}N_2O_9 \cdot HCl$: C, 55.92; H, 5.44; N, 5.22; Cl, 6.60. Found: C, 55.32; H, 5.32; N, 5.30; Cl, 6.83.

Rapid titration in aqueous solution shows an equivalent weight of 519 (calcd. 542), pK_a 3.8, 5.5 and 7.2.

The ultraviolet absorption spectrum in acid–ethanol is substantially identical to that of anhydroterramycin (Fig. 5). In alkaline ethanol, the ultraviolet spectrum undergoes a rapid irreversible change to a stable curve which is identical with that of a mixture of apoterramycins. The infrared spectrum in Nujol mull shows carbonyl absorption at 6.03 μ, but none at 5.8 μ as would be expected if the acetone were present as a solvate.

Acetone was recovered from an aqueous solution of acetonylanhydroterramycin by distillation and identified as its 2,4-dinitrophenylhydrazone derivative, m.p. 126–127°.

Anhydroterramycin, prepared by dissolving 4 g. of acetonylanhydroterramycin in 20 ml. of water, and adjusting rapidly to *p*H 5 with 5% sodium bicarbonate, precipitates as an amorphous solid which can be recrystallized readily only from aqueous acetone with which it forms the acetone solvate. The product was dried at 100° (0.1 mm.), for analysis, m.p. 180–190° dec., $[\alpha]^{25}D$ +52° (1:1 methanol–dioxane).

This compound as well as the subsequent members of the acid degradation series gives characteristic phenolic color tests, *e.g.*, a green color with ferric chloride, red-green color with nitrous acid and an intensive blue color with dilute bromine solutions.

Anal. Calcd. for $C_{22}H_{22}N_2O_8 \cdot CH_3COCH_3$: C, 59.87; H, 5.82; N, 5.59. Found: C, 59.56; H, 5.88; N, 5.49.

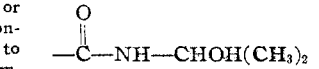
The ultraviolet spectrum in acid ethanol (Fig. 3) has λ_{max} 271 mμ, log ε 4.56, and λ_{max} 425 mμ, log ε 3.80. The infrared spectrum (Nujol mull) shows a carbonyl band at 5.83 μ characteristic of acetone.

8,9,10-Trihydroxy-1-keto-1,2,3,4-tetrahydroanthracene (XXIX).[59]—A solution of 3 g. of 1,8-dihydroxyanthraquinone (m.p. 193–194°) in 50 ml. of 4% aqueous sodium hydroxide was hydrogenated over 1 g. of 5% palladium–charcoal catalyst in a Parr shaker. One mole of hydrogen was absorbed within 5 minutes and a second mole of hydrogen was absorbed within 2.5 hours. No further hydrogen uptake was observed. The reaction mixture was filtered rapidly into excess dilute hydrochloric acid, and the crystalline product was recrystallized from aqueous acetone (charcoal) to yield 1.2 g. of product, m.p. 180–182°, and 0.5 g. of a second crop, m.p. 164–167°. An analytical sample was prepared by sublimation of first crop material at 170° (0.02 mm.). The red needles melt at 186–188°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.57; H, 4.97.

Titration shows pK_a 8.3, neut. equiv. 226 (calcd. 244). The ultraviolet absorption spectrum in acid–methanol (Fig. 5) shows its major peaks at λ_{max} 267 mμ, log ε 4.55, and λ_{max} 425 mμ, log ε 3.83. The infrared spectrum in dioxane solutions shows strong hydroxyl absorption at 3.0 μ, and a single carbonyl band at an extraordinarily long wave length, 6.15

(58) The absence of the acetone carbonyl band in the infrared spectrum of acetonylanhydroterramycin, together with the rapid elimination of acetone in either acid or basic solution, has forced the conclusion that acetone is bonded to the amide nitrogen in this compound as in xxix.



xxix

(59) K. Zahn and H. Koch, *Ber.*, **71**, 172 (1938), have prepared 9,10-dihydroxy-1-keto-1,2,3,4-tetrahydroanthracene by catalytic reduction of 1-hydroxyanthraquinone.

μ. 1,8-Dihydroxy-2-naphthaldehyde likewise shows its carbonyl absorption at this position.

Benzenesulfonylanhydroterramycinonitrile (10-benzenesulfonoxy-4-dimethylamino-1,4,4a,5,12,12a-hexahydro-3,5,11,12a-tetrahydroxy-6-methyl-1,12-dioxo-2-naphthacenenitrile) was prepared from benzenesulfonylterramycinonitrile by simple solution in anhydrous acetone–hydrogen chloride at 5° overnight. Ether precipitation yields the crystalline product directly. After 2 recrystallizations from dimethylformamide–ethanol, and drying at 100° (0.1 mm.) over P_2O_5, the yellow prisms have $[\alpha]^{25}D$ −390° (dimethylformamide).

Anal. Calcd. for $C_{28}H_{24}N_2O_9S$: C, 59.55; H, 4.28; N, 4.97; S, 5.68; mol. wt., 565. Found: C, 59.22; H, 4.56; N, 5.13; S, 6.17; equiv. wt., 589.

This compound is a weak acid pK_a 6.3. Its ultraviolet spectrum, λ_{max} 275, log ϵ 4.58, and λ_{max} 400, log ϵ 3.88, is similar to that of anhydroterramycin, but shifted to shorter wave lengths by the 10-benzenesulfonoxy substituent. The infrared absorption spectrum shows no carbonyl band below 6 μ, but has characteristic nitrile absorption at 4.5 μ.

α- and β-Apoterramycin (3-[(4-Carbamoyl-2-dimethylamino-3,6-dihydroxy-5-oxo-3-cyclohexen-1-yl)-hydroxymethyl]-1,8-dihydroxy-4-methyl-2-naphthoic acid γ-lactone) (**LVI**).—A solution of 50 g. of Terramycin hydrochloride in 100 ml. of 0.5 *N* hydrochloric acid was heated to 60° for 19 hours, the clear, yellow solution diluted to 375 ml., and adjusted to *p*H 3.5 with 10% sodium hydroxide. The amorphous precipitate of α- and β-apoterramycins was separated by filtration, washed thoroughly with water, and dissolved in 500 ml. of hot ethanol. The crystalline α-apoterramycin, which separated almost quantitatively within 24 hours,[60] was filtered, and the filtrate reserved for the isolation of β-apoterramycin. The solid product was suspended in 50 ml. of water and dissolved by the addition of 12 *N* hydrochloric acid to *p*H 1. The filtered solution was concentrated *in vacuo* to a thick sirup, and allowed to crystallize for 24 hours. The crystalline α-apoterramycin hydrochloride was filtered, washed with ice-cold 6 *N* hydrochloric acid, and dissolved in water. Reprecipitation of α-apoterramycin and recrystallization from ethanol, as described above, yielded pure α-apoterramycin, free of the β-isomer, which was dried at 100° (0.1 mm.) for 3 hours for analysis. Yield 16 g., m.p. 190–200° dec., $[\alpha]^{25}D$ −45° (dimethylformamide).

Anal. Calcd. for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01; N, 6.33; C-methyl (1), 3.40. Found: C, 59.46; H, 5.10; N, 6.46; C-methyl, 2.58.

The ultraviolet absorption spectrum in acid–ethanol shows its major peaks (Fig. 12) at λ_{max} 250 mμ, log ϵ 4.77, and λ_{max} 377 mμ, log ϵ 3.87. The infrared spectrum shows a well-defined carbonyl band at 5.82 μ in dioxane solution.

Pure α-apoterramycin hydrochloride, prepared as described in the isolation procedure, was dried at 80° (10 mm.) in a slow stream of hydrogen chloride for analysis, $[\alpha]^{25}D$ +123° (ethanol), m.p. 180–195° dec.

Anal. Calcd. for $C_{22}H_{22}N_2O_8 \cdot HCl$: C, 55.17; H, 4.84; N, 5.80; Cl, 7.40. Found: C, 54.85; H, 5.13; N, 5.97; Cl, 7.19.

Titration shows pK_{a_1} 4.0, pK_{a_2} 5.1, pK_{a_3} 8.4, equiv. wt. 467 (calcd. 479). The infrared spectrum shows a broad band at 5.75–5.85 μ in Nujol mull.

The filtrate from the first alcohol crystallization of α-apoterramycin was concentrated *in vacuo* to 100 ml., acidified with 60 ml. of 2.5 *N* hydrochloric acid, and cooled to 5° for 24 hours. β-Apoterramycin hydrochloride crystallized as colorless needles; yield 21 g. in 2 crops. In order to obtain a product free of α-apoterramycin, the β-apoterramycin hydrochloride was twice recrystallized by dissolving in hot ethanol, and adding 0.4 volumes of water. The β-apoterramycin hydrochloride was dried at 50°, 5–10 mm. pressure in a slow stream of hydrogen chloride for analysis; $[\alpha]^{25}D$ −28° (ethanol), m.p. 195–205° dec.

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; H_2O, 3.63. Found: C, 52.90; H, 4.76; N, 5.65; Cl, 6.90; H_2O (Karl Fischer), 1.87.

Titration shows pK_{a_1} 3.6, pK_{a_2} 5.2, pK_{a_3} 7.8. The ultraviolet spectrum (Figs. 6 and 12) shows its major peaks at λ_{max} 248 mμ, log ϵ 4.78, and at λ_{max} 375 mμ, log ϵ 4.00. The infrared spectrum in Nujol mull shows well-defined carbonyl absorption at 5.70 μ, a shoulder at 6.0 μ.

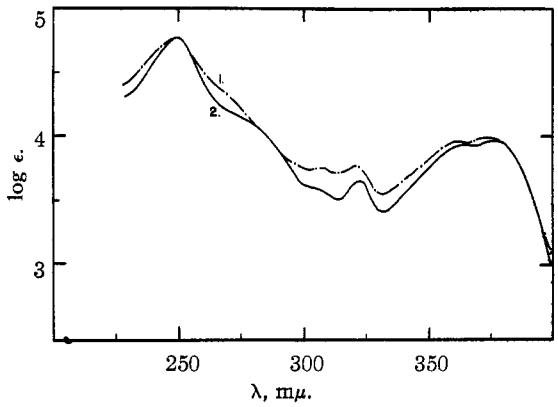


Fig. 12.—Ultraviolet spectra in acid–ethanol: 1, β-apoterramycin; 2, α-apoterramycin.

Amphoteric β-apoterramycin was not obtained in crystalline form; α- and β-apoterramycins are readily interconverted in both acid (*p*H 1) and basic (*p*H 8) solutions. This interconversion is most readily demonstrated by paper chromatography (*vide infra*). β-Apoterramycin hydrochloride forms an extremely stable solvate with methanol. The solvent is not removed on prolonged drying at 100° *in vacuo*.

Triacetyl β-Apoterramycin.—A solution of 1.0 g. of β-apoterramycin hydrochloride in 2.5 ml. of pyridine and 2.5 ml. of acetic anhydride was heated to 100° for 90 minutes, then poured onto 50 ml. of ice. The amorphous product was filtered, washed with water and dried *in vacuo* over calcium chloride. This material was dissolved in 150 ml. of anhydrous ether; crystalline triacetyl-β-apoterramycin hydrochloride was precipitated by the addition of anhydrous hydrogen chloride. The crystalline product, 0.5 g., was twice recrystallized from 5 ml. of methanol to yield 0.10 g. of pure product, m.p. 201.5–202.5° dec., after drying at 80° (0.1 mm.), for 2 hours.

Anal. Calcd. for $C_{28}H_{28}N_2O_{11} \cdot HCl \cdot {}^1/_2H_2O$: C, 54.77; H, 4.92; N, 4.56; Cl, 5.77; acetyl, 21.03; H_2O, 1.46. Found: C, 54.82; H, 4.76; N, 4.64; Cl, 5.05; acetyl, 21.59; H_2O (Karl Fisher), 1.5 ± 0.5.

Titration showed an equivalent weight of 629 (calcd. 614), pK_{a_1} 3.4 and pK_{a_2} 7.2.

Paper Chromatography of Apoterramycins.—The presence of small quantities of α- and β-apoterramycins in the presence of large amounts of the other isomer, or in the presence of Terramycin or terrinolide, is readily demonstrated by paper chromatography. A descending system with water–butanol–acetic acid, 5:4:1, as solvent shows R_f values of 0.42 for Terramycin, 0.21 for α-apoterramycin, 0.74 for β-apoterramycin and 0.91 for terrinolide. All four compounds are readily detected by their fluorescence under ultraviolet light. As little as 1% β-apoterramycin could be readily detected in α-apoterramycin.

Alkali Fusion of α-Apoterramycin.—A mixture of 20 g. of sodium hydroxide, 30 g. of potassium hydroxide and 4 g. of α-apoterramycin was powdered in a mortar, transferred to a nickel crucible, and placed in a metal-bath at 240°. After 10 minutes, when foaming had nearly ceased, the melt was cooled, dissolved in 400 ml. of ice and water and acidified to *p*H 1.2 with 6 *N* sulfuric acid (cooling with added ice). The acid solution was extracted with five 150-ml. portions of ether, the ether extract dried briefly over calcium chloride and concentrated to about 5 ml. on a steam-bath. The crystalline precipitate which formed was removed by filtration, washed with a few ml. of cold dioxane and combined with a second crop of crystals which precipitated from the mother liquor. The product, 0.42 g., was sublimed at 125° (0.02 mm.), to yield 50 mg. of red crystals, which were further purified by resublimation, two crystallizations from hot dioxane, and a third sublimation to yield 22 mg. of pure **2,5-dihydroxybenzoquinone.**

2,5-Dihydroxybenzoquinone was identified by comparison of its ultraviolet absorption spectrum, λ_{max} 285 mμ, log ϵ

(60) Crystalline α-apoterramycin is quite insoluble in ethanol, though the amorphous compound dissolves readily.

4.27 in acid–ethanol, and its infrared spectrum in dioxane solution, which shows strong absorption at 6.05 μ and 6.14 μ, with those of an authentic sample. The diacetyl derivative melted at 159–160° (Kofler hot stage); mixture melting point with an authentic sample not depressed.

The portion of the crystalline alkali fusion product which did not sublime at 125° was recrystallized 3 times from dioxane to yield 20 mg. of a relatively insoluble yellow product, which appeared to be a mixture of 4,5-dihydroxy-1-methyl-2,3-naphthalenedicarboxylic acid and its anhydride.

Anal. Calcd. for $C_{13}H_{10}O_6$: C, 59.55; H, 3.85. Found: C, 60.39; H, 3.81.

The infrared absorption spectrum of this product shows, in addition to salicylic acid type carbonyl absorption at 6.12 μ and aromatic acid carbonyl at 5.80 μ, weaker bands at 5.47 and 5.57 μ arising from the acid anhydride. The mixture melted with prior decomposition over a broad range at 260–270°. An attempt to obtain the acid, free of anhydride by heating in dioxane–water, gave, besides a low yield of the original mixture of acid and anhydride, substantial amounts of terranaphthoic acid.

The alkali fusion product mother liquors, from which the anhydride–dicarboxylic acid had been originally crystallized, yielded, on crystallization from dioxane and finally from methanol–water, 100 mg. of pure terranaphthoic acid, m.p. 235° dec., identified through comparison with an authentic sample.

Benzenesulfonylapoterramycinonitrile (3-(4-cyano-2-dimethylamino-3,6-dihydroxy-5-oxo-3-cyclohexene-1-yl)-hydroxymethyl-8-benzenesulfonoxy-1-hydroxy-4-methyl-2-naphthoic acid γ-lactone).—A suspension of 5 g. of benzenesulfonylterramycinonitrile in 50 ml. of methanol was saturated with hydrogen chloride at 0°. The solution was held at 0° for 1 hour, and then heated to 60° for 1 hour. During heating, a heavy precipitate of colorless needles separated, yield 3.2 g. The dried crystalline product, which from titration appears to be a half-hydrochloride salt, was recrystallized from dimethylformamide–ethanol–water to yield benzenesulfonylapoterramycinonitrile, as rectangular plates, $[\alpha]^{25}D$ +29° (dimethylformamide). The product was dried at 100° (0.1 mm.), for analysis.

Anal. Calcd. for $C_{28}H_{24}N_2O_9S \cdot H_2O$: C, 57.73; H, 4.50; N, 4.82; S, 5.49; mol. wt., 582; H_2O, 3.1. Found: C, 57.62; H, 4.53; N, 4.98; S, 6.10; equiv. wt., 584; H_2O (Karl Fischer), 0.7.

Benzenesulfonylapoterramycinonitrile is a dibasic acid, pK_a 5.7 and 8.5. The ultraviolet spectrum is similar to that of apoterramycin, but shifted to 10 mμ shorter wave length, and the infrared spectrum shows the same characteristic 5.75 μ band, measured in Nujol mull.

Terrinolide (1,8-Dihydroxy-4-methyl-3-(4-carbamoyl-α,-2,3,5-tetrahydroxybenzyl)-2-naphthoic acid γ-lactone) (XLVI).—A solution of 50 g. of Terramycin hydrochloride in 100 ml. of 0.5 *N* hydrochloric acid was heated to 60°, and aerated at the rate of about 2 ml. per minute. Paper chromatographic examination of the clear solution after 48 hours showed the presence of approximately equal amounts of α- and β-apoterramycins. After 9 days aeration at 60°, 22.5 g. of crude terrinolide was separated by filtration, and 7.5 g. more crude product was obtained after a further 5 days. The combined crude products were recrystallized from isopropyl alcohol–water to yield 25 g. of terrinolide in 3 crops.

A portion of this material was recrystallized 3 times from methanol-free acetone to yield pure terrinolide which was dried at 100° (0.1 mm.), for 5 hours for analysis; $[\alpha]^{25}D$ −16° (1:1 methanol–0.1 *N* hydrochloric acid), m.p. 210–215° dec.

Anal. Calcd. for $C_{20}H_{15}NO_8$: C, 60.46; H, 3.81; N, 3.53; active hydrogen (7), 1.76. Found: C, 60.46; H, 4.10; N, 3.52; active hydrogen (Zerewitinoff), 1.71.

The ultraviolet absorption spectrum (Fig. 7) has its major peaks at λ_{max} 249 mμ, log ϵ 4.75, and λ_{max} 360 mμ, log ϵ 4.08 in acid–ethanol. The infrared spectrum shows carbonyl absorption at 5.85 μ and 6.05 μ (shoulder) in Nujol mull. Terrinolide is a moderately strong acid, pK_{a1} 4.6, pK_{a2} 7.5, equiv. wt., 390 (calcd. 397.4). It is soluble in alcohol, acetone and sodium bicarbonate, and insoluble in benzene, ether and water. The ferric chloride test is green, the Wildi[61] catechol test is positive, and the Fehling test is positive. Terrinolide increases the acidity of boric acid to a degree comparable to 1,8-naphthalenediol (Table I). Terrinolide forms solvates with water and methanol which are stable at 100° (0.1 mm.), for many hours.

Terrinolide also can be prepared, more slowly, but in comparable yield by simply holding an acid solution of Terramycin at 60° in a *loosely stoppered* flask for 1 to 2 months. Small amounts of oxygen are desirable; no terrinolide is formed in a nitrogen atmosphere at this temperature, while with excess air or oxygen, a tarry intractable polymeric product is formed to the virtual exclusion of terrinolide. Traces (0.07 mole) of ferric chloride may be substituted for oxygen, though the yield in a single experiment of this type was unsatisfactory. Simple hydrolysis of Terramycin in 0.1 *N* hydrochloric acid at 100° for several days yields racemic terrinolide (*vide infra*).

Pentaacetylterrinolide[62] was prepared by heating 1 g. of terrinolide, 0.5 g. of anhydrous sodium acetate and 5 ml. of acetic anhydride on the steam-bath for 1 hour. The cooled reaction mixture, which had precipitated tan colored crystals, was stirred into 80 ml. of ice-water, the product filtered and recrystallized twice from acetone–methanol to yield pentaacetylterrinolide as colorless needles, m.p. 229–230°, $[\alpha]^{25}D$ +34° (acetone).

Anal. Calcd. for $C_{30}H_{25}NO_{13}$: C, 59.31; H, 4.15; N, 2.31; acetyl, 35.42. Found: C, 59.10; H, 4.43; N, 2.65; acetyl, 34.80.

This compound is soluble in chloroform and acetone, slightly soluble in ethanol. It gives a negative ferric chloride test, and is only slowly soluble in dilute ammonium hydroxide.

Pentamethylterrinolide.—A solution of 3 g. of terrinolide and 40 ml. of methyl iodide in 600 ml. of acetone was heated under reflux with 30 g. of anhydrous potassium carbonate for 4 days. The hot solution was filtered from the potassium carbonate, diluted with 20 ml. of water, and concentrated *in vacuo* to a viscous oil. After thorough washing with water to remove potassium iodide, the residual oil was crystallized first from acetone, then from acetone–ethanol to yield 1.6 g. of pure pentamethylterrinolide, m.p. 225–227°, $[\alpha]^{25}D$ −9.2° (acetone).

Anal. Calcd. for $C_{25}H_{25}NO_8$: C, 64.23; H, 5.39; N, 3.00; methoxyl, 33.20. Found: C, 64.53; H, 5.62; N, 3.05; methoxyl, 32.71.

The ultraviolet spectrum of this alkali insoluble ether is similar to that of the parent polyphenol (Fig. 7). The two major peaks occur at λ_{max} 250 mμ, log ϵ 4.71, and λ_{max} 362 mμ, log ϵ 3.94. The infrared spectrum in chloroform solution shows carbonyl absorption at 5.70 μ and at 6.00 μ.

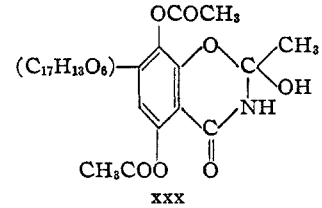
1,8-Dimethoxy-4-methylnaphthalene-2,3-dicarboxylic Acid Anhydride (xii).—Pentamethylterrinolide, 0.3 g., was partially demethylated by heating under reflux with 5 ml. of 15% hydrochloric acid and 25 ml. of glacial acetic acid for 4 hours.[63] The amorphous product obtained on removing the solvent *in vacuo* could not be readily crystallized, but from its methoxyl content (21.9%) it was essentially a mixture of trimethylterrinolides.

A portion of the product, 0.2 g., was suspended in 5 ml. of 2% sodium bicarbonate, and dissolved by the addition of a minimum amount of 10% sodium hydroxide. The solution was cooled to 0° and 5% potassium permanganate, 7.2 ml., added portionwise until the permanganate color persisted for 10 minutes.

Manganese dioxide was dissolved by the addition of sodium bisulfite, the solution acidified and extracted with ether. The ether extracts were concentrated to dryness,

(61) B. S. Wildi, *Science*, **113**, 188 (1951).

(62) The complex nature of the infrared spectrum of this compound, which shows carbonyl absorption at 5.65, 5.80 and 5.90 μ in chloroform, suggests that it is the benzoxazine, xxx, or an isomer.



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(63) This procedure was suggested by the reported use of pyridine hydrochloride–acetic acid in the cleavage of phenolic ethers, V. Prey, *Ber.*, **74**, 1219 (1941), *et seq.*

the oily product recrystallized from ethanol, and then sublimed at 175° (0.05 mm.), to yield 6 mg. of colorless crystals. This product sublimed at 165°, and melted at 230–235° on a Kofler hot-stage.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.20; H, 4.42; mol. wt., 272.3. Found: C, 66.47; H, 4.40; mol. wt. (Rast), 266.

The infrared spectrum in chloroform solution shows carbonyl bands at 5.50, 5.67 μ, but no hydroxyl absorption. The ultraviolet spectrum shows λ_{max} 247 mμ, log ϵ 4.42, λ_{max} 308 mμ, log ϵ 3.79, and λ_{max} 338 mμ, log ϵ 3.74. The anhydride is soluble in hot aqueous sodium hydroxide. The aqueous solution precipitates no acid on simple acidification, but does precipitate the anhydride on heating. It gives a negative ferric chloride test.

Racemic terrinolide was prepared by heating a solution of 10 g. of Terramycin hydrochloride in 300 ml. of 0.1 *N* hydrochloric acid under reflux in a nitrogen atmosphere for 10 days. The partially crystalline brown precipitate was separated and purified by 4 recrystallizations from hot dimethylformamide to yield 2.5 g. of colorless crystals, containing solvent of crystallization. Prolonged stirring (3 days) in ether, followed by drying at 100° (0.1 mm.) yielded the pure compound. Racemic terrinolide is quite insoluble in the common organic solvents.

Anal. Calcd. for $C_{20}H_{15}NO_8$: C, 60.45; H, 3.81; N, 3.53; mol. wt., 397. Found: C, 60.16; H, 4.05; N, 3.72; equiv. wt., 389.

Racemic terrinolide has an ultraviolet absorption spectrum identical with that of the levorotatory form. The infrared spectrum (in mull) shows only minor differences from that of terrinolide in the 7–16 μ region.

Racemic pentaacetylterrinolide,[62] prepared by acetylation in pyridine solution, was crystallized rapidly from ethanol to yield first a low-melting form, m.p. 198–200° dec., which on more prolonged heating in ethanol was converted to a relatively insoluble stable form, m.p. 222–223° dec. These two forms show identical infrared spectra in dioxane solution though the spectra differ slightly in mull. The mixture melting point with the optically active analog is depressed.

Anal. Calcd. for $C_{30}H_{25}NO_{13}$: C, 59.31; H, 4.15; N, 2.31; acetyl, 35.42. Found: C, 59.52; H, 4.35; N, 2.41; acetyl, 35.70.

Methylation of racemic terrinolide by the procedure described for levorotatory terrinolide, but for 48 hours only, yielded a tetramethyl ether, m.p. 238–239°, as well as the pentamethyl ether, m.p. 234.5–235.5°, mixture melting point with the optically active analog depressed. The two ethers were readily separated by chromatography on Florisil with acetone as solvent. The infrared spectra of the two pentamethyl ethers in dioxane solution are identical.

Decarboxamidoterrinolide (1,8-Dihydroxy-4-methyl-3(α-2,3,5-tetrahydroxybenzyl)-2-naphthoic acid γ-lactone) (XLIII).—A suspension of 10 g. of finely powdered terrinolide in 120 ml. of 12 *N* sulfuric acid was heated under reflux in a nitrogen atmosphere for 72 hours. The insoluble product was separated by filtration, washed with water until free of sulfate and dried *in vacuo*. This material (7 g.) was dissolved in 150 ml. of acetone, filtered from a small insoluble residue and chromatographed on a 40 × 3 cm. column containing 150 g. of acid-washed Florisil. The eluate, at first dark yellow and fluorescent, was collected until pale yellow in color, and acidified by the addition of 100 ml. of 2 *N* hydrochloric acid. The acetone was removed *in vacuo* at room temperature and the crystalline decarboxamidoterrinolide, 3.75 g., recrystallized from ethanol, then from ethanol–benzene and dried at 100° (0.1 mm.) to yield 2.5 g. of pure decarboxamidoterrinolide, which decomposes without melting at 215–250°. Decarboxamidoterrinolide has only been obtained in the racemic form.[64]

Anal. Calcd. for $C_{19}H_{14}O_7$: C, 64.40; H, 3.98; C-methyl (1), 4.25. Found: C, 64.10; H, 4.41; C-methyl, 3.82.

The ultraviolet absorption spectrum (Fig. 7) has its two major peaks at λ_{max} 247 mμ, log ϵ 4.70, and λ_{max} 375 mμ, log ϵ 4.00. The infrared spectrum in dioxane solution shows a single carbonyl peak at 5.75 μ. Titration showed two acid constants, pK_{a_1} 4.7, pK_{a_2} 10.2, equiv. wt., 348 (calcd. 354.3).

Decarboxamidoterrinolide gives a positive Wildi test[61] for *o*- or *p*-dihydric phenols, a positive aminoantipyrine test, and a green color with ferric chloride in alcohol. Alkaline solutions are susceptible to oxidation. The deep red color generated on aeration of ammoniacal solutions is readily reversed by bisulfite. Decarboxamidoterrinolide is soluble in ethanol and acetone, insoluble in benzene and chloroform. Like terrinolide, it forms a very stable solvate with methanol. Alkali fusion of decarboxamidoterrinolide yielded terranaphthoic acid, but no other readily identified products.

Decarboxamidoterrinolide from β-Apoterramycin.—Two grams of β-apoterramycin was dissolved in 100 ml. of 12 *N* hydrochloric acid, and the solution heated under reflux in a slow stream of nitrogen which had been carefully freed of oxygen over hot copper. The effluent gases were passed through 1 *N* barium hydroxide solution. After 24 hours, when carbon dioxide evolution had substantially ceased, an amorphous precipitate (1.1 g.) was separated by filtration and recrystallized from acetone to yield 1.0 g. (70%) of crystalline decarboxamidoterrinolide, identified through its ultraviolet and infrared absorption spectra. The barium carbonate collected from the gas wash bottle weighed 0.810 g. (102%). **Pentamethyldecarboxamidoterrinolide** was prepared by the procedure described for pentamethylterrinolide (*vide supra*). The derivative was purified by crystallization from ethanol, m.p. 150–151° (when cooled, it remelts at 81–85°).

Anal. Calcd. for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70; methoxyl (5), 36.59; mol. wt., 424. Found: C, 67.85; H, 5.74; methoxyl, 35.95; mol. wt. (Rast), 428.

This compound is insoluble in cold ethanolic sodium hydroxide, but does dissolve in 10% aqueous ethanolic sodium hydroxide on prolonged heating at 120°. Acidification of the cooled solution precipitates the lactone directly. The ultraviolet spectrum is virtually identical to that of the free phenol in acid–ethanol. **Pentaacetyldecarboxamidoterrinolide** was prepared by the procedure described for pentaacetylterrinolide, and purified by recrystallization from acetone–petroleum ether, m.p. 243–245° dec.

Anal. Calcd. for $C_{29}H_{24}O_{12}$: C, 61.70; H, 4.29; acetyl, 38.12. Found: C, 61.34; H, 4.49; acetyl, 37.12.

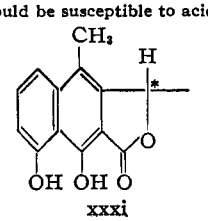
Penta-*p*-toluenesulfonyldecarboxamidoterrinolide.—A solution of 1 g. of decarboxamidoterrinolide in 15 ml. of anhydrous pyridine and 5 g. of *p*-toluenesulfonyl chloride was held at 25° for 28 hours, then poured into 125 ml. of water. The dry amorphous solid product dissolved in 25 ml. of acetone was diluted with 25 ml. of ethanol to yield a crystalline product. A second crop was obtained on concentration, yield 2.6 g. The pure penta-*p*-toluenesulfonyl derivative, obtained on recrystallization from acetone–benzene, was dried at 100° (0.1 mm.) for 24 hours, m.p. 154–158°.

Anal. Calcd. for $C_{54}H_{44}O_{17}S_5$: C, 57.64; H, 3.94; S, 14.25. Found: C, 57.81; H, 4.07; S, 14.41.

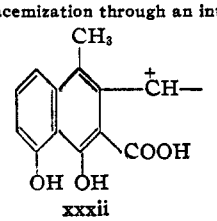
Decarboxamidoterrinolidic Acid Pentamethyl Ether (1,8-Dimethoxy-3-(α-hydroxy-2,3,5-trimethoxybenzyl)-naphthalene-2,4-dicarboxylic acid γ-lactone) (XL).[65]—Potas-

(64) It will be evident that the asymmetric center (starred) of substances containing the dihydroxybenzophthalide system (xxxi) should be susceptible to acid-catalyzed racemization through an intermediate such as xxxii. In the case of the formation of terrinolide, acid conditions were found which permitted retention of configuration, or racemization, while the removal of the carboxamide group requires treatment so vigorously that racemization invariably occurs.

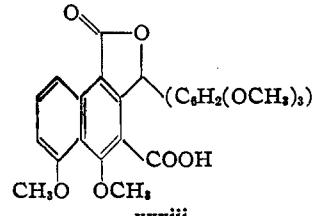
(65) This acid might be formulated either as XL (above), or as xxxiii. This ambiguity does not affect our structural argument.



xxxi



xxxii



xxxiii

sium permanganate, 29 g., was added portionwise over a 2-hour period to a stirred solution of 3.5 g. of pentamethyldecarboxamidoterrinolide in 40 ml. of pyridine and 15 ml. of water at 75°. Additional pyridine (20 ml.) and water (25 ml.) were added to keep the reaction mixture fluid. After 1 hour of further stirring, the excess permanganate was destroyed with hydrogen peroxide, and the reaction mixture freed of pyridine by concentration *in vacuo*, with repeated addition of water. The aqueous suspension was freed of manganese dioxide by filtration, and adjusted to *p*H 2. The yellow amorphous product was recrystallized twice from ethanol–water, and the pale yellow crystals dried at 100° (0.1 mm.), m.p. 210–212.5°, yield 0.23 g.

Anal. Calcd. for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88; methoxyl (5), 34.14; mol. wt., 454.4. Found: C, 63.02; H, 4.98; methoxyl, 34.13; neut. equiv., 454; pK_a 5.1.

The ultraviolet spectrum is similar to that of pentamethyldecarboxamidoterrinolide with the two major peaks at λ_{max} 256 mμ, log ε 4.56, and λ_{max} 340 mμ, log ε 3.92. The infrared spectrum shows a broad carbonyl band at 5.75–5.8 μ in chloroform solution.

3-Methoxy-6-methylpyromellitic acid anhydride (XXXIV) was obtained from the nitric acid oxidation of pentamethyldecarboxamidoterrinolide. Pentamethyldecarboxamidoterrinolide, 1 g., was dissolved in 20 ml. of concentrated nitric acid at its freezing point, and the solution held at 30° for 7 days, and at 25° for a further 6 days. The amorphous precipitate (0.20 g.) was removed by filtration and sublimed at 75° (0.1 mm.) to yield 0.10 g. of oxalic acid. The unsublimed residue was recrystallized 4 times from acetone–benzene and sublimed at 140° (0.05 mm.), to yield 50 mg. of pure 3-methoxy-6-methylpyromellitic acid anhydride, m.p. 270–271°.

Anal. Calcd. for $C_{12}H_6O_7$: C, 54.98; H, 2.31; methoxyl, 11.82; C-CH_3, 6.16; mol. wt., 262.2. Found: C, 55.28; H, 2.35; methoxyl, 12.25; C-CH_3, 5.17; mol. wt. (Rast), 279.

Titration of this anhydride in water solution showed a neutral equivalent of 75 (calcd. 66.5). The infrared spectrum in dioxane solution shows 4 carbonyl bands of progressively increasing intensity between 5.35 and 5.60 μ, while the sodium salt shows only carboxylate ion absorption at 6.30 μ in the carbonyl region.

The ultraviolet absorption spectrum of this product in concentrated sulfuric acid (Fig. 8) shows λ_{max} 252 mμ, log ε 4.19, and λ_{max} 400 mμ, log ε 3.90. Dimethoxypyromellitic acid shows a similar ultraviolet absorption spectrum.[25]

Lithium Aluminum Hydride Reduction of Pentamethyldecarboxamidoterrinolide to the Glycol (XLI).—Twenty ml. of a 0.5 *M* solution of lithium aluminum hydride in ether was added to 0.42 g. of pentamethyldecarboxamidoterrinolide in 20 ml. of tetrahydrofuran, the mixture diluted with an additional 150 ml. of ether and the turbid solution stirred at 25° for 3 hours. Excess hydride was then decomposed by the careful addition of 50 ml. of water, and the aqueous phase was extracted with three 100-ml. portions of ether. The ether extracts were dried over calcium chloride, and evaporated to dryness to yield 0.41 g. of crude product. Three recrystallizations from ether yielded 0.10 g. of pure 2-hydroxymethyl-4-methyl-3-(α-hydroxy-2,3,5-trimethoxybenzyl)-1,8-dimethoxynaphthalene (XLI), m.p. 114–115°.

Anal. Calcd. for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59; methoxyl, 36.20; act. hydrogen, 2. Found: C, 67.09; H, 6.69; methoxyl, 35.80; act. hydrogen,[66] 1.92.

The ultraviolet absorption spectrum of this compound (Fig. 9) has its two major peaks at λ_{max} 238 mμ, log ε 4.85, and λ_{max} 292 mμ, log ε 3.94. The infrared spectrum shows hydroxyl absorption, but no carbonyl bands.

1,3-Dihydro-8,9-dimethoxy-4-methyl-3-(2,3,5-trimethoxyphenyl)-naphtho[2,3-c]furan (XLII) was prepared by heating a solution of 50 mg. of the glycol (XLI) in 1 ml. of dioxane containing 0.05 ml. of 6 *N* hydrochloric acid to 100° for 1.5 hours. The red solution was evaporated to dryness *in vacuo*, and the amorphous residue purified by sublimation at 220° (0.1 mm.) and then recrystallized twice from ethanol to yield 8 mg. of pure product, m.p. 148.8–150.8°.

Anal. Calcd. for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39; MeO, 37.80; mol. wt., 410.5. Found: C, 70.10; H, 6.65; MeO, 36.60; mol. wt. (Rast, in exaltone), 400.

(66) F. A. Hochstein, THIS JOURNAL, **71**, 305 (1949).

The infrared spectrum in dioxane shows no hydroxyl absorption. The ultraviolet spectrum is similar to that of XLI, λ_{max} 237 mμ, log ε 4.87, and λ_{max} 292 mμ, log ε 3.94, but has a longer wave length peak, λ_{max} 370 mμ, log ε 2.39.

Desdimethylaminoterramycin (1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide).—Fifty grams of zinc dust (Mallinckrodt analytical reagent grade zinc dust from a freshly opened bottle) was added portionwise to a stirred solution of 50 g. of Terramycin dihydrate in 300 ml. of glacial acetic acid. The solution was stirred for 8 hours at 30°, the zinc removed by filtration[67] and the filtrate freeze-dried. The amorphous yellow product was dissolved in 300 ml. of methanol, containing 25 ml. of concentrated hydrochloric acid, and the solution poured into 500 ml. of water. The resulting slurry (*p*H 1.0) was extracted with four 200 ml. portions of ether and the ether concentrated to dryness at 10°. The solid, ether-soluble product was separated from a little water, and triturated with acetone to yield 11.4 g. (27%) of desdimethylaminoterramycin as pale yellow plates. Recrystallization from ether, then from methanol-chloroform yielded the pure compound, m.p. 216–217° dec., $[\alpha]^{25}D$ −137° (methanol), $[\alpha]^{25}D$ −47° (acetone).

Anal. Calcd. for $C_{20}H_{19}NO_9$: C, 57.55; H, 4.59; N, 3.36; mol. wt., 417. Found: C, 57.42; H, 4.62; N, 3.34.

Titration in dimethylformamide–water showed an equivalent weight of 418, pK_a 6.8 and 8.9. The ultraviolet absorption spectrum (Fig. 11) is similar to that of Terramycin, λ_{max} 261 mμ, log ε 4.25, and λ_{max} 363 mμ, log ε 4.17. The infrared spectrum is very similar to that of Terramycin.

Anhydrodesdimethylaminoterramycin.—A solution of 0.5 g. of desdimethylaminoterramycin in 10 ml. of methanol and 1 ml. of concentrated hydrochloric acid was heated to boiling for 1 minute. The heavy yellow crystalline precipitate which formed was filtered from the cooled solution, and recrystallized from dioxane–methanol to yield 0.4 g. of pure anhydrodesdimethylaminoterramycin, m.p. 232–233° dec., $[\alpha]^{25}D$ +170° (dioxane).

Anal. Calcd. for $C_{20}H_{17}NO_8$: C, 60.15; H, 4.29; N, 3.51. Found: C, 60.00; H, 4.47; N, 3.52.

The ultraviolet absorption spectrum is substantially identical to that of anhydroterramycin in either acid or alkaline ethanol solution.

Desdimethylaminoapoterramycin was prepared by dissolving 0.23 g. of anhydrodesdimethylaminoterramycin in 2 ml. of 0.5 *N* sodium hydroxide under nitrogen. After 2 hours, the solution was acidified, and the colorless crystalline precipitate recrystallized from dimethylformamide–methanol.

Anal. Calcd. for $C_{20}H_{17}NO_8$: C, 60.15; H, 4.29; N, 3.51. Found: C, 60.07; H, 4.52; N, 3.58.

Titration disclosed a dibasic acid, pK_{a_1} 4.6, pK_{a_2} 8.1; equiv. wt. 404 (calcd. 399). The ultraviolet absorption spectrum in acid–ethanol is similar to that of the apoterramycins with the two major peaks at λ_{max} 251 mμ, log ε 4.63, and λ_{max} 375 mμ, log ε 4.06. The infrared spectrum shows the characteristic lactone carbonyl at 5.75 μ, and a weak carboxamide carbonyl at 6.05 μ in Nujol mull.

Desdimethylaminodesoxyterramycin (1,4,4a,5,5a,6,11,-12a-Octahydro-3,5,6,10,12-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide) (LXXI).—Terramycin, zinc and acetic acid, in the proportions described for the preparation of desdimethylaminoterramycin, were stirred together for 4 days at 25–30°, the zinc removed by filtration[67] and the filtrate concentrated to a sirup at 35°. The viscous residue was stirred with 500 ml. of water, the amorphous precipitate filtered, washed with water, dried and extracted exhaustively in a Soxhlet apparatus with ether. The ether solution was evaporated to dryness, and the amorphous residue triturated with acetone to yield a crystalline product. Recrystallization from acetone yielded 21 g. (50%) of desdimethylaminodesoxyterramycin, which contained acetone of crystallization, m.p. 180–181° dec. when placed in a bath at 165°, temperature rising 2° per minute; $[\alpha]^{25}D$ +112° (acetone). The product was dried to constant weight at 25° (0.05 mm.) for analysis. Prolonged drying at 80° removed only a portion of the acetone of crystallization.

Anal. Calcd. for $C_{20}H_{19}NO_8 \cdot {}^1/_2C_3H_6O$: C, 59.99; H,

(67) CAUTION: The zinc becomes pyrophoric when dry.

5.15; N, 3.26; C_3H_6O, 6.74. Found: C, 59.99; H, 5.17; N, 3.29; C_3H_6O (by infrared), 7 ± 1.

Titration in dimethylformamide–water shows pK_a 7.1 and ~11.5, equiv. wt. 444 (calcd. 430). The infrared spectrum in dioxane shows carbonyl absorption at 5.80 μ (due to acetone) and at 6.08 μ. The ultraviolet absorption spectrum (Fig. 10) shows λ_{max} 263 mμ, log ϵ 4.31, and λ_{max} 320 mμ, log ϵ 4.22. Attempted recrystallizations from solvents other than acetone (*e.g.*, methanol, chloroform, acetic acid or dioxane) yielded only an amorphous product unless acetone were present. The presence of acetone of crystallization was established by distillation from a xylene–ethanol solution and preparation of the 2,4-dinitrophenylhydrazone.

Isodesoxydesdimethylaminoterramycin (4,4a,5,6,7,8-hexahydro-1,3,5-trihydroxy-6-(7-hydroxy-3-methylphthalidyl)-8-oxo-2-naphthamide) (LXII).—Two grams of desoxydesdimethylaminoterramycin was dissolved in 50 ml. of 0.5 *N* alcoholic potassium hydroxide. The fluorescent orange color faded within a few hours, and the entire mass set to a semi-solid gel. After 12 hours, glacial acetic acid was added dropwise until the gel was converted to a granular crystalline precipitate, which was separated and recrystallized twice from acetic acid–water, twice from ethanol–water. After drying at 100° (0.1 mm.) for 18 hours, this compound has $[\alpha]^{25}D$ −32° (acetone). It decomposes without melting at 210–220°.

Anal. Calcd. for $C_{20}H_{19}NO_8$: C, 59.85; H, 4.77; N, 3.49; mol. wt., 401. Found: C, 59.82; H, 5.06; N, 3.55.

Titration shows a neutral equivalent of 210, pK_a 7.2 and 9.2. The ultraviolet spectrum shows λ_{max} 242 mμ, log ϵ 4.16, λ_{max} 256 mμ, log ϵ 4.14, and λ_{max} 314 mμ, log ϵ 4.29. The infrared spectrum in chloroform solution shows peaks at 5.75 and 6.15 μ in the carbonyl region.

7-Hydroxy-3-methylphthalide from LXII.—One hundred mg. of isodesoxydesdimethylaminoterramycin was placed in a 10 × 200 mm. Pyrex tube, attached to a vacuum system at 0.1–0.5 mm. pressure and placed in a metal-bath at 400° for 5 minutes. The volatile product which collected in the cool section of the tube was distilled at 100° (0.1 mm.) to yield 3.5 mg. of 7-hydroxy-3-methylphthalide. After recrystallization from water, the hydrated product melted at 108–110°; mixture melting point with an authentic sample,[9] m.p. 108–110°, not depressed.

Terrarubein.—Ten grams of Terramycin dihydrate was added in portions to a stirred solution of 80 ml. of sulfuric acid in 30 ml. of water at 10°. The solution was then allowed to warm to room temperature and stirred overnight in an nitrogen atmosphere. The red reaction mixture was transferred to a beaker and slowly diluted by the addition of 800 g. of clean ice over a 1-hour period. Gentle intermittent stirring is desirable, but rapid mixing is to be avoided. The mixture of crystalline and amorphous red products was filtered from the cold diluted solution, washed with water, then with acetone and dried *in vacuo*. The product, 1.8 g., was suspended in 20 ml. of dimethylformamide, filtered on a sintered glass funnel and the insoluble residue washed with small volumes of dimethylformamide until the color of the wash was a very pale yellow. After thorough washing with 100 ml. of acetone, 280 mg. (3%) of terrarubein was obtained as red-orange needles, and dried at 100° *in vacuo*. It decomposes without melting at 250–260°.

Anal. Calcd. for $C_{22}H_{20}N_2O_6$: C, 64.69; H, 4.94; N, 6.86. Found: C, 64.38; H, 5.32; N, 6.60.

This product is soluble in hot dimethylformamide, but appears to decompose. It is slightly soluble in glacial acetic acid, and virtually insoluble in the other common solvents. The infrared absorption spectrum of terrarubein shows carbonyl absorption at 5.80 and 6.07 μ in mull, as well as hydroxyl absorption at about 2.9 to 3.1 μ. The ultraviolet absorption in acetic acid–dioxane–ethanol gives a rather flat curve with λ_{max} 255 mμ, log ϵ 4.47, and λ_{max} 435 mμ, log ϵ 3.94. Terrarubein also can be obtained in somewhat lower yield from the reaction of Terramycin with concentrated hydrochloric acid.

Desdimethylaminoterrarubein was prepared by dissolving 2.1 g. of desdimethylaminodesoxyterramycin in 65 ml. of methanol saturated with hydrogen chloride. Desdimethylaminoterrarubein starts to precipitate immediately. After 3 hours, 1.83 g. (97%) of mixed microcrystalline and amorphous product was separated by filtration, and purified by 2 recrystallizations from dimethylformamide. The pure orange-red crystalline product (yield 50%) shows no melting point, but chars and decomposes at 200–300°.

Anal. Calcd. for $C_{20}H_{15}NO_8$: C, 65.74; H, 4.15; N, 3.83. Found: C, 65.75; H, 4.30; N, 4.15.

The product is slightly soluble in hot glacial acetic acid or pyridine, and quite soluble (dec.) in boiling nitrobenzene, but virtually insoluble in the other common solvents, dimethylformamide excepted. The ultraviolet absorption spectrum in 1:9 acetic acid–ethanol has λ_{max} 271 mμ, log ϵ 4.41, and λ_{max} 315, 355 and 450 mμ, log ϵ 4.00 to 4.05. The infrared spectrum in Nujol mull shows carbonyl absorption at 5.93 and 6.02 μ. An attempt to titrate this compound in dimethylformamide–water solution led to obvious decomposition.

Desdimethylaminoterrarubein also may be prepared, though less satisfactorily, by the action of hot glacial acetic acid, or hot formic acid, on desdimethylaminodesoxyterramycin.

Naphthacene from Desdimethylaminoterrarubein and Terrarubein.—Twenty grams of zinc dust, purified as described above for the preparation of 1,3-dimethylnaphthalene from terranaphthol, was mixed in a mortar with 200 mg. of crystalline desdimethylaminoterrarubein, packed in seven portions in 8-mm. Pyrex tubes and heated to nearly red heat in a slow stream of hydrogen. The distilled products (6.0 mg.) were combined and purified by recrystallization from chloroform, from xylene, and finally by sublimation at 180–200° *in vacuo* to yield 3.0 mg. (2.5%) of pure naphthacene which was identified by its ultraviolet absorption spectrum. The very rich spectrum was identical to that of an authentic sample of pure naphthacene and shows peaks (in benzene solution) at 280, 296.5, 355.5, 374.5, 396, 418.5, 444 and 474.5 mμ. On a Kofler hot-stage, the hydrocarbon sublimed without melting at 290°, a behavior exactly paralleling that of authentic naphthacene (reported m.p. 335°) and distinguishing it unequivocally from 5-methylnaphthacene, m.p. 160°.[68]

Forty mg. of terrarubein was mixed with 3.5 g. of purified zinc, and distilled as described above. The crude distillate was purified by 2 sublimations to yield 0.25 mg. of pure naphthacene which was identified through its ultraviolet absorption spectrum.

Acknowledgment.—We should like to express our deep appreciation to Dr. W. A. Lazier for his encouragement to our group throughout the course of this work. We are greatly indebted to Mr. G. B. Hess, Dr. J. A. Means, Mr. T. J. Toolan and Dr. K. Murai for analytical data and spectral and acidity measurements. Further, we should like to express our appreciation to Mr. R. A. Carboni for his contributions to the isolation of certain acid degradation products of Terramycin.

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(68) E. Clar and J. Wright, *Nature*, **163**, 921 (1949).