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# EXPERIMENTS ON THE SYNTHESIS OF SUBSTANCES RELATED TO TETRACYCLINES

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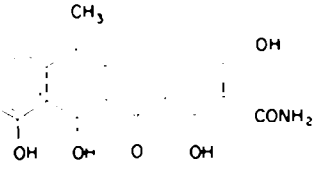
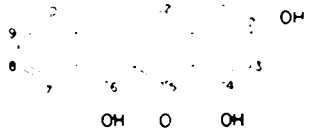
**Abstract**—The structures of tetracycline antibiotics are very complex. The total synthesis of these compounds, and of their degradation products such as anhydro-derivatives and desdimethylaminoterrarubein (I) would not only further contribute to the elucidation of their structures but also provide, in attempts at these syntheses, interesting findings concerning the chemistry of polycyclic compounds.



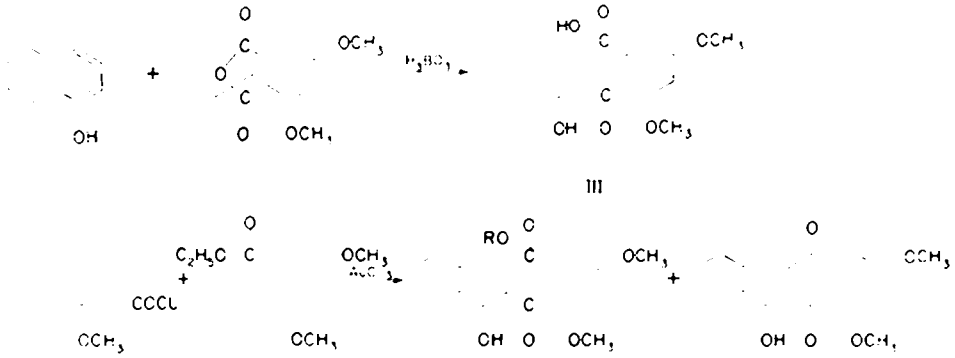
I



II

We have devised two possible routes for the synthesis of desdimethylaminoterrarubein (I) and the synthesis of 2,4,6-trihydroxy-5-oxo-5,12-dihydronaphthacene (II) was chosen as a model experiment.[1] Other synthetic experiments have also been directed toward the total synthesis of tetracycline and anhydrotetracycline.

CONDENSATION of α-naphthol with 3,5-dimethoxyphthalic anhydride in the presence of boric acid, gave 2-(α-hydroxy-β-naphthoyl)-3,5-dimethoxy benzoic acid (III) and Friedel-Crafts acylation of α-methoxy-β-naphthoyl chloride with ethyl-3,5-dimethoxybenzoate was shown to give three products, namely compounds III, IV and V.



III

III R = H
IV R = $C_2H_5$

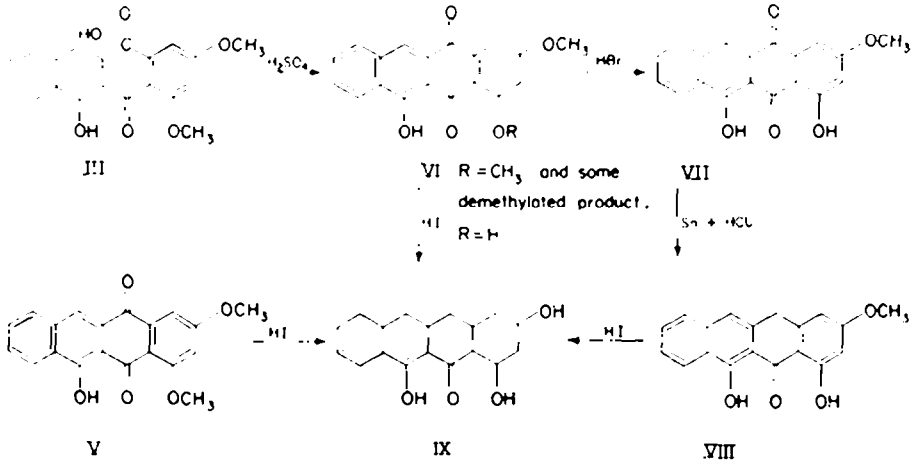
V

[1] Huang Yao-Tseng, Sheng Huai-Yu, Tai Li-Hsin and Tu Tung-Yuan, *Acta Chim. Sinica* **24**, 53 (1958).

The fact, that compound III was obtained from both routes, indicated that in the boric acid condensation, the anhydride linkage was split in the manner indicated by the broken line in the reaction formula, and in the Friedel–Crafts reaction, the methoxy group on the naphthalene ring was demethylated. It is of interest to note that compounds III, IV and V were obtained simultaneously from the Friedel–Crafts acylation reaction. Owing to partial demethylation, the product of the sulphuric acid cyclization of compound III was a mixture (VI), but the ultra-violet absorption spectrum of VI was almost identical with that of the compound V, evidently V was the cyclization product in the Friedel Crafts reaction.

Treatment of V and VI separately with hydriodic acid gave rise to the same product, 2,4,6-trihydroxy-5-oxo-5,12-dihydronaphthacene (IX), m.p. 246° (decomp.) which possesses the basic structure of desdimethylaminoterrarubein (I).

The action of hydriodic acid on compound V is twofold, namely demethylation and the reduction of quinone to anthrone. In order to clarify this reaction mechanism, the mixture VI was treated with hydrobromic acid to demethylate the methoxy groups completely but leave the $C_{12}$ keto group intact. In two runs, refluxed for 15 hr, the elementary analytical data and the methoxy group determination of the reaction product, showed that the product was a mono-methylated compound, 2-methoxy-4,6-dihydroxy-5,12-dioxo-5,12-dihydronaphthacene (VII). It was then reduced to VIII with tin and hydrochloric acid in acetic acid, a reagent which is commonly used for converting anthraquinone to anthrone. Treating VIII with hydriodic acid, furnished 2,4,6-trihydroxy-5-oxo-5,12-dihydronaphthacene (IX), identical with the compound previously obtained directly from compound V.

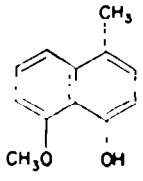



The assignment of the carbonyl group in our reduction product IX at $C_5$ but not at $C_{12}$ was confirmed by the infra-red absorption spectra.[2] Compound VII showed a free carbonyl band at 1676 $cm^{-1}$ and a hydrogen bonded carbonyl at 1613 cm [1,3] In compounds VIII and IX, there was no absorption in the region of 1650 1680 $cm^{-1}$ but the bands expected for hydrogen bonded carbonyl groups were found in lower frequencies, in VIII at 1619 cm [1] and in IX at 1631 $cm^{-1}$. These are inconsistent with

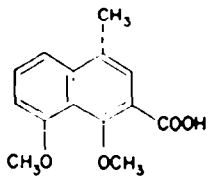
[2] Al. Steyermark and J. H. Gardner, *J. Amer. Chem. Soc.* **52**, 4887 (1930)
[3] M. St. C. Flett, *J. Chem. Soc.* 1441 (1948).

the assumption that $C_{12}$ carbonyl was reduced. Except for a very strong hydroxy band at 3324 $cm^{-1}$ found in IX, the absorption of any free hydroxy group had not been found in VII and VIII. Therefore, during the demethylation of mixture VI, it is the $C_4$ but not the $C_2$ methoxy group that was demethylated.

For the synthesis of desdimethylaminoterrarubein (I), two useful intermediates, namely 4-methyl-8-methoxy-naphthol-1 (X) and 1,8-dimethoxy-4-methyl-2-naphthoic acid (XI) have been prepared and their structures ascertained.[4]



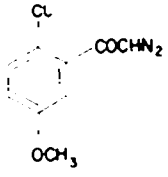

X



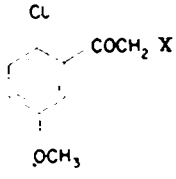

XI

The synthesis of 4-methyl-8-methoxynaphthol-1 (X) was accomplished by two different routes. One consists of three stages: 1,8-naphthalenediol was methylated to give 8-methoxy naphthol-1 which was converted to 4-hydroxy-5-methoxynaphthaldehyde-1 by Gattermann aldehyde synthesis and then reduced into the requisite compound X by Huang-Minlon reduction.

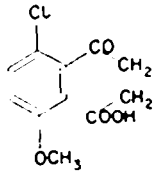
Another synthesis of X consists of the following sequence of reactions: 2-chloro-5-methoxybenzoyl chloride was condensed with diazomethane to give the diazoketone



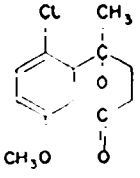

XII



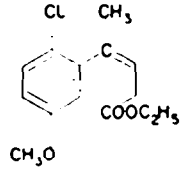

XIII



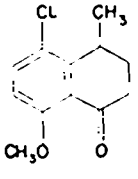

XIV




XV




XVI




XVII

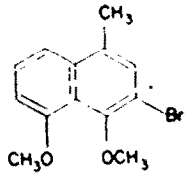
(XII) which was then treated with HCl or HBr to form phenacyl chloride (XIII, X = Cl) or bromide (XIII, X = Br) respectively. Either one was allowed to condense with diethyl sodiomalonate giving, after hydrolysis of the resulting ester, 2-chloro-5-methoxy phenacyl malonic acid, which in turn produced $\beta$-(2-chloro-5-methoxy

[4] Huang Yao-Tseng, Tsung Hui-Chuan, Tai Li-Hsin, Sheng Huai-Yu and Tu Tung-Yuan, *Acta Chim. Sinica* **24**, 311 (1958).

benzoyl)-propionic acid (XIV) by pyrolysis. γ-Hydroxy-γ-(2-chloro-5-methoxyphenyl)-valerolactone (XV) was obtained by treating this acid with methyl magnesium bromide. The lactone afforded an unsaturated ester (XVI) by successive treatment with thionyl chloride, ethanol and finally by pyrolysis. Hydrogenation in the presence of Adams' catalyst followed by hydrolysis converted this unsaturated ester into γ-(2-chloro-5-methoxyphenyl)-valeric acid, the chloride of which was cyclized to 4-methyl-5-chloro-8-methoxytetralone-1 (XVII). Bromination of this compound with one mole of bromine gave 2-bromo-4-methyl-5-chloro-8-methoxytetralone-1. Dehydrobromination of this compound was effected readily by heating with morpholine on a water bath for 3 min giving 4-methyl-5-chloro-8-methoxynaphthol-1. Finally it was converted into 4-methyl-8-methoxy-naphthol-1 (X) by hydrogenolysis in the presence of Pd-$SrCO_3$ catalyst.

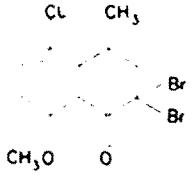
The behaviour of the product (X) obtained by two different routes was shown to be identical in all respects.

Another useful intermediate (XI) for the synthesis of desdimethylaminoterrarubein has been synthesized as follows. Compound X was first brominated to form 2-bromo-4-methyl-8-methoxynaphthol-1 which was then methylated, giving 2-bromo-4-methyl-1,8-dimethoxynaphthalene (XVIII). Successive treatment with n-butyl lithium and carbon dioxide converted it into compound XI.

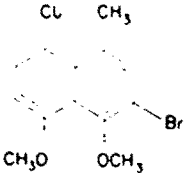



XVIII

The structure of XI was proved as follows: Bromination of 4-methyl-5-chloro-8-methoxytetralone-1 (XVII) with two moles of bromine afforded 2,2-dibromo-4-methyl-5-chloro-8-methoxytetralone-1 (XIX). It was converted into 1,8-dimethoxy-2-bromo-4-methyl-5-chloro-naphthalene (XX) when treated with sodium methoxide and dimethyl sulphate simultaneously.

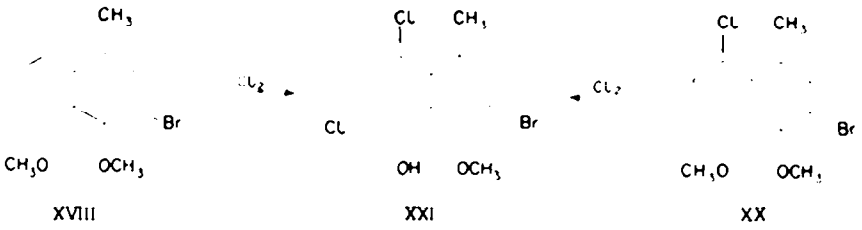



XIX




XX

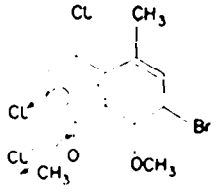
On the other hand, chlorination of 2-bromo-4-methyl-1,8-dimethoxy naphthalene (XVIII) produced, instead of the expected XX, 2,4-dichloro-5-methyl-7-bromo-8-methoxynaphthol-1 (XXI). Since XXI could also be obtained by chlorination of XX,



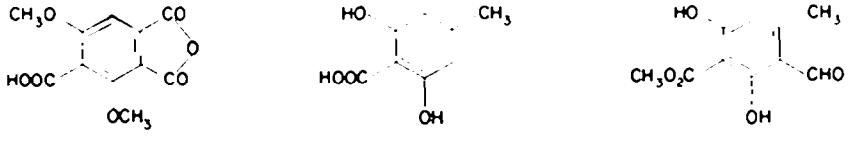
XVIII XXI XX

the location of bromine in XVIII was thus demonstrated and therefore the structure of XI ascertained.

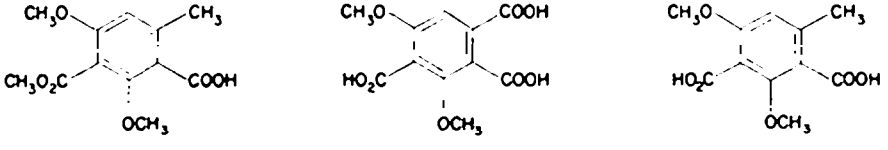
It was suggested that the formation of XXI may be attributed to the electrophilic attack of chlorine at the position *ortho* to methoxy group in the naphthalene ring with the concerted action of the chlorine ion on the methoxy group, thus resulting in simultaneous chlorination and demethylation.



For the synthesis of desdimethylaminoterrarubein, another component, i.e. 3,5-dimethoxy-4-carboxyphthalic anhydride (XXII) has been prepared from orcinol by the following reactions.[5] Orcellinic acid (XXIII) prepared from orcinol was esterified to give its methyl ester which on formylation by Gattermann aldehyde synthesis afforded methyl 2,6-dihydroxy-3-formyl-4-methyl-benzoate (XXIV) in 95 per cent



XXII XXIII XXIV



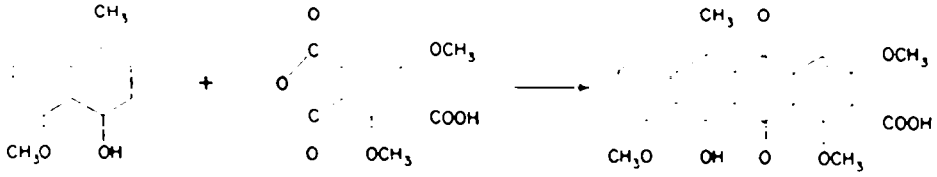
XXV XXVI XXVII

yield. Methylation of the latter gave rise to methyl 2,6-dimethoxy-3-formyl-4-methyl benzoate, which on oxidation with potassium permanganate in neutral medium produced methyl 2,6-dimethoxy-3-carboxy-4-methyl-benzoate (XXV), while in alkaline medium produced two compounds: 3,5-dimethoxy-trimellitic acid (XXVI) m.p. 234-235° and 2,6-dimethoxy-4-methyl-isophthalic acid (XXVII). Either XXV or

[5] Huang Yao-Tseng, Tu Tung-Yuan and Tai Li-Hsin, *Acta Chim. Sinica* **24**, 322 (1958).

XXVII could be further oxidized to XXVI. The anhydride, 3,5-dimethoxy-4-carboxy-phthalic anhydride (XXII), was finally obtained by treating XXVI with acetic anhydride.

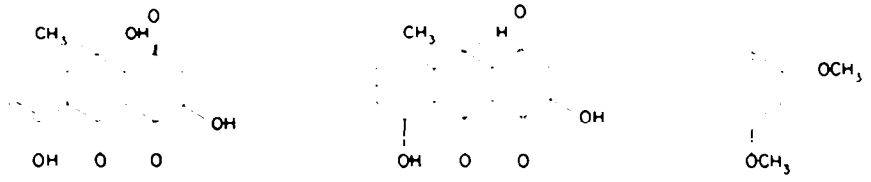
For the synthesis of desdimethylaminoterrarubein, preliminary experiment showed that the condensation product XXVIII can be obtained from X and XXII.[6]



X XXII XXVIII

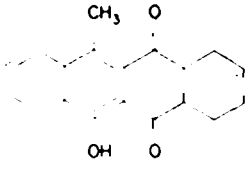
Other synthetic experiments have also been directed toward the total synthesis of tetracycline and anhydrotetracycline.

One possible synthetic route[7] which we devised involves the following steps, namely preparation of key intermediate compounds XXIX and XXX possessing the 1,4-anthraquinone structure, condensation of these compounds with suitable dienes such as derivatives of 1,3-dimethoxy-butadiene-1,3 (XXXI) and finally production of tetracycline or anhydrotetracycline analogue.



XXIX XXX XXXI

As a model experiment, the synthesis of 1,4,4a,5,12,12a-hexahydro-6-hydroxy-11-methyl-5,12-dioxonaphthacene (XXXII) has been achieved.

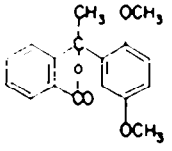


XXXII

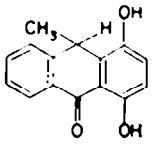
3-Methyl-3-(2′,5′-dimethoxyphenyl)-phthalide (XXXIII) was obtained by the action of 2-(2′5,-dimethoxy-benzoyl)-benzoic acid with methyl magnesium iodide. Reduction of this compound by means of zinc–sodium hydroxide followed by cyclization and demethylation afforded 1,4-dihydroxy-10-methyl-anthrone-9 (XXXIV), which on oxidation with lead tetra-acetate gave rise to crystalline 9,10-dihydro-9-oxo-10-methyl-anthraquinone-1,4 (XXXV) almost quantitatively. Condensation of the

[6] Huang Yao-Tseng, Tai Li-Hsin and Tu Tung-Yuan, unpublished.
[7] Huang Yao-Tseng, Nee Da-Nan, Hsu Yuen-Yao, Fung Hui-Min and Tsung Hui-Chuan, *Acta Chim. Sinica* **24**, 62 (1958).

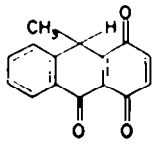
latter with 1,3-butadiene produced the requisite 1,4,4a,5,12,12a-hexahydro-6-hydroxy-11-methyl-5,12-dioxonaphthacene (XXXVI), m.p. 160–161°.



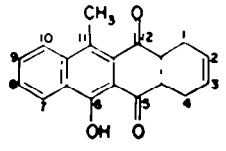
XXXIII



XXXIV

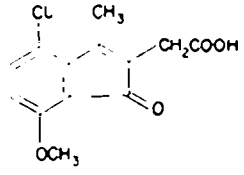


XXXV

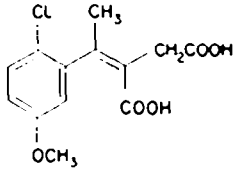


XXXVI

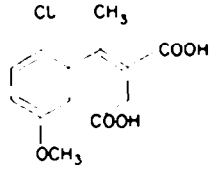
Another route to the synthesis of tetracycline or anhydrotetracycline has been started from the Stobbe condensation with 2-chloro-5-methoxy-acetophenone.[8] From the condensation product, two acids have been isolated, one melting at 157–158° and the other at 163–164°. Since the latter could be cyclized to an indenone derivative (XXXVII), it was assigned the structure XXXVIII and the acid (m.p. 157–158°) the structure XXXIX.



XXXVII

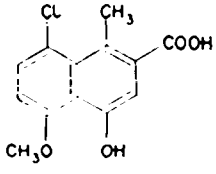


XXXVIII

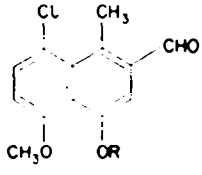


XXXIX

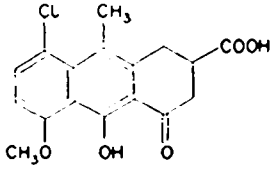
It is expected that, the acid XXXIX or its hydrogenated product would finally cyclize to a naphthalene derivative (XL) which on reduction would give a naphthaldehyde (XLI). Once more Stobbe condensation followed by reduction and cyclization would produce tetrahydroanthracene derivative (XLII) which would lead to anhydroaureomycin by a series of further treatments.



XL



XLI

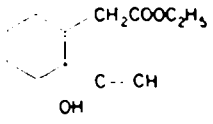


XLII

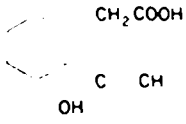
Since the structures of tetracyclines possess a 1,3-diketone system with an angular hydroxy group, we have devised a convenient method to synthesize the compound with such a structure feature and obtained satisfactory results.[9] Ethyl 2-ethynyl-2-hydroxycyclohexaneacetate (XLIII) and its corresponding acid (XLIV) were obtained by the ethynylation of ethyl cyclohexanone-2-acetate. Hydration of XLIII followed by

[8] Huang Yao-Tseng, Nee Da-Nan and Tang Ru-Yong, *Kexue Tongbao Scientia* 428 (1959).
[9] Huang Yao-Tseng and Hsu Yuen-Yao, *Acta Chim. Sinica* 24, 47 (1958).

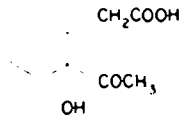
hydrolysis, gave 2-acetyl-2-hydroxycyclohexaneacetic acid (XLV). Its methyl ester was cyclized by sodium methoxide to form 9-hydroxydecaline-1,3-dione (XLVI) which showed characteristic concentration-dependent ultra-violet absorption spectra of 1,3-diketones. On the basis of the stability of the $\gamma$-hydroxy acids, XLIV and XLV, and



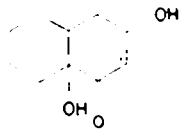

XLIII




XLIV




XLV




XLVI

the difficulty of lactonization of the latter, *cis* fusion of the two rings in compound XLVI is assigned.