Rotenoids. XX.[1] Total Synthesis of Rotenone

Masateru Miyano[2]

Contribution from the Institute of Applied Microbiology, Tokyo University, Tokyo, Japan. *Received April 5, 1965*

A mixture of salicylic acid, dicyclohexylcarbodiimide, and the morpholine enamine of cyclohexanone reacted to give five crystalline products: N,N'-dicyclohexylurea, tetrahydroxanthone (IV), salicyl morpholide (V), the cyclic imide VI, and cyclohexylaminocarbonyl morpholide (VII). The reaction was successfully applied to condensation of the pyrrolidine enamine IXa with tubaic acid (Xa) to afford dehydrorotenone (XI). Since dehydrorotenone had been converted to rotenone, this report constitutes a total synthesis of natural rotenone. The mechanism of the dicyclohexylcarbodiimide condensation is discussed. Alternatively, the unstable tubaic acid chloride (Xb) upon condensation with the morpholine enamine IXb or pyrrolidine enamine IXa afforded also dehydrorotenone.

The gross structure of rotenone (I), an insecticidal principle which occurs in members of the Leguminosae, was determined by Butenandt,[3] LaForge,[4] and Takei[5] in 1932. The stereochemistry was elucidated later by Büchi and Crombie.[6] The first *formal* total synthesis of rotenone[7,8] consisted of ten steps from the known compound II; however, the yield of the immediate precursor of rotenone, *dl*-derrisic acid (III), was only 0.01%. This low yield, due to the unusual acid lability of the side-chain double bond,[9,10] discouraged further experiments in approaches involving acid-catalyzed condensations.

A successful total synthesis of rotenone, requiring no relays, was initiated with the study of the reaction of the morpholine enamine of cyclohexanone (1 mole) and salicylic acid (1 mole) in the presence of dicyclohexylcarbodiimide (1 mole). Five crystalline products were isolated: dicyclohexylurea and compounds A ($C_{13}H_{12}O_2$), B ($C_{11}H_{13}O_3N$), C ($C_{14}H_{14}O_3N$), and D ($C_{11}H_{20}O_2N_2$).

The infrared spectrum of compound A in chloroform solution showed maxima for a conjugated carbonyl (1633 cm.$^{-1}$), double bond (1574 cm.$^{-1}$), and aromatic ring (1614 and 1469 cm.$^{-1}$). The n.m.r. spectrum in deuteriochloroform showed no vinylic proton, but did have four protons centered at τ 7.35 and four protons centered at 8.20. Spectral data, elemental analyses, and mechanistic considerations (Figure 1) led to assignment of structure IV (tetrahydroxanthone) to compound A. Although isolation of dicyclohexylurea as a product of the condensation suggests mechanism a, the odor of isocyanate from the reaction mixture and, more definitely, isolation of compound D (structure VII) suggests mechanism b.

The infrared spectrum of compound B in chloroform showed no NH absorption, but did exhibit a broad hydroxyl at 3500–3100 and an amide carbonyl at 1630 cm.$^{-1}$. Further, B was extracted with aqueous alkali from the chloroform solution. From this information, structure V was assigned to B.

The infrared spectrum of compound C in chloroform solution showed neither OH nor NH absorption, but did have carbonyl absorptions at 1767 and 1698 as well as aromatic ring maxima at 1621, 1603, and 1471 cm.$^{-1}$. Of the two probable structures (VI and XIII), suggested by elemental analyses and mechanistic considerations, the former was favored by chemical evidence and the n.m.r. spectra; compound C did not react with the morpholine enamine of cyclohexanone to give IV even under forcing conditions; the n.m.r. spectrum of C in deuteriochloroform indicated long-range deshielding of a part of cyclohexyl protons by a neighboring carbonyl group(s). Formation of VI is rationalized by a four-center transition to an imide followed by cyclization (Figure 2).

The infrared spectrum of compound D in chloroform solution showed NH absorption at 3505 and carbonyl absorption at 1640 cm.$^{-1}$. The n.m.r. spectrum in deuteriochloroform showed a modified A_2B_2 pattern which is characteristic of morpholine. The structure VII was assigned to this compound. It was probably formed from the intermediate isocyanate [XIV, Figure 1b] and morpholine.

This novel condensation was then applied to synthesis of dehydrorotenone (XI). The β-keto ester VIIIa[11] was converted through the ketone VIIIb into the crystalline morpholine enamine IXb. The dicyclohexylcarbodiimide cyclization of *l*-tubaic acid (Xa)[12] with IXb yielded XII as the sole crystalline product (based upon spectral evidence together with elemental composition). When the more reactive[13] pyrrolidine enamine (IXa) was condensed with tubaic acid, dehydrorotenone (XI) and the imide XII were formed in equal amounts. The synthetic dehydrorotenone was identical with an authentic sample in melting point, mixture melting point, infrared spectrum in chloroform solution, and n.m.r. spectrum in deuteriochloroform.

To enhance the reactivity of tubaic acid in its reaction with the morpholine enamine IXb, the preparation of tubaacyl chloride was investigated. Due to the great lability of the side-chain double bond,[7,9,10] the usual methods of acyl chloride preparation were untenable. However, dried potassium tubaate sus-

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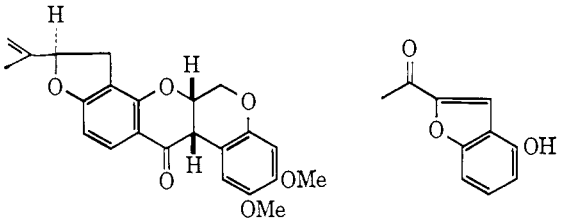
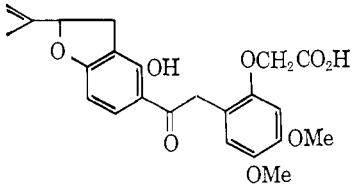


I

II



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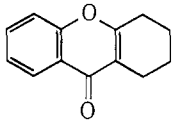

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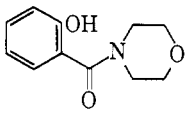

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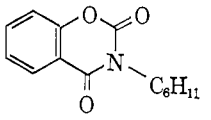
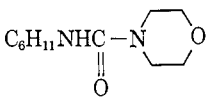
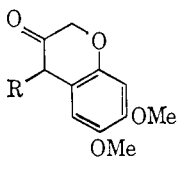


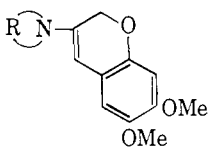
VI



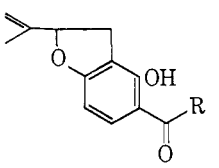
VII



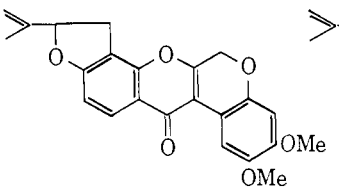
VIIIa, R = CO_2Et
VIIIb, R = H



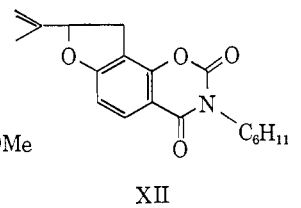
IXa, R = $(CH_2)_4$
IXb, R = $(CH_2)_2O(CH_2)_2$



Xa, R = OH
Xb, R = Cl



XI



XII

pended in benzene was converted to the chloride by oxalyl chloride at room temperature within a few minutes. The condensation of tubaic acyl chloride (Xb) with the morpholine enamine IXb afforded dehydrorotenone as the sole crystalline product but in a lower yield.

Finally the condensation between two of the more active counterparts, tubaacyl chloride (Xb) and the pyrrolidine enamine IXa, yielded dehydrorotenone in more than 14.6% yield after recrystallization. This represents a distinct improvement when compared to the published synthesis[7] of derrisic acid (0.01%) followed by cyclization[5] to dehydrorotenone (23%).

Since *l*-tubaic acid (Xa) has been totally synthesized[12] and dehydrorotenone has been converted[8] into rotenone,

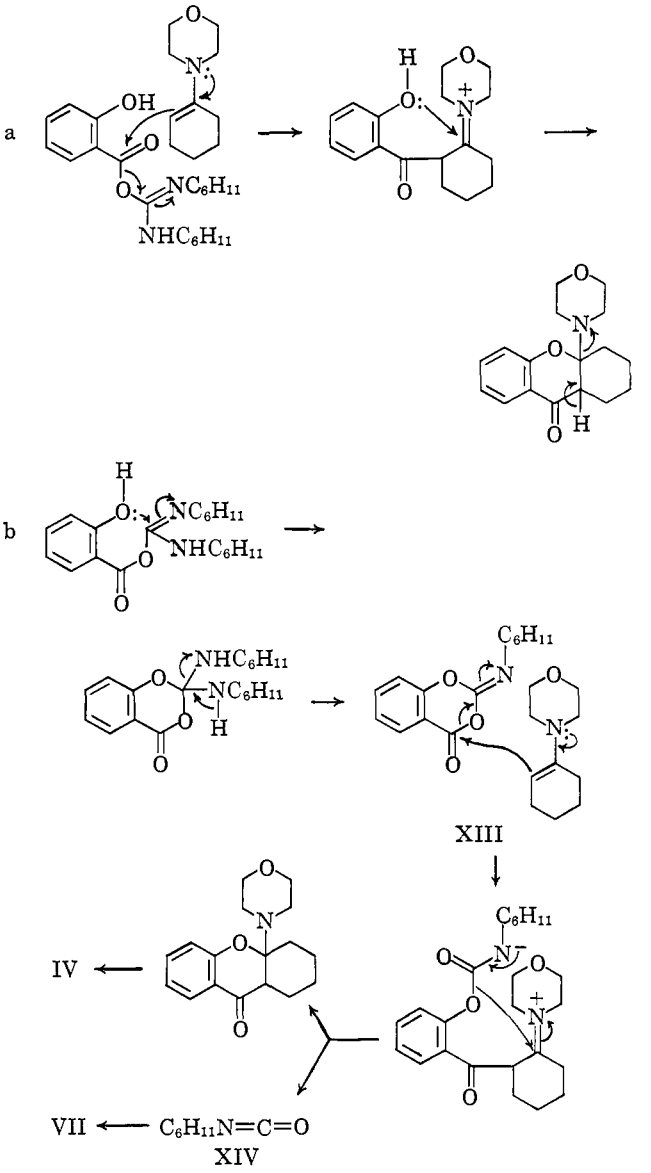


Figure 1.

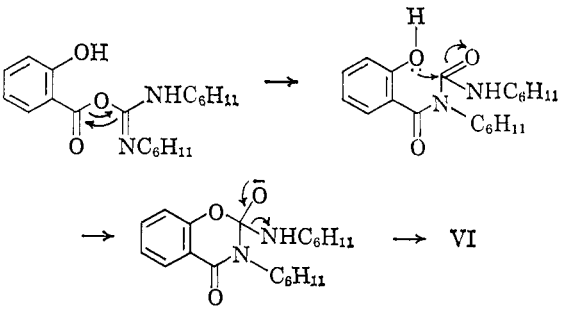


Figure 2.

this communication constitutes the total synthesis of natural rotenone.

Experimental

Condensation of Morpholine Enamine of Cyclohexanone with Salicylic Acid. To 30 ml. of anhydrous dioxane were added 5.7 g. (0.034 mole) of the morpholine enamine of cyclohexanone, 7.0 g. (0.034 mole) of dicyclohexylcarbodiimide, and 4.6 g. (0.033 mole) of salicylic acid. A white, crystalline mass was formed

with heat evolution. The mixture was boiled for 24 hr. and then allowed to stand overnight. The crystals were removed by filtration, washed with ether, and recrystallized from 150 ml. of ethanol. The crystals (4.8–5.0 g.), m.p. 231°, showed no depression on admixture with authentic dicyclohexylurea. To the dioxane–ethereal mother liquor was added 50 ml. of 10% aqueous hydrochloric acid. After 3 hr. of gentle refluxing and cooling, the reaction mixture was extracted with chloroform. The extract was washed twice with water, once with bicarbonate solution, three times with 2% aqueous sodium hydroxide solution, and finally with water. The solution was dried over potassium carbonate and concentrated. A crystalline mass (5.01 g.) was obtained (neutral fraction). The aqueous alkaline washings were acidified with hydrochloric acid and extracted with chloroform; the extract was washed with water, dried over sodium sulfate, and concentrated. The residue, recrystallized from methanol, afforded 1.18 g. of salicyl morpholide (V) as stout needles, m.p. 173.5°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.70; H, 6.21; N, 6.63.

The neutral fraction obtained above was chromatographed on 100 g. of Brockmann neutral alumina. Fraction 1, eluted with 300 ml. of benzene, gave 2.05 g. of the imide VI which melted at 138° after recrystallization from cyclohexane.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71; O, 19.57. Found: C, 68.51; H, 6.16; N, 5.80; O, 19.21.

Fraction 2, eluted with 300 ml. of benzene, gave 0.13 g. of crystals which, after recrystallization from cyclohexane, weighed 0.05 g. and melted at 93–94° (on slow heating). Long needles were obtained by recrystallization from aqueous methanol which melted at 93–94°. The spectral data (*vide supra*) showed this compound to be tetrahydroxanthone (IV).

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.08; H, 6.03.

Fraction 3, eluted with 300 ml. of benzene, gave 0.13 g. of semicrystalline material. Fraction 4, eluted with 300 ml. of chloroform, gave 1.30 g. of crystals which melted at 174° after recrystallization from benzene. A mixture melting point with V (m.p. 173.5°) showed a marked depression. The spectral data (*vide supra*) and the elemental analyses indicated structure VII for this compound.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20. Found: C, 62.53; H, 9.53; N, 13.44.

Mother liquors of the fractions 1, 2, and 3 were combined and chromatographed on 25 g. of alumina. After washing with 150 ml. of cyclohexane the column was eluted with 50 ml. of benzene, giving 0.22 g. of crystals. Subsequent elution with 250 ml. of benzene gave 0.14 g. of crystals, which was recrystallized from cyclohexane to yield 0.12 g. of IV, m.p. 93–94° (no depression on admixture with IV).

The above condensation when carried out in the presence of 2 ml. of triethylamine yielded dicyclohexylurea (4.8 g., m.p. 231°) salicyl morpholide (V, 0.86 g., m.p. 173.5°), imide (VI, 0.99 g., m.p. 135°), tetrahydroxanthone (IV, 0.15 g., m.p. 93–94°), and cyclohexylaminocarbonyl morpholide (VII, 0.46 g., m.p. 174°).

Attempted Condensation of Imide VI with the Morpholine Enamine of Cyclohexanone. To 15 ml. of anhydrous dioxane were added 5.0 g. of morpholine enamine and 0.70 g. of imide VI. After refluxing for 51 hr., 20 ml. of ether and 35 ml. of 10% aqueous hydrochloric acid were added. The resulting solution was refluxed for 5 hr. Organic material was recovered by ether extraction and recrystallized from cyclohexane to afford 0.56 g. of VI, m.p. 138° (no depression on admixture with the starting material).

6,7-Dimethoxychroman-3-one (VIIIb).[14] A suspension of 3.00 g. of 6,7-dimethoxy-4-carbethoxychroman-3-one (VIIIa)[11] in 50 ml. of 10% aqueous sulfuric acid was refluxed for 2 hr. After cooling, the reaction mixture was extracted with chloroform, and the extract was washed with water, three times with cold 2% sodium hydroxide solution, and with water. The solution was dried over potassium carbonate and concentrated. The crude crystalline residue (1.73 g.) was recrystallized from ethanol to afford Xb, m.p. 126–128°. The infrared spectrum in chloroform solution showed a ketonic carbonyl at 1737 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.45; H, 5.86.

The aqueous alkaline solution was acidified with hydrochloric acid and extracted with chloroform from which 0.22 g. of ketone (VIIIb) and 0.39 g. of the starting keto ester were recovered. The combined yield of VIIIb amounted to 87.5% (1.95 g.).

Morpholine Enamine (IXb) of 6,7-Dimethoxychroman-3-one. To 50 ml. of benzene were added 5.0 g. of 6,7-dimethoxychroman-3-one (VIIIb) and 4.18 g. of morpholine, and the solution was percolated for 19 hr. with gradual separation of water. The reaction mixture was concentrated *in vacuo*, dissolved in 20 ml. of xylene, and concentrated *in vacuo* again. Recrystallization from 15 ml. of benzene gave 4.64 g. of crystals melting at 111°. The infrared spectrum in chloroform solution showed no OH, no NH, and no carbonyl absorption, but did exhibit strong absorption at 1635 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.95; H, 6.85; N, 5.07.

Additional crystals of IXb (1.00 g., m.p. 106–107°) were obtained on concentration of the mother liquor. The total yield (5.64 g.) amounted to 84.8%.

Pyrrolidine Enamine (IXa) of 6,7-Dimethoxychroman-3-one. To 50 ml. of benzene were added 6.00 g. of ketone (VIIIb) and 5.90 g. of pyrrolidine, and the solution was percolated for 3 hr. with gradual separation of water. The pyrrolidine enamine formation was much faster than that of the morpholine enamine. Addition of benzene and concentration *in vacuo* were repeated four times. The sirupy concentrate was used for the following reaction without further purification.

A part of the concentrate was purified by distillation yielding the pure enamine, b.p. 140° (0.01 mm.). The infrared spectrum in chloroform solution showed no carbonyl bands but did show strong absorption at 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 67.18; H, 7.07; N, 5.73.

(14) This ketone was first prepared by Dr. M. Matsui, Department of Agricultural Chemistry, Tokyo University (not yet published).

The distillate crystallized spontaneously at room temperature.

Dehydrorotenone (XI) from the Pyrrolidine Enamine IXa. A. From Tubaic Acid Chloride (Xb). A solution of 1.0 g. (4.54 mmoles) of *l*-tubaic acid[9,15,16] in a small amount of ethanol was neutralized with 1 *N* potassium hydroxide solution to the pink coloration of phenolphthalein. A trace of tubaic acid was added to just cause disappearance of the pink color. The solution was concentrated *in vacuo* to a crystalline residue which was dried *in vacuo* over phosphorus pentoxide for 3 days at room temperature. The dried potassium salt was ground to a powder and then covered with 50 ml. of benzene to which 2.0 g. of oxalyl chloride was added. After a few minutes of shaking the tubaate was converted to the acyl chloride and clear crystals of potassium chloride appeared. The reaction mixture was boiled for 10 min. to expel hydrogen chloride and then was concentrated *in vacuo*. Dry benzene was added and the solution was concentrated *in vacuo*. The residue was dissolved in 15 ml. of anhydrous dioxane containing the pyrrolidine enamine IXa (prepared from 1.89 g. of 6,7-dimethoxychroman-3-one (Xb)). The mixture was stirred to a homogeneous suspension and refluxed for 14 hr. After cooling, 50 ml. of ether and 100 ml. of 10% aqueous hydrochloric acid were added. After refluxing for 5 hr., the reaction mixture was extracted with chloroform. The extract was washed with water, twice with dilute sodium hydroxide solution, and with water. The solution was dried over potassium carbonate and concentrated. The semicrystalline brown product (2.70 g.) was chromatographed on 100 g. of Brockmann neutral alumina. Fraction 1, eluted with 250 ml. of benzene, and fraction 2, eluted with 200 ml. of 1:1 benzene–chloroform, yielded nothing. Fraction 3 eluted with 200 ml. of benzene–chloroform (1:1) gave 0.18 g. of almost pure dehydrorotenone as a pale yellow, crystalline substance. Recrystallization from chloroform–ethanol provided pale yellow needles, m.p. 217° (on slow heating), no depression on admixture with the authentic dehydrorotenone, m.p. 217°. The infrared spectrum in chloroform solution was identical with an authentic sample in every detail. Survival of the side-chain double bond was assured by its absorption at 908 $cm.^{-1}$. The n.m.r. spectrum in deuteriochloroform was also identical with that of the authentic sample.

Fraction 4, eluted with 200 ml. of 1:1 benzene–chloroform, gave 0.40 g. of semicrystalline brown material which was recrystallized from chloroform–ethanol, yielding an additional 0.08 g. of pure dehydrorotenone.

The combined yield of dehydrorotenone amounted to at least 0.26 g. (0.663 mmole, 14.6%). A small amount of additional dehydrorotenone was obtained on chromatography of the neutral residue on Mallinckrodt silicic acid using chloroform or chloroform containing 2 vol. % methanol as eluent.

B. Dicyclohexylcarbodiimide Condensation of Tubaic Acid (Xa). To a mixture of 3 ml. of benzene and 12 ml. of dioxane were added the pyrrolidine enamine IXa prepared from 1.42 g. (6.83 mmole) of ketone Xb, 1.50 g. (6.83 mmole) of *l*-tubaic acid, and 1.41 g. (6.83 mmole) of dicyclohexylcarbodiimide. Crystals precipitated with heat evolution and the mixture was refluxed for 20 hr. After cooling, the stout needles were removed by filtration, washed with ether, and recrystallized from 40 ml. of ethanol. Colorless needles (0.96 g., m.p. 231°) were obtained which showed no depression of melting point on admixture with authentic dicyclohexylurea.

The mother liquor was boiled in dioxane–ether with 50 ml. of 10% hydrochloric acid for 5 hr. and set aside overnight. Approximately 20 mg. of yellow crystals separated and were washed with ethanol to yield XI, m.p. 214–215°, no depression on admixture with the authentic dehydrorotenone. The mother liquors were extracted with chloroform and the extract was washed with water, bicarbonate solution, three times with aqueous alkaline solution, and finally with water. The solution was dried over potassium carbonate and concentrated, yielding a neutral fraction of 3.74 g. From the bicarbonate solution, nothing was recovered by acidification and extraction with ether, assuring that no tubaic acid remained unreacted. From the alkaline washings, 0.32 g. of resinous material was recovered by acidification and ether extraction.

The neutral fraction was chromatographed on 80 g. of neutral alumina. Fraction 1, eluted with 100 ml. of benzene, gave 0.13 g. of white crystals which after recrystallization from cyclohexane melted at 163° (60 mg.). The infrared spectrum in chloroform showed the absence of OH and NH and the presence of two carbonyl groups at 1759 and 1691 $cm.^{-1}$. The similarity of the infrared spectrum to that of compound VI, together with elemental analyses, indicated the structure XII for this material.

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.78; H, 6.56; N, 4.23.

Fraction 2, eluted with 500 ml. of benzene, gave 0.08 g. of crystals which after recrystallization from chloroform–ethanol melted at 216.5° (26.3 mg.). Mixture melting point with authentic dehydrorotenone showed no depression.

Fraction 3, eluted with 500 ml. of benzene, gave 0.12 g. of crystalline dehydrorotenone which after recrystallization from chloroform–ethanol melted at 217° (29.8 mg.), no mixture melting point depression on admixture.

Fraction 4, eluted with 120 ml. of chloroform, gave 0.17 g. of crystals which were not dehydrorotenone.

The combined yield of pure dehydrorotenone amounted to at least 76 mg. A small additional amount of dehydrorotenone was obtained by chromatography of neutral residues on Mallinckrodt silicic acid, the product being eluted slowly with chloroform.

Dehydrorotenone from the Morpholine Enamine IXb. A. From Tubaic Acid Chloride (Xb). The dry potassium tubaate was prepared from 1.00 g. (4.54 mmole) of tubaic acid and was converted into the acyl chloride by oxalyl chloride in benzene. To the acyl chloride in 20 ml. of anhydrous dioxane was added 2.52 g. (9.07 mmoles) of the morpholine enamine IXb. After boiling the solution for 15 hr., the reaction was diluted with 50 ml. of 10% hydrochloric acid. The mixture was refluxed for 4 hr., cooled, and extracted with chloroform. The extract was washed with water,

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twice with dilute alkaline solution, and with water; it was dried over potassium carbonate and concentrated. The resulting neutral fraction, 2.35 g., was chromatographed on 100 g. of Brockmann neutral alumina. Fraction 1, eluted with 500 ml. of benzene, and fraction 2, eluted with 350 ml. of 1:1 benzene–chloroform, yielded nothing. Fraction 3, eluted with 50 ml. of 1:1 benzene–chloroform, gave 0.10 g. of crystals which after recrystallization from chloroform–ethanol melted at 217° (26.5 mg.), no depression on admixture with authentic dehydrorotenone. Fraction 4, eluted with 200 ml. of the same solvent, gave 0.42 g. of resinous material from which an additional amount of dehydrorotenone was obtained. The neutral residues were combined and chromatographed on 50 g. of Mallinckrodt silicic acid (100 mesh). Chloroform was used as eluting solvent. Starting from the colored front, 350 ml. of eluate was collected and concentrated. The residue was recrystallized from chloroform–ethanol to yield 22.7 mg. of crystalline dehydrorotenone.

B. Attempted Cyclization by Dicyclohexylcarbodiimide. In 15 ml. of anhydrous dioxane were dissolved 1.00 g. of enamine IXb, 0.79 g. of tubaic acid, and 0.74 g. of dicyclohexylcarbodiimide. After refluxing for 16 hr. followed by acid treatment, the reaction product was treated as described before. Imide XII (50 mg., m.p. 163°) was obtained upon chromatography of the neutral fraction on neutral alumina. Little if any dehydrorotenone was separated in the crystalline state.

Increasing the reaction time to 51 hr. yielded the imide XII as the only crystalline product beside dicyclohexylurea.

Acknowledgment. The author gratefully thanks Dr. W. F. Johns of G. D. Searle & Co., for his extensive correction of the English in this and the following paper.

Rotenoids. XXI.[1] Cyclization of Derrisic Acid to Dehydrorotenone

Masateru Miyano[2]

Contribution from the Institute of Applied Microbiology, Tokyo University, Tokyo, Japan. *Received April 5, 1965*

Derrisic acid (Ia) and deguelinic acid (IVa) are converted into dehydrorotenone (II) and dehydrodeguelin (V), respectively, by dicyclohexylcarbodiimide in the presence of a tertiary base followed by mild base treatment. The intermediate imido esters Ib and IVb are isolable. The mechanism of this cyclization is discussed.

Derrisic acid (Ia) was first converted to dehydrorotenone (II) by Takei[3] by a novel reaction in acetic anhydride in the presence of sodium acetate. However, the yield was as low as 23%. Since this cyclization constituted a relay step in our first total synthesis[4] of rotenone, an improved cyclization has been investigated.

Derrisic acid (Ia) reacted with dicyclohexylcarbodiimide (DCC) in the presence of a tertiary base to give thick sirup which could not be extracted from chloroform solution either with aqueous hydrochloric acid or bicarbonate solution. Mild base treatment of the sirup gave dehydrorotenone (II) in more than 40% yield based upon Ia.

To elucidate the mechanism of the cyclization, the sirupy material was chromatographically separated and two crystalline materials were obtained. The first compound, m.p. 137°, showed an ester group at 1700 and a chelated carbonyl group at 1643 cm.$^{-1}$; together with its elemental composition $C_{36}H_{46}O_8N_2 \cdot C_2H_5OH$, this data suggested structure Ib. The second compound, m.p. 155°, showed no ester group, but did have hydroxyl group(s) at 3400 and 3460, carbonyl groups at 1663 (amide), and at 1643 cm.$^{-1}$ (chelated ketone). Elemental analysis was in agreement with the empirical formula $C_{59}H_{68}O_{15}N_2$. Since the infrared spectrum was inconsistent with a β-diketone structure, the only mechanistically plausible structure is III. The formation of III can be rationalized by a nucleophilic attack of the ester Ib followed by a rearrangement through a four-center transition state (Figure 1). That the ester Ib was actually an intermediate of the cyclization was demonstrated by the conversion of Ib into a mixture of dehydrorotenone (II), the urea derivative III, and dicyclohexylurea (DCU) by reaction with potassium propionate in boiling ethanol, the preferred, base-catalyzed treatment. The cyclization of Ib to dehydrorotenone may be rationalized in a way shown in Figure 2.

The generality of the cyclization reaction was proved in an application to the deguelin series. Deguelinic acid (IVa) on treatment with DCC gave a sirup which was converted into dehydrodeguelin (V) by mild base treatment. Ester IVb was isolated as an intermediate and the urea derivative VI was isolated as a minor product.

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