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.

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

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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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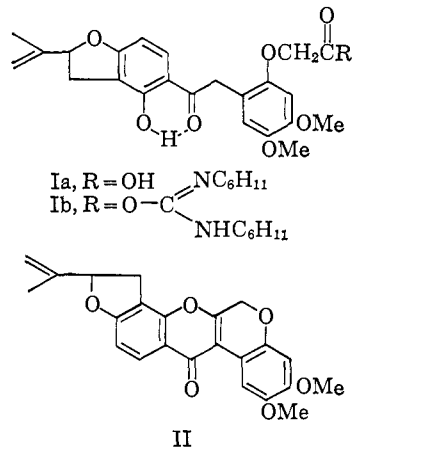
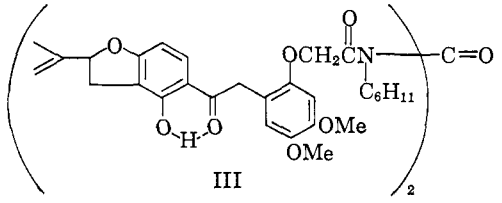
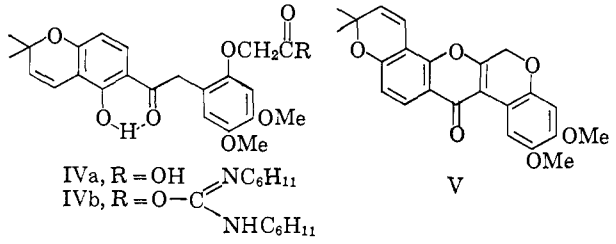


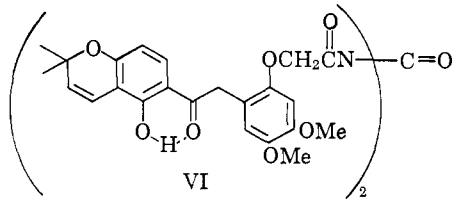
II



III

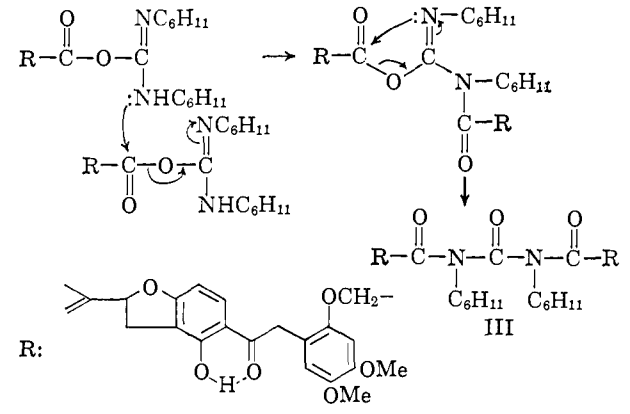


V



VI

Figure 1.



III

Figure 2.

Experimental

O-Derrisyl-N,N'-dicyclohexylisourea (Ib) and N,N'-Diderrisyl-N,N'-dicyclohexylurea (III). To 50 ml. of chloroform solution containing 4.3 g. of derrisic acid (Ia) and 4.0 g. of DCC was added 5 ml. of triethylamine and the solution was allowed to stand for 70 hr. at room temperature. The reaction mixture was poured into aqueous, iced hydrochloric acid. The chloroform layer was then washed with water and bicarbonate solution, dried over sodium sulfate, and concentrated. Chromatographic separation on 150 g. of Brockmann neutral alumina gave four fractions: the first, eluted with 500 ml. of chloroform, weighed 4.43 g.; the third fraction, eluted with 500 ml. of 5% methanol–chloroform, weighed 1.15 g.; and the fourth, eluted with 500 ml. of methanol, weighed 0.41 g. Each fraction was dissolved in a small amount of chloroform, filtered (to remove the white crystals of DCU, m.p. 230°), and concentrated. The first fraction, dissolved in 10 ml. of ethanol, slowly deposited crystals which were collected and washed with ethanol. The crude crystals (1.5 g., m.p. 149°) were recrystallized from 7 ml. of ethanol. The material was dissolved in a small amount of chloroform, filtered to remove the DCU, and recrystallized from 7 ml. of ethanol. The pure sample, m.p. 155°, was obtained by a further recrystallization.

Anal. Calcd. for $C_{59}H_{68}N_2O_{15}$: C, 67.81; H, 6.56; N, 2.68. Found: C, 68.29; H, 6.83; N, 2.62.

Fractions 2, 3, and 4 were combined and dissolved in 15 ml. of ethanol and set aside in the refrigerator. A total of 1.86 g. of colorless crystals was collected and recrystallized from ethanol to yield the product, m.p. 137°.

Anal. Calcd. for $C_{36}H_{46}N_2O_8$: C, 68.12; H, 7.31; N, 4.41. Calcd. for $C_{36}H_{46}N_2O_8 \cdot C_2H_5OH$: C, 67.03; H, 7.70; N, 4.12. Found: C, 67.32; H, 7.32; N, 4.15.

Another crystal form, m.p. 112.5°, was also obtained; however, both forms showed identical infrared spectra in chloroform solution and similar elemental analyses.

Dehydrorotenone (II) from Derrisic Acid (Ia). A. To a solution of 2.2 g. (4.64 mmoles, as the ethanol

solvate) of derrisic acid in 50 ml. of pyridine was added 2.0 g. of DCC. The mixture was set aside overnight at room temperature, heated on the steam bath for 30 min., and concentrated *in vacuo*. The residue was dissolved in 100 ml. of ethanol containing 3.0 g. of anhydrous potassium propionate and refluxed for 1 hr. Dehydrorotenone began to crystallize after 35 min. of heating. After cooling the crystals were collected, washed with ethanol, and dried, yielding 0.78 g. of product (1.86 mmoles, 40.2%), m.p. 206–211°. Recrystallization from ethanol provided crystals, m.p. 217°, which gave no depression on admixture with authentic dehydrorotenone. The infrared spectrum in chloroform solution was identical with the authentic specimen in every detail.

Treatment with potassium acetate or potassium carbonate in boiling ethanol also gave dehydrorotenone in less satisfactory yields.

B. To a solution of 2.6 g. (5.48 mmoles, as the ethanol solvate) of derrisic acid and 2.3 g. of DCC in 100 ml. of chloroform was added 3 ml. of triethylamine. The reaction was set aside at room temperature for 30 hr. The white crystals of DCU were removed by filtration. The chloroform solution was washed consecutively with 2% aqueous hydrochloric acid, water, and bicarbonate solution, and then was concentrated *in vacuo*. The residue was dissolved in 50 ml. of ethanol containing 1.5 g. of anhydrous potassium propionate, and the resulting solution was refluxed for 1.5 hr. The solution was chilled and after 18 hr. the crystals of dehydrorotenone were collected, washed with ethanol, and dried, yielding 0.89 g. (2.27 mmoles, 41.3%).

Dehydrorotenone (II) and N,N'-Diderrisyl-N,N'-dicyclohexylurea (III) from O-Derrisyl-N,N'-dicyclohexylisourea (Ib). An ethanol solution (50 ml.) containing 10 mg. (1.17 mmoles, as the ethanol solvate) of Ib and 1.5 g. of anhydrous potassium propionate was boiled for 2 hr. After being cooled to room temperature, the solution was filtered. The precipitate was washed with ethanol and dried, yielding 79.5 mg. (0.194 mmole, 16.5%) of dehydrorotenone, m.p. 217°. The identity was confirmed by mixture melting point with an authentic sample and comparison of the infrared spectrum in chloroform solution.

The mother liquor was poured into water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and concentrated. Crystalline DCU was removed by filtration. The chloroform filtrate was concentrated and dissolved in 5 ml. of ethanol. Crystals of dehydrorotenone (281 mg., m.p. 150°) separated. On admixture with III the melting point was 150.5–151°.

In another run, 32.6 mg. (0.794 mmole, 21.8%) of dehydrorotenone was obtained from 247.1 mg. (3.63 mmoles, as ethanol solvate) of Ib.

Dehydrodeguelin (V), O-Deguelinyl-N,N'-dicyclohexylisourea (IVb), and N,N'-Dideguelinyl-N,N'-dicyclohexylurea (VI) from Deguelinic Acid (IVa). Analogous treatment (see the first section of the Experimental) of 4.3 g. of deguelinic acid with DCC in chloroform gave four fractions from chromatography of the product on 150 g. of Brockmann neutral alumina. The first fraction (4.18 g.) was eluted with 500 ml. of chloroform, the second fraction (0.74 g.) with 500 ml. of 2% methanol–chloroform, the third fraction (0.53 g.) with 500 ml. of 5% methanol–chloroform, and the last fraction (0.2 g.) with methanol. The fractions were triturated with 8, 2, 2, and 1 ml. of ethanol, respectively. The ethanol solution from the first fraction soon gave yellow crystals (238.7 mg., m.p. 206–213°). After recrystallization from ethanol the material had m.p. 226° (no depression (226.5°) on admixture with authentic dehydrodeguelin). Comparison of the infrared spectra in chloroform solution confirmed the identity of the product. The mother liquor on standing overnight gave 93.4 mg. of crystals, m.p. 155°. Recrystallization from ethanol yielded the isourea IVb, m.p. 158°; $\nu_{max}^{CHCl_3}$ 1700 (ester carbonyl), 1643 (chelated ketone), and complicated absorptions between 1650–1690 cm.$^{-1}$.

Anal. Calcd. for $C_{36}H_{46}N_2O_8$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.04; H, 7.27; N, 4.38.

The mother liquor of IVb gave 348.8 mg. of needles (m.p. 147°) which were dissolved in a small amount of chloroform to remove the DCU and then recrystallized from ethanol to yield VI, m.p. 151°; $\nu_{max}^{CHCl_3}$ 3390 (NH), 1643 (chelated ketone), and 1663 cm.$^{-1}$ (amide carbonyl). No ester band was seen.

Anal. Calcd. for $C_{59}H_{68}N_2O_{15}$: C, 67.81; H, 6.56; N, 2.68. Found: C, 68.08; H, 6.80; N, 2.69.