Syntheses and Configurational Analysis of Rotenoids, XIX¹⁾ The Total Synthesis of Natural Rotenone

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Received May 2, 1961

d,l-Derrisic acid (IIa, R': H) was synthesized from *d,l*-hydroxy-dihydrotubanol (Ve) by Hoesch condensation with a nitrile (VI). The possible optical resolution of *d,l*-IIa was demonstrated by a conventional "reversed resolution" method.

This communication and previous works constitute the first total synthesis of natural rotenone (Ia).

The structure of rotenone (Ia), which is the main insecticidal principle of derris root, was determined by Butenandt²⁾, La Forge³⁾, and Takei⁴⁾ in 1932. Since that time much synthetic work has been carried out by several groups, especially by Robertson and his co-workers⁵⁾. The first partial synthesis of natural rotenone was accomplished by Miyano and Matsui^{6,7)} in 1958, while the total syntheses of dihydrorotenone (Ib)^{8,9)} and *d,l*-nordihydrotubanol (Ic)¹⁰⁾, which have closely analogous structures to natural rotenone, were carried out by the same authors.

As the starting material of the partial synthesis^{6,7)}, we chose dehydrotubanol (III), which is an oxidation product of rotenone and had been derived by Takei⁴⁾ from derrisic acid (IIa, R': H) by intramolecular dehydra-

tion with acetic anhydride in the presence of sodium acetate as a catalyst. III was reduced to rotenol (IV) with sodium borohydride, then converted into mutarotenone by Oppenauer oxidation. The latter is a stereoisomer (or a molecular compound of stereoisomers) of rotenone, from which the natural form was obtained by thermal isomerization.

We also synthesized¹¹⁾ *l*-tubaic acid (Vd), which is an important degradation product of rotenone and was decarboxylated to *l*-tubanol by other investigators¹²⁾.

To prove the direct relationship of the totally synthetic *l*-tubanol and the partial synthesis of natural rotenone from *l*-derrisic acid and to accomplish the total synthesis of rotenone, we attempted at first a Hoesch condensation of *l*-tubanol and a nitrile (VI)¹³⁾. While dihydrotubanol (Vb) or *d,l*-nordihydrotubanol (Vc) easily underwent a Hoesch reaction with VI to give *l*-dihydroderrisic acid (IIb) or *d,l*-nordihydroderrisic acid (IIc)⁸⁻¹⁰⁾, analogous condensation of Va into IIa under various conditions (different temperatures,

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2) A. Butenandt and McCartney, *Liebigs Ann. Chem.*, **494**, 17 (1932).

3) F. B. La Forge and H. L. Holler, *J. Amer. Chem. Soc.*, **54**, 810 (1932).

4) S. Takei, S. Miyajima and M. Ohno, *Ber.*, **65**, 1041 (1932).

5) A. Robertson and coworkers, *J. Chem. Soc. (London)*, **1931**, 2432 (*ibid.*, **1936**, 423; *ibid.*, **1948**, 1672).

6) M. Miyano and M. Matsui, *This Journal*, **22**, 128 (1958).

7) M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2044 (1958).

8) M. Matsui and M. Miyano, *Proc. Japan Acad.*, **35**, 175 (1959).

9) M. Miyano and M. Matsui, *Chem. Ber.*, **92**, 2487 (1959).

10) M. Miyano and M. Matsui, *ibid.*, **93**, 54 (1960).

11) M. Miyano and M. Matsui, *Chem. Ber.*, **93**, 1194 (1960).

12) S. Takei and M. Koide, *Ber.*, **62**, 3030 (1929).

13) A. Robertson, *J. Chem. Soc. (C)*, **1933**, 1163.

and catalysts, etc.) has so far been unsuccessful. The dihydrofuran-ring of the derrisic acid may be hydrochlorolytically cleaved under the influence of dry hydrogen chloride in the presence of anhydrous zinc chloride, since it is fairly unstable owing to its allyl-aryl-etheral nature. This view was confirmed by the treatment of authentic derrisic acid with dry hydrogen chloride in ether in the presence of zinc chloride; no starting acid was recovered and the nature of the oily product was very similar to the Hoesch condensation product mentioned above (for instance, both IR spectra were similar to derrisic acid but had

no $>C=CH_2$ peak near 910 cm^{-1}). Attempted back-cyclization of the hydrochlorolysis product to derrisic acid was also unsuccessful.

Secondly we chose an alternative and successful route. *d,l*-Hydroxydihydrotubanol (Ve)¹¹, an intermediate of our synthesis of tubanol, was subjected to Hoesch condensation with the nitrile (VI) under a specified condition. The following hydrolysis gave *d,l*-hydroxydihydroderrisic acid (IIe) as the main product accompanied by *d,l*-chlorodihydroderrisic acid (II d) and an isomer (VII) of IIe. Among these products, only VII was isolated in the crystalline form, while II d and II e were

FIG 1.

converted to the corresponding methyl esters and purified chromatographically on alumina. IR Spectra of these compounds were consistent with their structure (see experimental parts). The methyl ester of IIe was then treated with phosphorus tribromide in cold pyridine. Through a series of purifications we obtained *d,l*-derrisic acid (IIa, R': H) in the crystalline form. After recrystallization from ethanol, the synthetic *d,l*-acid and the authentic levorotatory acid of natural origin showed completely identical IR spectra in chloroform solution.

Because only a small amount of the synthetic acid was available we did not carry out direct optical resolution, but demonstrated a possible resolution by an indirect, "reversed resolution." Levorotatory derrisic acid of natural origin, when treated with *d,l*- α -phenyl-ethylamine in ethanol, gives only *l*-derrisic acid-*l*- α -phenyl-ethylamine salt as ethanol insoluble crystals. In other words *d,l*- α -phenyl-ethylamine can be resolved by *l*-derrisic acid. Recrystallized from ethanol, the salt was completely identical with the authentic sample prepared from *l*-derrisic acid and optically pure *l*- α -phenyl-ethylamine in every respect (analytical value, m.p., mixed m.p., $[\alpha]_D$, IR spectrum). *d*-Derrisic acid-*l*- α -phenyl-ethylamine salt must be soluble in ethanol, although it has not been actually obtained, it must have the same solubility as *l*-derrisic acid-*d*- α -phenyl-ethylamine salt. Therefore it is quite clear that *l*-derrisic acid can be separated from the synthetic *d,l*-acid by optical resolution with *l*- α -phenylamine only if a sufficient amount of the *d,l*-acid is available¹⁴. *l*-Derrisic acid was recovered from *l*- α -phenyl-ethylamine salt by the ordinary method.

This report formally constitutes the total synthesis of natural rotenone. As the rote-

none had been converted by other workers¹⁵⁻¹⁸) through isodihydrotentenone into dihydrodeguelin (VIII), this communication constitutes also a chemical synthesis of the latter compound.

EXPERIMENTAL

Melting points are not corrected. The term "in vacuo" means reduced pressure obtained by an aspirator (approximately 12~20 mm Hg).

***d,l*-Derrisic Acid (IIa).** To a suspension of 5.0 g of *d,l*-hydroxy-dihydrotubanol (Ve) and 8.0 g of derric acid half ester nitrile (VI) in 45 ml of anhydrous ether was added 8.0 g of anhydrous zinc chloride. Under vigorous stirring and cooling with an ice bath, dry hydrogen chloride was passed into the mixture until it was saturated. The mixture was stirred further for 50~70 hrs at 2~3°C. On standing several minutes, the brownish coloured emulsion formed two layers¹⁹) which were poured into 500 ml of ice water, kept overnight at 0°C, and then warmed to 50°C on a steam bath. The cooled mixture, from which ether had evaporated spontaneously, was extracted with 500 ml of ethyl acetate. The organic layer was washed twice with 10% sodium chloride solution, concentrated in vacuo, dissolved in 50 ml ethanol, and concentrated in vacuo. The resulting brown gum was dissolved in 200 ml of 90% ethanol, heated 2 hrs with 6 g of potassium hydroxide, poured into 500 ml water, and freed from ethanol in vacuo. The aqueous alkaline solution was washed with ether to remove neutral substances, acidified with hydrochloric acid, extracted with 400 ml of ethyl acetate, washed with sodium bicarbonate solution then with water, and concentrated in vacuo. The thick residue, which crystallized spontaneously, melted at 147~150°C after recrystallization from aqueous methanol, and showed no depression (150°C) when mixed with Ve. The sodium bicarbonate solution was acidified with hydrochloric acid, extracted with 500 ml of ethyl acetate, washed twice with 300 ml of 5% sodium chloride solution, dried over sodium sulfate, and concentrated

15) H. L. Haller and F. B. LaForge, *J. Amer. Chem. Soc.*, **53**, 4460 (1931).

16) S. Takei, S. Miyajima and M. Ohno, *Ber.*, **66**, 479 (1933).

17) H. L. Haller, *J. Amer. Chem. Soc.*, **53**, 733 (1931).

18) S. Takei, S. Miyajima and M. Ohno, *Ber.*, **66**, 1826 (1933).

19) In some cases, especially when excessive amount of ether was used yellowish crystals proved to be the imidochloride derived from VI were separated. The Hoesch reaction was prevented by the appearance of the imidochloride because of its insoluble nature.

14) *l*-Derrisic acid salts of strychnine, quinine, cinchonine and brucine were oil and soluble in ethanol, methanol, chloroform etc.

in vacuo. The residual acidic material amounted to 4.1 g²⁰⁾, which was dissolved in 50 ml of ethyl acetate, treated with 3~4 times as much as the calculated amount of ethereal diazomethane, allowed to react for 30 seconds, and treated with acetic acid to decompose excess diazomethane. The solution was diluted to 1.2 l with ethyl acetate, washed with sodium bicarbonate solution²¹⁾, dried over sodium sulfate, concentrated in vacuo, dissolved twice in 50 ml benzene, and concentrated in vacuo. The residual oil was dissolved in a minimum amount of benzene, adsorbed on a 100 g of activated aluminum oxide (Wakô Pure Chemical Co. Ltd., 200~300 mesh), washed with 400 ml benzene, then with 400 ml benzene:chloroform (1:1). The column was carefully washed with chloroform until a small amount of yellow coloured impurity was just eluted (450 ml of chloroform was necessary). The column was eluted with 800 ml chloroform (fraction 1), and then with 300 ml chloroform:methanol (4:1) (fraction 2). On evaporation, fraction 1 gave a small amount of oil which was increased by a prolonged Hoesch reaction and showed an IR spectrum very similar to methyl dihydroderisate (IIb, R':CH₃) in chloroform over all the IR region. Therefore we suggest the structure (IIc) for this product. Fraction 1 sometimes contains methyl ester of the nitrile (VI). The latter crystallized spontaneously. Fraction 2 was concentrated in vacuo to a thick syrup (0.9 g); its IR spectrum in chloroform was very similar to that of IIb but showed absorptions of tertiary OH at 3610 cm⁻¹ (weak) and 1150 cm⁻¹ (strong). Therefore the main portion of fraction 2 is clearly IIc (R':CH₃). Attempted crystallization of

both fractions has so far been unsuccessful. To a solution of 0.9 g IIc (R':CH₃) in anhydrous pyridine (14 ml) was added 1 ml phosphorous tribromide under ice cooling and stirring. The solution was set aside for 5 days in a refrigerator²²⁾. Excess bromide was decomposed with 5 ml of water (24 hrs at room temperature²³⁾). The mixture was poured into 300 ml of dilute hydrochloric acid, extracted 3 times with 500 ml of ethyl acetate, washed with 20% sodium chloride solution, dried over sodium sulfate, concentrated in vacuo, dissolved in 20 ml ethanol, and concentrated in vacuo. The residual oil was refluxed 1.5 hrs after the addition of 120 ml of ethanol, 10 ml of water and 4 g of potassium hydroxide. The mixture was poured into cold water, washed with ether to remove neutral substances, acidified with hydrochloric acid, extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. The residual oil was then esterified by refluxing 4 hrs after the addition of 50 ml of methanol and 1.5 ml of concentrated sulfuric acid. The mixture was poured into water, extracted with ethyl acetate, washed with sodium bicarbonate solution, dried over sodium sulfate, concentrated in vacuo, dissolved in 30 ml benzene, and concentrated. The residual oil was dissolved in 5 ml benzene, adsorbed on 5 g of activated aluminum oxide, washed with 30 ml benzene, and eluted with 150 ml chloroform. The last fraction gave an almost colourless oil (70 mg) which showed essentially the identical IR spectrum²⁴⁾ with methyl derisate (IIa, R':CH₃) in chloroform. The 70 mg of synthetic methyl *d,l*-derisate was dissolved in 10 ml ethanol containing 100 mg of potassium hydroxide, heated to reflux 1.5 hrs, poured into 100 ml of dilute hydrochloric acid, extracted with 150 ml of ethyl acetate, washed with 100 ml of water then with 100 ml of 3% sodium chloride solution, dried over sodium sulfate, and concentrated in vacuo. The IR spectrum²⁵⁾ of the residual oil showed that this is essentially the desired derisic acid and contains no or only little amount of isoderisic acid. The oily synthetic *d,l*-derisic acid was dissolved in 3 ml benzene, adsorbed on 10 g silicic acid (Mallinckrodt) and eluted with benzene:ethyl acetate (10:1) in each 30 ml

20) On standing, crystals of m. p. 168°C were separated which showed depression (145°C) when mixed with derisic acid (m. p. 169°C) and no depression when mixed with derisic half acid nitrile (VI, H instead of CH₃, m. p. 174°C).

21) The isomeric acid (VII), which is a minor product of the Hoesch' reaction can be isolated at this stage. The acetic ester solution was shaken vigorously 3 times with 3% potassium carbonate solution and the combined aqueous solution was left standing over night at room temperature, acidified with hydrochloric acid and extracted with ethyl acetate. The last acetic ester solution was extracted with sodium bicarbonate solution, acidified with hydrochloric acid, extracted with ethyl acetate, washed with water, and concentrated in vacuo. The residue crystallized spontaneously on standing over night. The crystals were collected and recrystallized from methanol. 35 mg, m. p. 153~155°C IR Spectrum in Nujol paste: OH 3520, 3440 (broad), 3300 cm⁻¹, carboxylic C=O 1725 cm⁻¹, ketonic C=O 1660 cm⁻¹. Because of the absence of intramolecular hydrogen bonding the ketone absorption (1660 cm⁻¹) is shifted to shorter wave lengths than every other derisic acid analogue (for example *l*-derisic acid shows ketonic absorption at 1645 cm⁻¹ in both chloroform solution and Nujol paste).

Anal. found: C, 60.18, H, 6.88; calcd. for C₂₃H₂₆O₉·CH₃OH (478.5) C, 60.24; H, 6.32.

22) The dehydration condition is the same as that of Ve→Va which was previously carried out successfully¹¹⁾.

23) If the mixture was not set aside at this stage, the final yield was reduced remarkably. The phosphorous acid residue bound to the phenolic OH is probably hydrolysed during this stage, so that the product becomes more soluble in the organic solvent.

24) It also showed an absorption at 1155 cm⁻¹ due to the presence of a tertiary OH of unreacted IIc.

fractions. Fractions No. 10~20²⁵⁾ contained a total of 10 mg of half-crystalline acid, which was recrystallized from 95% ethanol. Yield 3 mg, m.p. 158~160°C. The IR spectrum of the synthetic *d,l*-acid in chloroform solution was completely identical with authentic *l*-derrisic acid of natural origin: carboxylic C=O approximately 1760 cm⁻¹ (broad), ketonic C=O 1645 cm⁻¹, aromatic C=C 1620, 1520 cm⁻¹, >C=CH₂ 908 cm⁻¹. Because only a limited amount of the synthetic acid was available, an elemental analysis was made using less than one tenth of the usual amount.

Anal. Found: C, 62.56; H, 8.21. Calcd. for C₂₃H₂₄O₈·C₂H₅OH: C, 63.28; H, 6.34%.

***l*-Derrisic Acid—*l*-α-Phenyl-ethylamine Salt.**

a) From *d,l*-α-phenyl-ethylamine: 500 mg *l*-derrisic acid of natural origin and 0.5 ml of *d,l*-α-phenyl-ethylamine were dissolved in 2 ml ethanol and left standing in a refrigerator over night. The colourless crystals were collected and recrystallized from 5 ml ethanol, m.p. 161~163°C [α]_D²² -49.8° (C = 2.65 in chloroform).

Anal. Found: C, 67.32; H, 6.62; N, 2.53. Calcd. for C₃₁N₃₅O₈N: C, 67.74; H, 6.42; N, 2.55%.

b) From *l*-α-phenyl-ethylamine: 1 g *l*-derrisic acid and 1 ml *l*-α-phenyl-ethylamine were dissolved in 15 ml ethanol. Crystals were collected and recrystallized from 12 ml ethanol. 0.6 g, m.p. 162~163°C [α]_D²² -49.0° (C = 2.72 in chloroform). The IR spectra in Nujol paste of a), b) salts were identical.

Anal. Found: C, 67.58; H, 6.78; N, 2.60. Calcd. for C₃₁N₃₅O₈N.

25) In another experiment the position of the peak of the desired acid was slightly varied, but it was easily checked by IR absorption at 908 cm⁻¹ (>C=CH₂).

***l*-Derrisic Acid From The *l*-α-phenyl-ethylamine Salt.** 1.0 g salt was decomposed in dil. hydrochloric acid by pulverizing with a glass rod and setting aside 30 min at room temperature. The filtered white precipitate was recrystallized from methanol, m.p. 151°C.

Anal. Found: C, 63.34; H, 6.19. Calcd. for C₂₃H₂₄O₈·CH₃OH: C, 62.61; H, 6.01%.

The authentic *l*-derrisic acid recrystallized from methanol also contains methanol as a crystalline solvent. The IR spectra of both authentic and recovered acids in Nujol paste were identical, and mixed m.p. showed no depression.

Acknowledgement. We are indebted to Prof. Dr. R. Yamamoto, Prof. Dr. Y. Sumiki and Dr. S. Tamura for their encouragement and necessary arrangements for this and previous work. Mr. K. Aizawa has greatly accelerated this work through his intuitive discussions on IR spectra of our compounds. Microanalyses were carried out by Misses K. Kamitō, M. Suzuki and I. Isobe, to whom we express our sincere thanks.

English sentence in this report was corrected by Dr. J. M. Steim, Agricultural and Biological Chemistry Department of Pennsylvania State University, to whom we express our sincere thanks. But his correction was confined only in serious mistakes.

We wish also to express our appreciation to The Mainichi Newspaper Co. Ltd. for research funds which enabled us to accomplish the total synthesis of natural rotenone.