[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Derivatives of Coumaran. VII. A New Synthesis of Isotubanol and Isotubaic Acid

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The development of methods for the condensation of substituted coumaran-3-ones with aldehydes and ketones and for the reduction of the products to substituted benzofurans and dihydrobenzofurans[1] has proved to be of value for the synthesis of this type of heterocyclic compound. These general procedures have now been utilized to effect a new synthesis of isobutanol and isotubaic acid.

Isobutanol has been synthesized by Reichstein and Hirt[2] by decarboxylation of the acid resulting from the condensation of 5-isopropylfurfuraldehyde with sodium succinate. In their synthesis the starting material contained the furan ring and the benzene ring was subsequently fused on. In the present synthesis the starting compound, resorcinol, contained the benzene nucleus and the furan ring was grafted on by means of the reactions summarized in Chart I.

The procedures used for the first four steps leading to 2,6-dihydroxyacetophenone were those described by Russell, Frye and Mauldin.[3] The 4-hydroxycoumaran-3-one (IV) was prepared by the reactions indicated according to the methods previously described.[1e] Since this compound was quite unstable to acidic reagents and to heat, a reagent had to be found which could effect the condensation of acetone with the coumaran-3-one in the cold. Potassium hydroxide in absolute ethanol was found to be the most suitable reagent for bringing about this condensation at room temperature.

All attempts to reduce the 4-hydroxy-2-isopropylidene coumaran-3-one (V) directly to the corresponding dihydrocarbinol failed. Benzoylation, which broke the chelation of the carbonyl group with the hydroxyl (V), led to the derivative (VI) which could be reduced catalytically with hydrogen and platinum provided a trace of hydrochloric acid was present. Dehydration occurred during the distillation of the carbinol (VII) and the benzoate of isotubanol (VIII) resulted. Hydrolysis of this derivative produced isotubanol (IX) which underwent the Kolbe reaction smoothly to yield isotubaic acid[4] (X).

In order to compare these synthetic compounds with those obtained by degradation of rotenone whose structure was established by LaForge and Haller,[5] a sample of rotenone was isomerized to isorotenone by treatment with sulfuric acid[6] and the isorotenone cleaved by alcoholic potassium hydroxide to isotubaic acid.[2,4,5,6] A comparison of isotubaic acid and its acetyl derivative, obtained in this way from rotenone, with the synthetic compound X and its acetate showed that they were identical.

Experimental

4-Hydroxy-2-isopropylidinecoumaran-3-one (V).—A mixture of 10 g. of 4-hydroxycoumaran-3-one,[1e] 35 cc. of dry acetone, 25 g. of powdered potassium hydroxide and 300 cc. of absolute ethanol was shaken for thirty-six hours at room temperature. The green solution turned red after twenty hours shaking. At the end of the reaction time, the red precipitate was filtered and carefully acidified with 50 cc. of 6 *M* hydrochloric acid. A yellow precipitate was obtained by this treatment. This was filtered and recrystallized twice from acetone to give a yield of 10.5 g. of orange prisms melting at 121°. The yield was 83% of the theoretical.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.25; H, 5.66.

4-Benzoxy-2-isopropylidinecoumaran-3-one (VI).—A mixture of 200 mg. of 4-hydroxy-2-isopropylidinecoumaran-3-one, 1 cc. of benzoyl chloride, 10 cc. of water, 10 cc. of acetone and 1.5 g. of sodium carbonate was refluxed for one hour. The hot solution was then poured into a mixture of ice and water with hand-stirring. Yellow crystals separated at standing. These were filtered and recrystallized from ethyl acetate. Yellow needles were obtained melting at 160°. The yield was 280 mg. (90.5% of the theoretical).

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.76. Found: C, 73.74; H, 5.02.

Phenylurethan of 4-Hydroxy-2-isopropylidinecoumaran-3-one.—In a dry Pyrex test-tube were placed 100 mg. of 4-hydroxy-2-isopropylidinecoumaran-3-one and 200 mg. of phenyl isocyanate. The tube was then strongly heated about one inch from the top in an oxygen flame and drawn out to a thin sealed end. The reaction tube was then heated in a steam cone twenty hours. At the end of this

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[1] (a) Shriner and Damschroder, THIS JOURNAL, **60**, 894 (1938); (b) Shriner and Anderson, *ibid.*, **60**, 1415 (1938); (c) *ibid.*, **60**, 1418 (1938); (d) Shriner, Matson and Damschroder, *ibid.*, **61**, 2322 (1939); (e) Shriner and Witte, *ibid.*, **61**, 2328 (1939); (f) Shriner and Anderson, *ibid.*, **61**, 2705 (1939).

[2] Reichstein and Hirt, *Helv. Chim. Acta*, **16**, 121 (1933).

[3] Russell, Frye and Mauldin, THIS JOURNAL, **62**, 1441 (1940).

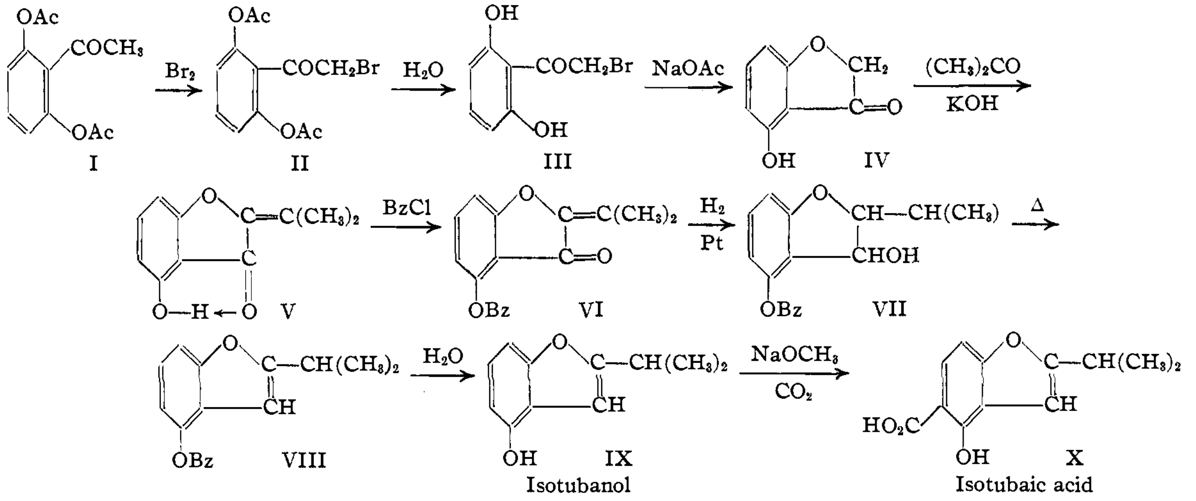
[4] Takei, *Ber.*, **62**, 3030 (1929).

[5] LaForge and Haller, THIS JOURNAL, **54**, 810 (1932); LaForge, Haller and Smith, *Chem. Rev.*, **12**, 181 (1933).

[6] Butenandt and Hildebrandt, *Ann.*, **477**, 245 (1930).

CHART I

SYNTHESIS OF ISOTUBANOL AND ISOTUBAIC ACID



time, it was removed and cooled. After breaking the sealed end, the contents of the tube were washed out with 20 cc. of an equal mixture of benzene and high-boiling petroleum ether. The benzene–petroleum ether solution was filtered and allowed to evaporate slowly at room temperature. White needles of the urethan precipitated which were filtered, washed with petroleum ether, and then again recrystallized from a mixture of benzene and high-boiling petroleum ether. The yield of product melting at 143° was 145.0 mg., which was 89.5% of the theoretical.

Anal. Calcd. for $C_{18}H_{15}O_4N$: N, 4.53. Found: N, 4.62.

2 - Isopropyl - 3 - hydroxy - 4 - benzoxydihydrobenzofuran VII and Isotubanol Benzoate VIII.—A mixture of 11.5 g. of 4-benzoxy-2-isopropylidinecoumaran-3-one, 0.5 g. of platinum oxide, 300 cc. of absolute ethanol and 4 drops of concentrated hydrochloric acid was shaken with hydrogen at an initial pressure of 48 pounds and at room temperature. The reaction mixture was removed when approximately 2 moles of hydrogen were taken up. The mixture was filtered and the ethanol was removed by distillation at 30 mm. and 30°. A yellow oily residue was obtained and could not be crystallized. The oil was then distilled at 3 mm. Three sharp cuts were obtained. At 65° a few drops of a colorless pine smelling oil came over. At 105–110° a very small amount of a colorless oil which soon crystallized was obtained. These two compounds could not be characterized. At 175–180°, 8 g. (73%) of a yellow oil came over. This compound proved to be the benzoate of isotubanol.

Since the benzoate of isotubanol was obtained, obviously upon distillation at 175–180°, a molecule of water split out from the 2-isopropyl-3-hydroxy-4-benzoxydihydrobenzofuran, which originally was formed in the reduction.

Isotubanol IX.—A mixture of 8 g. of isotubanol benzoate, 400 cc. of 95% ethanol and 60 cc. of 10% aqueous sodium hydroxide was refluxed two hours. At the end of this time, 350 cc. of ethanol was distilled off, the mixture was cooled and then treated with an excess of solid carbon dioxide. It was then extracted five times with 30-cc. portions of diethyl ether. The ether solution was dried over anhydrous sodium sulfate, filtered and the ether was distilled, leaving a yellow oil. This oil was distilled and at 170° and 3 mm. pressure a colorless oil came over which was isotubanol; yield, 4 g. (79%). This compound gave no test with ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.96; H, 6.87. Found: C, 75.18; H, 7.00.

Phenylurethan of Isotubanol.—A mixture of 0.1 g. of isotubanol and 0.3 g. of phenyl isocyanate was placed in a dry test-tube. The tube was sealed and placed in a steam-cone for ten hours. A crystalline mass had formed at the end of the above reaction time. This was washed out with 20 cc. of an equal mixture of high-boiling petroleum ether and benzene. The solvents were slowly evaporated and the solid residue was recrystallized three times from the same solvent mixture. A yield of 0.14 g. (84%) of colorless plates was obtained, melting at 142°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.19; H, 5.81; N, 4.74. Found: C, 73.27; H, 6.11; N, 4.70.

Isotubaic Acid X.—Two-tenths of a gram of metallic sodium was placed in 2 cc. of dry methanol in a bomb of 35-cc. capacity. After the initial reaction of the sodium and the methanol had taken place, 0.3 g. of isotubanol and 5 g. of solid carbon dioxide were added. The bomb was closed tightly and placed in an oil-bath. The bath was heated to 180° and kept at that temperature for two hours. The bomb was then removed and cooled. The contents were washed out with 20 cc. of distilled water. The aqueous solution was carefully acidified with hydrochloric acid. The cloudy mixture was then extracted four times with 25-cc. portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered and the ether was removed by distillation to leave a pasty residue. The residue was taken up in 20 cc. of boiling toluene, the solution filtered and cooled in an ice-salt mixture. Long white needles of the acid were obtained which melted at 183°. The yield was 0.3

g. (86.5%). The melting point agreed with that recorded by Reichstein and Hirt.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.42; H, 5.49. Found: C, 65.39; H, 5.57.

Extraction of Rotenone from Commercial Rotenone Resin.—A 100 g. sample of commercial rotenone resin was placed into 200 cc. of boiling carbon tetrachloride. The solution was then filtered hot. The carbon tetrachloride solution was then cooled in an ice-salt mixture to yield a mass of yellow needles. These were filtered and washed three times with 10-cc. portions of cold carbon tetrachloride. The yellow needles were then recrystallized from absolute ethanol after treatment with Norit. A yield of 30 g. of white tablets melting at 162° was obtained. Upon working up the mother liquors, an additional 6 g. of product was obtained. The total yield was 36 g., which was 36% of the resin used.

Isorotenone.—A modification of the procedure of Butenandt and Hildebrandt[6] was used. A mixture of 10 g. of rotenone, 600 cc. of water and 330 cc. of concentrated sulfuric acid was refluxed for eight hours. A clear solution was never obtained. At the end of the reaction time, the mixture was allowed to cool and to stand at room temperature for twelve hours. The isorotenone which precipitated was filtered and washed five times with water. It was then pressed dry on the filter and recrystallized twice from absolute ethanol to give white prisms melting at 183°. The yield was 7.5 g. (75%).

Isotubaic Acid from Isorotenone.—A mixture of 8 g. of potassium hydroxide, 200 cc. of 95% ethanol, and 3 g. of isorotenone was refluxed four hours. A dark red solution resulted. At the end of this time, 30 cc. of water was added and 175 cc. of alcohol was distilled from the mixture. An excess of dry carbon dioxide was added to the residual liquor. The mixture was then extracted with five 20-cc. portions of diethyl ether. The remaining alkaline solution was then slowly acidified with dilute sulfuric acid. A cloudy solution resulted. This was extracted with four 20-cc. portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate, then filtered. The ether was slowly evaporated off to leave a reddish pasty residue. This was taken up in toluene, the toluene solution brought to boiling, then filtered. At cooling, long needles of the acid soon formed. The yield of the acid was 100 mg. (5.75%). The melting point was 184°.

A mixed melting point of the synthetic isotubaic acid and the natural acid obtained by the above degradation gave no depression. The melting point of the mixture was 184°. Thus the two acids were found to be the same.

Isotubaic Acid Acetate.—A mixture of 30 mg. of isotubaic acid, 1 g. of acetic anhydride and 1 g. of pyridine was allowed to stand at room temperature for five hours with occasional shaking. The reaction mixture was then slowly evaporated in a hood until a gray paste was obtained. This was recrystallized once from toluene to give plates which melted at 135°. These plates were then sublimed at 1 mm. and 150° (outside bath) to give 20 mg. of a white powder melting at 153°. This compares favorably with the melting point reported in the literature. A mixed melting point with the acetate of isotubaic acid obtained from the degradation of isorotenone showed no depression.

Summary

The synthesis of isotubanol and isotubaic acid was effected by the following sequence of reactions: resorcinol → 4-methyl-7-hydroxycoumarin → 4-methyl-7-acetoxycoumarin → 4-methyl-7-hydroxy-8-acetocoumarin → 2,6-dihydroxyacetophenone → 2,6-diacetoxyacetophenone → 2,6-diacetoxy-ω-bromoacetophenone → 2,6-dihydroxy ω-bromoacetophenone → 4-hydroxycoumaran-3-one → 2-isopropylidine-4-hydroxycoumaran-3-one → 2-isopropylidine-4-benzoxycoumaran-3-one → 2-isopropyl-3-hydroxy-4-benzoxydihydrobenzofuran → isotubanol benzoate → isotubanol → isotubaic acid.

A sample of isotubaic acid was obtained from the alkaline scission of isorotenone and was found to be the same as the synthetic acid. The synthetic acid was further characterized through its acetate.

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