activation energy with the number of carbon atoms in the solvents. The theoretical implications of the minimum found are discussed.

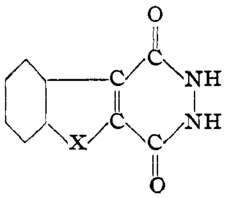
BROOKLYN, N. Y. RECEIVED MARCH 15, 1941

[CONTRIBUTION NO. 251 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

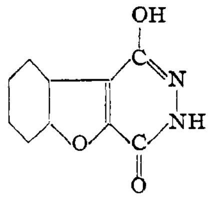
The Synthesis of the Cyclohydrazides of Coumarone-, Thionaphthene- and Indole-2,3-dicarboxylic Acids

BY ERNEST H. HUNTRESS AND WILLIAM M. HEARON[1,2]

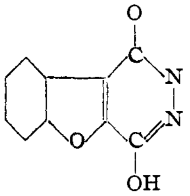
In the course of another investigation to be reported later it became necessary to prepare the cyclohydrazides of certain α,β-dicarboxylic acids of the coumarone (I, X = O), thionaphthene (I, X = S), and indole (I, X = NH) series, none of which have previously been reported. The present paper describes the syntheses and properties of all three compounds together with certain new information on the intermediates used.



I



II-A



II-B

The most generally satisfactory method involved the reaction of the dimethyl esters of the corresponding acids with hydrazine hydrate. This gave almost the theoretical yields of the coumarone (94%) and thionaphthene (90%) derivatives and a very satisfactory result (76%) with the indole analog. The coumarone and thionaphthene derivatives were also prepared from the acids themselves and the latter was also prepared from the corresponding anhydride but the yields by these methods were never as high as from the esters.

These three analogously constituted cyclohydrazides are all colorless, high-melting solids sparingly soluble in most solvents. They all act as mono-enols, however, and can be titrated as such with dilute aqueous alkali. They all form monoacetates and give colorations with ferric chloride but do not reduce ammoniacal silver nitrate solution. In the case of the cyclohydrazide of coumarone-2,3-dicarboxylic acid, both the enol and keto forms were isolated but only one desmotrope was observed for the corresponding cyclohydrazides of the other two series.

The synthesis of these cyclohydrazides thus required the preparation of the respective 2,3-dicarboxylic acids and/or their dimethyl esters.

At the time this work was carried out, coumarone-2,3-dicarboxylic acid had been reported only once,[3] but by two rather similar methods both starting from isatin. The first passed through the following sequence (yields in parentheses): isatin → (30%) coumarandione-2,3 → (39.6%) *o*-oxalophenoxyacetic acid → (100% ?) dimethyl *o*-oxalophenoxyacetate → (32.5%) coumarone-2,3-dicarboxylic acid. Assuming quantitative methylation at the third stage (for which no data were reported), the over-all yield was 30 × 39.6 × 100 × 32.5 = 3.9%. The second method was: isatin → (30%) coumarandione-2,3 → (39.6%) *o*-oxalophenoxyacetic acid → (16.3%) coumarone-2,3-dicarboxylic acid. For this method the over-all yield was therefore 30 × 39.6 × 16.3 = 2.0%. It thus appears definite that Reichstein's conversion of isatin to coumarone-2,3-dicarboxylic acid gave an over-all yield of only 2–4%.

By the methods detailed in the experimental part, Reichstein's method has been so greatly improved that the over-all yield is about seven times as great, *i. e.*, 30.5%. This improvement is attributable to two principal factors. First, the conversion of isatin to coumarandione-2,3 has been developed to give yields of 50%. Second, the transformation of this dione to coumarone-

---

(1) This paper is contributed from part of a dissertation submitted in June, 1940, by W. M. Hearon to the Faculty of the Massachusetts Institute of Technology in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Eastman Kodak Company, Rochester, New York.

(3) Titoff, Müller and Reichstein, *Helv. Chim. Acta*, **20**, 883–892 (1937).

2,3-dicarboxylic acid has been simplified to a one-step process without isolation of the intermediates as a result of which the yield has been raised ten fold, *i. e.*, to 61%.

Thionaphthene-2,3-dicarboxylic acid was readily converted to the corresponding cyclohydrazide either by heating directly with hydrazine hydrate, by conversion to the anhydride, or best to the dimethyl ester and allowing these intermediates to react with hydrazine hydrate.

Unlike the two preceding analogs, indole-2,3-dicarboxylic acid itself has not been reported. For the synthesis of its dimethyl ester, however, we employed the remarkable reaction discovered by Diels and Reese[4] in which dimethyl acetylenedicarboxylate and hydrazobenzene react in methyl alcohol to form an intermediate addition compound, mere refluxing of which in xylene gives the desired dimethyl indole-2,3-dicarboxylate together with aniline. The claims of Diels and Reese were completely confirmed. The crystalline adduct was readily obtained in 75% yield (recorded[4] 81.5%) and from it the dimethyl indole-2,3-dicarboxylate resulted in 63% yield (recorded[4] 70%) accompanied by an equivalent quantity of aniline. During the preparation of the cyclohydrazide from dimethyl coumarone-2,3-dicarboxylate, two different materials were obtained which appear to be the keto (I, X = O) and monoenol (II) forms of the hydrazide. Although these compounds had substantially different melting points, and differed in their appearance, solubilities, reactions with diazomethane and color with ferric chloride, yet the analytical data demonstrated that the two materials were isomeric and that they both corresponded to the expected cyclohydrazide. Moreover, not only did they both yield the same monoacetate but the lower melting one (which we regard as the enol) was readily convertible to the higher melting isomer (which we regard as the keto). Despite many attempts, no method was found which would effect the reverse transformation. No evidence as to whether the enol form is to be represented by II-A or II-B is submitted but the keto form must possess the structure shown in (I, X = O).

Experimental Work

Coumarone Series

Coumarandione-2,3.—Isatin (50 g. = 0.34 mole) was dissolved in a warm solution of sodium hydroxide (20.4 g. = 0.51 mole) in water (250 ml.) and boiled for ten minutes. Solid sodium nitrite (24.1 g. of 97% = 23.4 g. of 100% = 0.34 mole) was added and the mixture cooled to 0°. Meanwhile a solution of 42.4 ml. of concentrated sulfuric acid (0.765 mole) in cold water (722 ml.), briskly motor-stirred in a 2-liter beaker was brought to exactly −3° by surrounding with solid carbon dioxide. The first solution was then introduced under the surface of the second within ten to fifteen minutes, *i. e.*, as rapidly as could be without rise of temperature above 5° or appreciable evolution of nitrogen oxides.

The resulting solution of diazotized isatinic acid was then added in small portions to a boiling suspension of copper bronze (10 g.) in water (400 ml.). After half the diazonium solution had been added, a second 5-g. portion of copper bronze was introduced, and a third 5-g. portion at the three quarter point. After cooling to room temperature the solution was filtered from solid matter and the 1400 ml. of solution thrice extracted with 400-ml. portions of ethyl acetate After concentration of the combined extracts to about 75 ml. and drying the residual oil in an air stream at 100°, there remained about 40 ml. of crude *o*-hydroxyphenylglyoxylic acid.

For ring closure of this compound by loss of water to coumarandione-2,3, this brown oil was merely distilled under reduced pressure (1–2 mm.). The use of a heating bath was found essential since otherwise local overheating decomposed the coumarandione to a salicylid polymer[5] while the *o*-hydroxyphenylglyoxylic acid lost carbon monoxide yielding salicylic acid.[6] Before starting the distillation the pressure was lowered to 1–2 mm. and the flask heated at 70° until all traces of solvents or water had distilled out. The bath temperature was then raised to 130–135°, while the coumarandione distilled at 108–113° as a clear yellow oil which solidified in the receiver. After recrystallization from hot anhydrous benzene, the fine yellow crystals were dried quickly at 50–70°. The yield of coumarandione-2,3 (25 g.) represented 50% of the theoretical yield and showed a melting point of 129–130° uncor. (recorded 134° cor.[5]). The value of 54° reported[7] by Reichstein is doubtless an error since the melting point of anhydrous *o*-hydroxyphenylglyoxylic acid is twice[5,8] reported elsewhere as 56–57°.

The identity of the product was supported by the ready formation of coumarandione-3-(mono) phenylhydrazone, m. p. 183–185° u. c. (recorded[9] m. p. 185°) on treatment with phenylhydrazine in boiling acetic acid, and of *o*-hydroxyphenylglyoxylic acid anil, m. p. 102° u. c. (recorded 102°)[9] on treatment in benzene solution with aniline.

***o*-Oxalophenoxyacetic Acid.**—Coumarandione-2,3 (5.0 g. = 0.34 mole) dissolved in 33% aqueous potassium hydroxide (17.5 ml.) was treated with 50% aqueous chloroacetic acid (12.5 ml.). After heating at 100° for one hour, cooling and diluting with 50 ml. of water, the solution was acidified with hydrochloric acid and cooled to room temperature. Since no precipitate formed the solution was saturated with salt and thrice extracted with 50-ml. portions of ethyl acetate. After evaporation of the solvent

---

[4] Diels and Reese. *Ann.*, **511**, 168–182 (1934).

[5] Fries and Pfaffendorf, *Ber.*, **45**, 154, 156 (1912).

[6] Schad, *ibid.*, **26**, 221 (1893).

[7] Ref. 3, p. 886–887.

[8] Stoermer, *Ber.*, **42**, 201 (1909).

[9] Ref. 5, p. 157–158.

and removal of unchanged yellow coumarandione by washing with benzene, there remained 3.8 g. of white *o*-oxalophenoxyacetic acid (50% theoretical) melting at 192–193° uncor. (recorded[7] 198–200° cor.) and giving a neutralization equivalent of 113 (theoretical 112).

This acid was soluble in water, ethyl alcohol, glacial acetic acid or ethyl acetate; slightly soluble in ether and insoluble in benzene. It gave no color with ferric chloride but on warming with concentrated sulfuric acid evolved carbon monoxide.

Coumarone-2,3-dicarboxylic Acid.—Coumarandione-2,3 (10.0 g. = 0.67 mole) and absolute ethanol (50 ml.) in a 500-ml. three-necked flask provided with mercury-sealed mechanical stirrer, reflux condenser and dropping funnel were refluxed at 100° for thirty minutes. Ethyl bromoacetate (7.5 ml.) was poured in and a solution of sodium (10 g. = 0.435 mole) in absolute ethanol (200 ml.) then added dropwise to the well-stirred refluxing solution. After addition of about 10 ml. of the sodium ethylate solution, sodium bromide began to precipitate. When after forty-five minutes a total of 20 ml. of the sodium ethylate had been added, a second unit of ethyl bromoacetate was put in through the condenser and dropwise addition of alcoholate continued until 62 ml. had been used, after which the remainder was added rapidly. On refluxing for another hour the mixture assumed a mahogany color.

Water (100 ml.) was then added cautiously to the mixture, the condenser and dropping funnel removed and a gentle air stream passed through the flask to distill out most of the alcohol. After the volume had diminished by 100 ml., another 50 ml. of water was added. Evaporation was continued until the final volume was 75 ml., which required about one and one-half hours.

The clear dark liquid was cooled, acidified with concentrated hydrochloric acid (70 ml.), cooled again, the precipitate filtered and washed with cold 5% hydrochloric acid (30 ml.). The crude brown product was dissolved in boiling water (150 ml.), treated with decolorizing carbon, filtered hot and cooled. Crystallization began on cooling and was completed by addition of concentrated hydrochloric acid (50 ml.). After filtration and washing with cold 5% hydrochloric acid. the product was dried at 70° until no test for chloride ion could be obtained with silver nitrate. The product weighed 8.5 g. (61% theoretical), melted 248–249° uncor. (recorded[7,10] 259–260° cor.), and gave a neutralization equivalent of 103.8 (theoretical 103).

The acid was soluble in water, methanol, ethanol, acetone, ethyl acetate, dioxane and hot glacial acetic acid; slightly soluble in ether or cold glacial acetic acid; insoluble in benzene, ligroin or petroleum ether.

Although the acid dissolved readily in acetic anhydride, refluxing the solution for two hours gave no evidence of anhydride formation and the original acid was recovered unchanged.

On heating at 190–200° with quinoline and copper bronze, however, the acid evolved carbon dioxide and yielded coumarone-3-carboxylic acid, m. p. 155–156° uncor. (recorded[7] 162° cor.), neutralization equivalent 163 (calculated 162).

Dimethyl Coumarone-2,3-dicarboxylate.—Coumarone-2,3-dicarboxylic acid (2.0 g.) suspended in ether was treated with ethereal diazomethane until no more nitrogen was evolved and the solution remained yellow. After filtering this through decolorizing carbon the ether was evaporated to small volume, cooled and seeded. The crystals of ester were washed with petroleum ether; weight 2.1 g. (93% theoretical); m. p. 61–62° uncor. Although this product was entirely satisfactory for further treatment, recrystallization from ethanol gave a maximum melting point of 63–64° uncor., while the yield dropped to 71%.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.30; sap. equiv., 117. Found: C, 61.3, 61.4; H, 3.90, 4.45; sap. equiv., 118.

The ester was soluble in the usual organic solvents, but was unattacked by hot sodium carbonate or cold dilute alkali. It was hydrolyzed slowly by hot aqueous alkali, but very easily by alcoholic alkali.

Coumarone 2,3-Dicarboxylic Acid Cyclohydrazide (I, X = O).—A. From the Dimethyl Ester.—The ester (2.1 g. = 0.009 mole) dissolved in 95% alcohol (12 ml.) and mixed with 42% hydrazine hydrate solution (3.1 g. = 0.026 mole) was placed in a heavy-walled Pyrex tube and heated overnight at 100°. The white precipitate was warmed with water (40 ml.) until solution occurred, filtered, cooled and acidified with excess hydrochloric acid. The product after washing and drying weighed 1.7 g. (94% theoretical) and melted at 316–318° uncor.

The compound titrated as a monobasic acid; neut. equiv. found, 205.1; calcd., 202.1. Ignition of a sample of its silver salt gave the silver content as 34.2%; calculated for mono-silver salt, 34.9%; for di-silver salt, 51.9%. All attempts at ordinary combustion analysis of the hydrazide, however, were unsuccessful and gave only very low results.

The hydrazide was a fine white powder, very sparingly soluble in cold water but slightly soluble in hot. It dissolved in dilute aqueous sodium hydroxide, ammonium hydroxide, sodium carbonate or even sodium bicarbonate solutions. A saturated aqueous solution gave with ferric chloride a red violet color but did not reduce ammoniacal silver nitrate. The hydrazide was practically insoluble in all organic solvents except hot glacial acetic acid.

B. From the Acid.—The acid (1.0 g. = 0.0485 mole) was added to a solution of 87% hydrazine hydrate (0.279 g. = 0.0485 mole) in water (15 ml.). The heavy gelatinous precipitate of monohydrazine salt dissolved on boiling and the solution was evaporated quickly to dryness. Since heating the powdered residue for six hours at 200° gave no evidence of cyclization, the solid was cautiously fused over a small free flame. Upon resolidification the brown residue was powdered, boiled with water (20 ml.) and filtered. The solid was redissolved in dilute sodium hydroxide, treated with decolorizing carbon, filtered, and acidified with concentrated hydrochloric acid. The yield of cyclic hydrazide was only 30% of the theoretical but it melted at 314–315° uncor. and did not depress the melting point of a specimen prepared from the ester.

C. Monoacetyl Derivative.—A small sample (0.5 g.) of the hydrazide dissolved in 10% aqueous sodium hydroxide (50 ml.) was shaken at 4° with excess of pure acetic anhydride. The white sandy precipitate was immediately

---

(10) While this paper was being written a new synthesis of this acid was reported by Koelsch and Whitney, This Journal, 63, 1762 (1941), in which the melting point of 249–250° confirms our value.

filtered off, washed with water and dried. The melting point was 224–226° uncor.

Anal. Calcd. for $C_{12}H_8O_4N_2$: C, 59.0; H, 3.30; sap. equiv., 122. Found: C, 59.0; H, 3.56; sap. equiv., 120. Calcd. for diacetyl derivative: C, 58.7; H, 3.49; sap. equiv., 244.

This monoacetyl derivative was a white solid, insoluble in water or sodium bicarbonate, but soluble in dilute sodium carbonate or sodium hydroxide. It was slightly soluble in organic solvents and could be recrystallized from hot glacial acetic acid. It gave no color with aqueous ferric chloride.

D. Keto and Enol Forms of Coumarone-2,3-dicarboxylic Acid Cyclohydrazide.—In the preparation of the hydrazide from the dimethyl ester, it was found that if after acidification the precipitate was immediately filtered from the hot solution, the filtrate on cooling deposited fine white needles. Although the initial precipitate from the hot solution melted at 316–318° uncor. and represented 42% of the expected yield, the second material which separated on cooling melted 280–282° uncor. and comprised 47% more. The total yield was thus 89%. The product obtained from the hot solution (or even that obtained when the solution was cooled in contact with the initial precipitate) appears to be the keto form; that which separated from the cold solution (after removal of the initial precipitate) appears to be an enol (see below).

Anal. Calcd. for $C_{10}H_6O_3N_2$: C, 59.4; H, 2.99; N. 13.9; neut. equiv., 202. Found: C, 59.6; H, 2.57; N, 14.1; neut. equiv., 200.

The material was soluble in hot water, cold dilute aqueous sodium carbonate, bicarbonate, or hydroxide, methanol, ethanol, acetone or ethyl acetate, but insoluble in ether. Its cold saturated aqueous solution gave with ferric chloride a deep purple color which on standing yielded a purple precipitate. It did not reduce ammoniacal silver nitrate.

This enolic form of melting point 280–282° uncor. dissolved when suspended in ether and treated with ethereal diazomethane. Evaporation of the solvent gave a white O-methyl ether which after recrystallization from hot methanol melted at 161–163° uncor. This was insoluble in hot dilute sodium carbonate but dissolved on warming with dilute sodium hydroxide. Its saturated aqueous solution gave no color with ferric chloride.

Anal. Calcd. for $C_{10}H_5O_2N_2OCH_3$: OCH_3, 14.4. Found: OCH_3, 14.4, 14.6.

The enolic form of m. p. 280–282° uncor. gave with acetic anhydride and alkali (as above) the same monoacetyl derivative as the keto variety, since a mixed melting point with that from the latter was not depressed.

Finally when the enol form was dissolved in alkali, refluxed a few minutes, cooled and acidified with hydrochloric acid, the product melted again at 315–316° uncor. and did not depress the melting point of an authentic sample of the keto form.

Thionaphthene Series

For the preparation of thionaphthene-2,3-dicarboxylic acid, thionaphthenequinone was converted to *o*-oxalophenylmercaptoacetic acid and the latter ring closed by boiling with aqueous alkali following previously reported methods.[11,12] Our over-all yield of 94% is somewhat better than the value of 75% previously reported.[12]

Thionaphthene-2,3-dicarboxylic Acid Cyclic Hydrazide (I, X = S)—A. From the Ester.—The ester (1.0 g. = 0.004 mole), dissolved in alcohol (6 ml.) and mixed with 43% hydrazine hydrate solution (1.5 g. = 0.013 mole) was placed in a heavy-walled Pyrex tube, a stopper wired on, and heated overnight at 100°. The hot tube was then about one-third filled with white needles and on cooling completely solidified. After dilution with 20 ml. of water, the solid was redissolved by warming, cooled and filtered. From the filtrate the product was obtained by acidification. The total weight of product was 0.85 g. corresponding to 98% of theoretical yield and melted at 360–361° uncor. without decomposition but after sintering about 350°.

Anal. Calcd. for $C_{10}H_6O_2NS$: C, 55.0; H, 2.77; N. 12.84; S, 14.7; neut. equiv. for mono-enol, 218; for di-enol 109. Found: C, 55.0, 54.8; H, 2.82, 2.73; N, 13.2, 12.4, 12.5; S, 14.2, 14.4; neut. equiv., 216.

This product is a white solid almost insoluble in hot or cold water, methanol, ethanol, acetone, ethyl acetate or benzene; but slightly soluble in hot glacial acetic acid and soluble in aqueous alkalies, carbonates or bicarbonates. It did not reduce ammoniacal silver nitrate, but gave with ferric chloride an orange coloration.

Acetyl Derivative.—A small sample (0.3 g.) of this hydrazide was dissolved in 40 ml. of 20% sodium hydroxide solution, cooled to 4°, and shaken with excess acetic anhydride below 10°. The resultant heavy white precipitate was filtered off, washed and dried; m. p. 195–196° uncor.

Anal. Calcd. for $C_{12}H_8O_3N_2S$ (monoacetyl): C, 55.3; H, 3.1; sap. equiv., 130.1. Found: C, 54.9, 55.2; H, 3.9, 3.4; sap. equiv., 131.8.

This monoacetate was insoluble in water, either cold or hot, in ether, or in benzene; it was somewhat soluble in ethanol, acetone or ethyl acetate; soluble in glacial acetic acid, dilute aqueous sodium hydroxide or carbonate. It gave no coloration with ferric chloride.

B. From the Anhydride.—Thionaphthene-2,3-dicarboxylic acid anhydride (0.3 g.) was warmed with 43% hydrazine hydrate until solution occurred, cooled, diluted with water (10 ml.), filtered from a little solid matter, and acidified with sulfuric acid. This acid solution was then boiled for a few minutes, cooled and filtered. The yield of cyclic hydrazide was 62% of theoretical and the product was identical in every respect with that prepared from the ester.

The sulfuric acid was found to be essential. If omitted a material precipitates which appears to be the hydrazine salt of an acyclic monohydrazide, since it reduces ammoniacal silver nitrate but is converted to the cyclic hydrazide by further boiling with acid.

C. From the Free Acid.—The acid (1.0 g. = 0.0045 mole) was dissolved in a solution of hydrazine sulfate (0.585 g. = 0.0036 mole) and crystallized sodium acetate (1.223 g. = 0.009 mole) in water (10 ml.) and the solution evaporated to dryness. The powdered solid was then baked at 160 ± 5° for two hours but since it was then still soluble in water was heated two hours more at 200 ± 5°. After addition of water the suspension was boiled and filtered hot. The brown precipitate was dissolved in dilute

---

(11) Bezdrik, Friedländer and Koeniger, *Ber.*, **41**, 227–42 (1908).

(12) Linstead, Noble and Wright, *J. Chem. Soc.*, 917 (1937).

sodium hydroxide solution, filtered and acidified, the resultant gelatinous precipitate changing to a flocculent one on boiling. The product melted at 358–359° uncor. after sintering about 348° and failed to depress the melting point of an authentic sample prepared from the ester. Owing to an accident part of the product was lost and the yield cannot be reported.

Indole Series

Indole-2,3-dicarboxylic Acid Cyclohydrazide (I, X = NH).—Dimethyl indole-2,3-dicarboxylate (1.0 g. = 0.0043 mole) dissolved in alcohol (6 ml.) and treated with 43% hydrazine hydrate solution (1.5 g. = 0.0129 mole) was heated overnight at 100° in a sealed tube. The mixture (which contained a precipitate of yellow needles) was cooled, diluted with water (20 ml.), treated with dilute sodium hydroxide and warmed until complete solution resulted. To this was added acetone (20 ml.) and an excess of concentrated hydrochloric acid. The resultant yellow precipitate was filtered off, washed and reprecipitated with hydrochloric acid from its solution in hot dilute ammonium hydroxide. The yield was 0.65 g. corresponding to 76%, and did not melt up to 360°.

Anal. Calcd. for $C_{10}H_7O_2N_3$: C, 59.7; H, 3.5; N, 20.9; neut. eq. (for mono-enol), 201.2. Found: C, 59.4, 59.8; H, 3.9, 5.1; N, 20.7, 20.7; neut. eq., 201.9.

The nearly white product was almost insoluble in hot or cold water, ethanol, ether, ethyl acetate, acetone, glacial acetic acid or benzene. It dissolved in dilute sodium hydroxide or in warm sodium carbonate or bicarbonate solution. It did not reduce ammoniacal silver nitrate but gave a deep red-orange color with ferric chloride.

Monoacetyl Derivative.—Indole-2,3-dicarboxylic acid cyclohydrazide (0.2 g.) dissolved in 10% sodium hydroxide (20 ml.) was cooled to 4° and shaken with excess acetic anhydride at this temperature. The resultant white precipitate was filtered off, washed and dried. It failed to show a definite melting point but gradually decomposed above about 270° with charring and gas evolution.

Anal. Calcd. for $C_{12}H_9O_3N_3$: C, 59.3; H, 3.7; sap. equiv. (for monoacetate), 121.6; (for diacetate), 243.2. Found: C, 59.2, 59.0; H, 3.9, 4.3; sap. equiv., 122.7.

Summary

1. The preparation of coumarone-2,3-dicarboxylic acid from coumarandione-2,3 has been developed to a one-step process giving ten times the yields previously reported.

2. The conversion of isatin to coumarandione-2,3 has been developed to give seven times the previously reported yields.

3. The hitherto unknown cyclohydrazides of coumarone-, thionaphthene- and indole-2,3-dicarboxylic acids, together with the corresponding monoacetates, have been prepared and characterized.

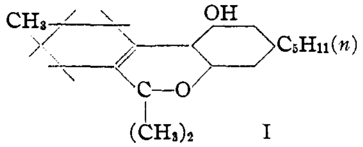
4. Two (presumably desmotropic) forms of coumarone-2,3-dicarboxylic acid cyclohydrazide have been isolated.

CAMBRIDGE, MASS. RECEIVED AUGUST 2, 1941

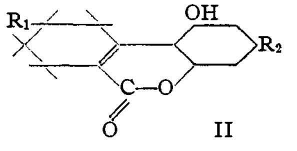
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Compounds of the Cannabinol Type. I. Synthesis of Some Compounds Related to Tetrahydrocannabinol[1]

T. H. BEMBRY AND G. POWELL



I



R_1 = H or CH_3
R_2 = Alkyl

II

A convenient method for the preparation of certain tetrahydrodibenzopyranes related to tetrahydrocannabinol (I) has been described.[2,3] It involves the use of the substituted tetrahydrobenzocoumarins of the type (II) as intermediates, which are accessible readily by the method of Sen and Basu.[4] As established by Adams and Baker,[2] the condensation of the cyclohexanone carboxylic esters with the 5-alkylresorcinols takes place between the two hydroxyl groups and the tetrahydrobenzocoumarins are unequivocally of constitution II. For inquiry into the relationship between marihuana activity and structure, since it has been demonstrated that the tetrahydrocannabinols possess marihuana activity first by Adams[5] and his associates and confirmed by other workers,[6,7] we have prepared a number of such

---

(1) A portion of a thesis by Thomas H. Bembry submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University.

(2) R. Adams and B. R. Baker, THIS JOURNAL, **62**, 2405 (1940).

(3) G. Powell and T. H. Bembry, *ibid.*, **62**, 2568 (1940).

(4) Sen and Basu, *J. Indian Chem. Soc.*, **5**, 467 (1928).

(5) Adams, Pease, Cain and Clark, THIS JOURNAL, **62**, 2402 (1940).

(6) Gosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).

(7) Powell, Salmon, Walton and Bembry, *Science*, **93**, 522 (1941).