[Contribution from the Cobb Chemical Laboratory, University of Virginia]

STRUCTURAL MODELS OF CORTIN COMPOUNDS IN THE NAPHTHALENE SERIES

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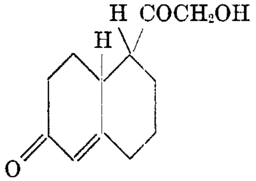
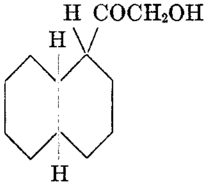
All of the potent crystalline compounds isolated from the adrenal cortex contain a ketol side chain, an α,β-unsaturated keto group, and a steroid nucleus. It is the purpose of the present investigation to synthesize a model compound in which a decahydronaphthalene skeleton will be substituted for the cyclopentanophenanthrene structure.

Attempts were made initially to prepare the octahydronaphthalene derivative I. As certain difficulties arose in the course of the synthesis, the decahydronaphthalene ketol II was synthesized in order to gain experience in handling the totally hydrogenated naphthalene nucleus.



I



II

As a starting material for compound I, it was desired to prepare 6-hydroxydecahydro-1-naphthoic acid. Two routes to this substance were examined. In one, 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) (1, 2) was hydrogenated to 1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV), and various methods were tried to convert the tetralol IV to the corresponding halide for a subsequent nitrile synthesis of 6-methoxy-1,2,3,4-tetrahydro-1-naphthoic acid. The method was abandoned after isolating 6-methoxy-3,4-dihydronaphthalene (V) from the reaction mixture resulting from the treatment of the tetralol with phosphorus tribromide or hydrobromic acid. This indicated the marked tendency for dehydration of this α-tetralol in the presence of halogenating agents. Also, using dry hydrogen chloride (3, 4), a product was obtained which could not be converted into the acid through the nitrile.

In the other route, hydrogenation of 6-hydroxy-1-naphthoic acid (IX)

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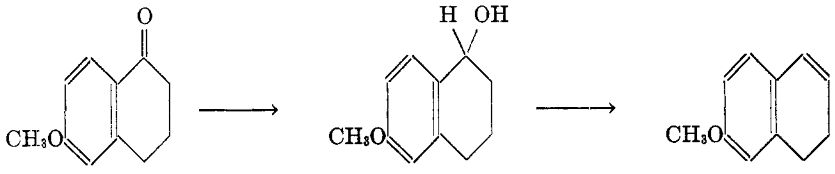
[1] Smith, Kline & French Research Fellow.

(5) was tried. 6-Methoxy-1-naphthoic acid[2] (VIII) was prepared by conversion of 6-methoxy-1-iodonaphthalene (VI) (7, 8, 9) to the nitrile VII with cuprous cyanide, followed by hydrolysis of the nitrile group with propanolic potassium hydroxide. The methoxyl group was hydrolyzed with a boiling hydrobromic acid-glacial acetic acid mixture.

Various conditions of hydrogenation were tested using platinum oxide (10) as a catalyst at atmospheric pressure. In all experiments in which the naphthalene nucleus was reduced completely, the hydroxyl group in position 6 was lost. The removal of the hydroxyl group during hydrogenation had not been anticipated for this compound because of the analogy to the hydrogenation under similar conditions of β-naphthol and 1-hydroxy-2-naphthoic acid to hydroxydecahydronaphthalenes by Hückel (11, 12). A possible explanation of this unexpected result may be the fact that in our case substituent groups are present in both rings of the naphthalene nucleus. The hydrogenation experiments included the use of various solvents, various amounts of reagents, and different reaction temperatures, as well as attempted protection of the hydroxyl group by acetylation and methylation. In a few reductions the effect of the esterification of the carboxyl group was tried, but the course of the hydrogenation could not be altered by this procedure.

As a result of these numerous hydrogenation experiments, an amount of decahydro-1-naphthoic acid (X) (13) accumulated which was sufficient for the synthesis of the ketol II. The diazo ketone XII was prepared by the Arndt-Eistert synthesis (14, 15), and the ketol was obtained from the diazo ketone by treatment with dilute sulfuric acid (16).

The physiological action of the ketol II has been tested by Professor S. W. Britton of the University of Virginia. The compound had no apparent toxic effects, but exhibited no influence on life maintenance and growth of adrenalectomized animals.



III IV V

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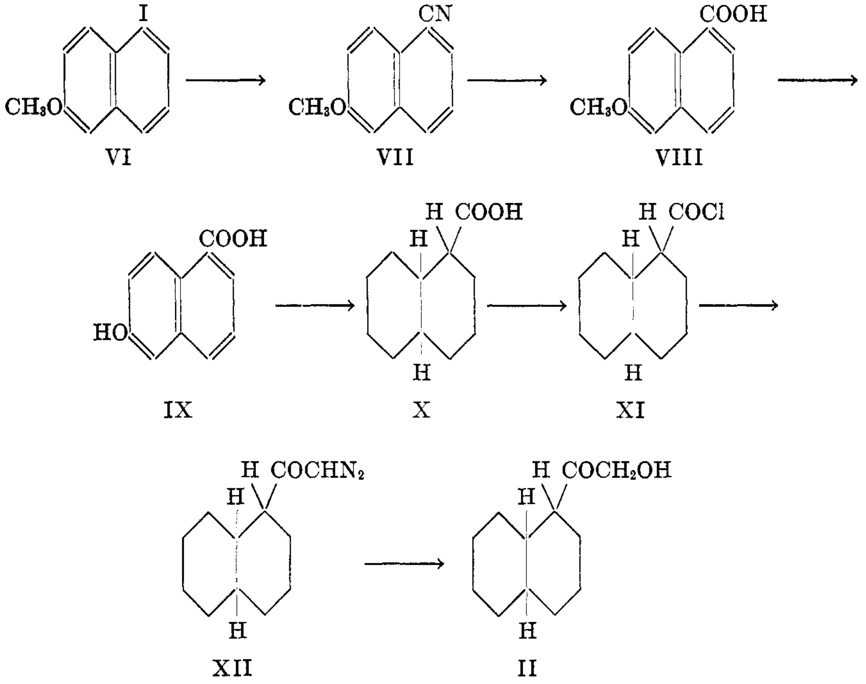
[2] Professor Henry Gilman of Iowa State College very kindly communicated to us the details of the preparation of this compound from furoic acid and anisole [*cf.* McCorkle and Turck (6)], but the method outlined in the text was adopted after comparative experimentation.



EXPERIMENTAL[3]

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV). A mixture of 5.0 g. of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) (1, 2), 100 cc. of 95% ethanol, and 0.1 g. of platinum oxide catalyst was shaken with hydrogen at atmospheric pressure and room temperature for ten hours. The catalyst was reactivated by shaking with air twice, and additions of 1 cc. of 0.1 *M* ferrous sulfate and 0.2 g. of platinum oxide catalyst were made during the course of the reduction. After absorption of 1.1 mole of hydrogen, the catalyst was filtered, the solvent was removed in vacuum, and the residual viscous, slightly yellow oil was fractionated at a pressure of 1 mm. The distillate was a clear, colorless oil, b.p. 109° (1 mm.). The yield was 4.9 g. (97%).

Anal. Calc'd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92.
Found: C, 73.87; H, 7.84.

The α-naphthylurethan was formed by heating the tetralol with an equivalent amount of α-naphthyl isocyanate on the water-bath for two minutes with exclusion of moisture. Extraction with ligroin and crystallization from the same solvent yielded colorless micro needles, m.p. 131–133°.

Anal. Calc'd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09.
Found: C, 76.42; H, 6.11.

6-Methoxy-3,4-dihydronaphthalene (V). To 1 g. of 1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV) placed in a 25 cc. Erlenmeyer flask with an elongated neck, cooled in an ice-water-bath, was added 9.2 cc. of 48% hydrobromic acid. The

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[3] Microanalyses by Mrs. Elizabeth Johnson Mathers.

flask was sealed at atmospheric pressure and placed on a shaking machine overnight. The reaction mixture was diluted with water, and the solid extracted with ether. The ether layer was washed with 5% sodium bicarbonate solution and water. After drying over anhydrous sodium sulfate, the ether was removed in a vacuum. The residual viscous, tan material was distilled at 1 mm. and crystallized from hexane. It melted at 70–73°; the yield was 0.35 g. (40%). For purification, crystallization from petroleum ether and sublimation in a high vacuum gave colorless shiny clusters, m.p. 73–74°.

Anal. Calc'd for $C_{11}H_{12}O$: C, 82.46; H, 7.55.
Found: C, 83.13; H, 7.86.

Since the possibility of the formation of 2-methoxynaphthalene (m.p. 72°) by dehydrogenation of our dihydro derivative could not be excluded, a mixture melting point of the two compounds was taken. A 20° depression was observed.[4]

In an attempted synthesis of 6-methoxy-1,2,3,4-tetrahydro-1-naphthoic acid, 2.9 g. of the tetralol IV was dissolved in 30 cc. of dry benzene, 1.5 g. of anhydrous calcium chloride was added (3, 4), and a rapid stream of dry hydrogen chloride was passed in at 0° for fifteen minutes. The red solution was filtered and allowed to evaporate. The oily residue, freed from hydrogen chloride, was treated with potassium cyanide, potassium iodide, and cupric sulfate at 0° according to the method of Ziegler and Hechelhammer (17). After standing overnight, the solution was boiled under reflux for five minutes, and poured into 45 cc. of 20% ethanolic potassium hydroxide solution. The mixture was boiled for 48 hours, and worked up in the customary way. Besides 0.3 g. of a resinous alkali-soluble material which could not be purified, the reaction product consisted largely of an alkali-insoluble oil which after distillation weighed 1.5 g. The colorless oil showed b.p. 107–108° (2 mm.), n_D^{25} 1.5080. It formed a low-melting red crystalline picrate which was not further investigated. The analysis agreed with the empirical formula $C_{14}H_{16}O$, but no compound which might be predicted from the reactions outlined could be fitted to these data.

Anal. Calc'd for $C_{14}H_{16}O$: C, 83.96; H, 8.05.
Found: C, 83.86; H, 8.07.

6-Methoxy-1-naphthonitrile (*VII*). Fifty grams of 1-iodo-6-methoxynaphthalene (VI) (7, 8, 9) was heated in a distilling flask with 20 g. of freshly prepared, dry cuprous cyanide at 220–230° for eight hours. The nitrile was distilled from the reaction mixture at 2 mm. pressure and purified by redistillation. The yield of crude material was 41 g. (82%), m.p. 78–79°.[5]

6-Methoxy-1-naphthoic acid (*VIII*). A hot solution of 15 g. of potassium hydroxide in 150 cc. of *n*-propanol was poured into a flask containing 9 g. of 6-methoxy-1-naphthonitrile (VII), and boiling under reflux was continued for forty-eight hours. After cooling, the solution was evaporated to dryness in a vacuum. The residue was dissolved in water, the aqueous solution was extracted with chloroform and ether, and the acid was liberated by acidification with concentrated hydrochloric acid, yielding 9.2 g. (93%) of crude product, m.p. 181–182°. Crystallization from 95% ethanol gave small colorless rods, m.p. 182–182.5° (6).

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[4] The preparation of 3,4-dihydro-6-methoxynaphthalene by a route similar to ours has been mentioned without experimental details by Salzer (18).

[5] Butenandt and Schramm (8) reported the preparation of the same compound, m.p. 79°, in 18% yield from 6-methoxy-1-naphthylamine hydrochloride by the Sandmeyer reaction.

Several experiments were made in an endeavor to obtain the maximum yield of the acid. The use of either ethanolic or isopropanolic potassium hydroxide gave approximately equal amounts of the acid and of *6-methoxy-1-naphthamide.* Crystallization of the amide from benzene yielded colorless rectangular prisms, m.p. 201–203°.

Anal. Calc'd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51.
Found: C, 71.98; H, 5.35.

6-Hydroxy-1-naphthoic acid (IX). A solution of 10 g. of crude 6-methoxy-1-naphthoic acid (VIII) in 150 cc. of 48% hydrobromic acid and 150 cc. of glacial acetic acid was boiled under reflux for five hours. The crystals which formed as the solution cooled to room temperature were collected and purified by crystallization from water with Norit. Almost colorless, thin rectangular prisms [8.4 g. (90%)] were obtained, which melted at 212.5–213° (5).

Ethyl-6-hydroxy-1-naphthoate was prepared by saturating an absolute ethanolic solution of 2 g. of the acid IX with dry hydrogen chloride, boiling under reflux for five hours, and working up the mixture in the usual manner. The crude product was crystallized from benzene and distilled at 1 mm., to yield 1.3 g. (57%) of colorless flat plates, m.p. 105–107°.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.20; H, 5.59.
Found: C, 71.92; H, 5.91.

Hydrogenation of 6-hydroxy-1-naphthoic acid (IX). A mixture of 1.0 g. of 6-hydroxy-1-naphthoic acid, 50 cc. of glacial acetic acid, and 1.0 g. of platinum oxide catalyst was shaken with hydrogen at atmospheric pressure and room temperature for five and one-half hours. The amount of hydrogen calculated for six moles was absorbed, the catalyst was filtered, the solvent removed in a vacuum, and the residual white waxy solid was dissolved in 20 cc. of 5% sodium bicarbonate solution. After filtration, the acid was precipitated by acidification with 10% hydrochloric acid. The yield of crude precipitate was 0.58 g. [55%, calculated as decahydro-1-naphthoic acid (X)]. Purification was accomplished by sublimation under 1 mm. pressure followed by crystallization from 95% ethanol, to yield colorless small rhomboids, m.p. 96–123°, which melted at 112–115° after resolidification. It is assumed that our decahydro acid consisted of a mixture of stereoisomers, and that partial interconversion took place during melting.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95.
Found: C, 72.64; H, 10.00.

Numerous hydrogenation experiments were completed in attempts to isolate 6-hydroxydecahydro-1-naphthoic acid from the reaction mixture. The temperature of hydrogenation, the amount and composition of the solvent, the amount of catalyst, and the starting material [including the use of ethyl 6-hydroxy-1-naphthoate and 6-acetoxy-1-naphthoic acid (5)] were varied without detecting in any reaction product the presence of an alcoholic hydroxyl group or its acetate.

1-(1'-Keto-2'-hydroxyethyl)decahydronaphthalene (II). Sixty-nine hundredths gram of decahydro-1-naphthoic acid (X) was added to an ice-cold solution of 1.5 cc. of thionyl chloride in 4 cc. of dry benzene to which 2 drops of dry pyridine had been added. After standing at room temperature for thirty minutes, the clear yellow solution was warmed to 40° for ten minutes. The benzene was evaporated under reduced pressure, 2 cc. of dry benzene added, and the solution again evaporated to dryness in vacuum. The residual acid chloride XI, a yellow oil, was dissolved in 16 cc. of dry benzene and added dropwise to an ice-cold solution of diazomethane in absolute ether (prepared from 4.5 cc. of N-nitroso-N-methylurethan using *n*-propanolic potassium hydroxide). After standing at room temperature for one hour, the solution was evaporated to dryness under reduced pressure, leaving a yellow crystalline residue of the diazo ketone XII. This method was patterned after that of Bachmann, Cole, and Wilds (15).

The diazo ketone was dissolved in 11 cc. of dioxane and 8 cc. of 2 *N* sulfuric acid was added (16). There was a slight evolution of gas. The solution was warmed to 40° for half an hour, when gas evolution appeared to have ended. Sixty cubic centimeters of water was added, and the emulsion was extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, and water, successively, dried over sodium sulfate, filtered, and the ether removed under reduced pressure. The residue crystallized in long, light yellow needles. After washing with absolute ether, and drying at 1 mm. over phosphorus pentoxide, the yellow crystalline ketol II melted at 83–84°; yield, 0.3 g. (40%). Sublimation at 1 mm. and 110° yielded thick colorless rectangular prisms, m.p. 82.5–83°.

Anal. Calc'd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27.
Found: C, 73.46; H, 10.56.

The ketol II, dissolved in methanol, reduced readily ammoniacal silver nitrate solution.

SUMMARY

A decahydronaphthalene derivative with a ketol side chain at position 1 has been synthesized as a simple model of the cortin series.

6-Methoxy-1-naphthoic acid was synthesized from 6-methoxy-1-iodonaphthalene by the nitrile synthesis in satisfactory yield.

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene has been prepared and the relative ease of its dehydration has been demonstrated.

The hydrogenation of 6-hydroxy-1-naphthoic acid with Adams' catalyst at room temperature and atmospheric pressure has been investigated, and the loss of the hydroxyl group under these conditions is reported.

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