the enzyme. This racemic acid does undergo resolution[20] when subjected to anilide formation in the presence of papain to give acetyl-L-phenylalanylglycine anilide. Evidently some stereospecific contact of the enzyme with the asymmetric region of benzoyl-DL-alanylglycine gives preference to the L-antipode. Such a differentiating contact with racemic *m*-(1-hydroxyethyl)aniline must be absent.

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LOS ANGELES 24, CALIF.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BRITISH COLUMBIA]

The Reaction of 2-Acetonaphthoxime with Carbon Monoxide and Hydrogen. A New Benzoquinoline Synthesis[1]

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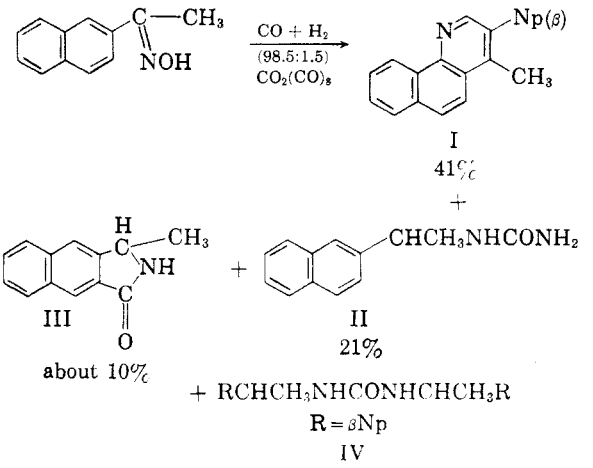
2-Acetonaphthoxime reacted with carbon monoxide and hydrogen at a pressure of about 4000 p.s.i. and at a temperature of about 220° in the presence of preformed dicobalt octacarbonyl as catalyst to yield 2-(β-naphthyl)-4-methylbenzo[h]quinoline, racemic 1-(β-naphthyl)ethylurea, and 3-methylbenzo[f]phthalimidine. Crystalline hydrochloride, methiodide, picrate and aldehyde derivatives of 2-(β-naphthyl)-4-methylbenzo[h]quinoline were obtained. The infrared and ultraviolet spectra of the aforementioned compounds are described.

This paper is concerned with an extension of our previous study[1,2] of the reaction of carbon monoxide with aromatic ketoximes. In particular, it deals with the reaction of 2-acetonaphthoxime with a mixture of carbon monoxide and hydrogen (98.5:1.5) at a pressure of about 4000 p.s.i. and at a temperature of about 220° in the presence of preformed dicobalt octacarbonyl as catalyst.

Whereas the expected cyclization reaction took place only to the extent of about 10% yielding product III, the main reaction was a condensation one resulting in the formation of 2-(β-naphthyl)-4-methylbenzo[h]quinoline(I) and racemic 1-(β-naphthyl)ethylurea(II).

Products I and II were easily isolated from the reaction mixture by fractional crystallization. 1-(β-naphthyl)ethylurea was slightly soluble in benzene or chloroform, whereas 2-(β-naphthyl)-4-methylbenzo[h]quinoline came down as the second product using ethanol as solvent. Direct chromatographic fractionation of the reaction mixture on alumina using benzene–petroleum ether as developer proved to be the best way to isolate product I (highly fluorescent) in pure form.



The empirical formula of compound I was $C_{24}H_{27}N$. Infrared analyses showed no NH stretching band. As compound I could not be reduced with magnesium in methanol it was assumed that the C=N—group must be part of an aromatic system. On the basis that compound I failed to react with maleic anhydride the linear benzoquinoline structure was eliminated.[3] A peak at 362 mμ in the ultraviolet spectrum of I suggested that the nucleus of

(1) Financial assistance by the National Research Council, Canada, and by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. Presented at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

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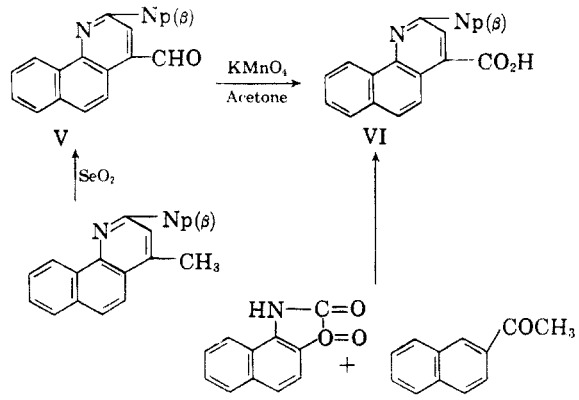
the compound contained the angular benzoquinoline structure.[3] Further support for the tentative assignment of a benzoquinoline nucleus was provided by the inertness of compound I towards prolonged heating with molten sodium hydroxide or with boiling concentrated hydrochloric acid. Selenium dioxide oxidation of I gave an aldehyde (V) indicating the presence of an active methyl group. Further controlled oxidation of the aldehyde with potassium permanganate in acetone at room temperature or with silver oxide in ethanol gave a carboxylic acid (VI) having a melting point of 248–250°. The reported[4] melting point of 2-(β-naphthyl)benzo[h]quinoline-4-carboxylic acid is 227–228°. As the melting point of compound VI was in question, although its solubility characteristics were similar to that of the reported carboxylic acid,[4] 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid, the latter compound was synthesized by the condensation of α-naphthisatin with 2-acetonaphthone.[4] Purification of the acid was achieved by the method of Robinson and Bogert.[5] This purified carboxylic acid had an identical melting point with that of compound VI. Furthermore, a mixed melting point of compound VI and the authentic sample showed no depression. Thus, compound I was proven to be 2-(β-naphthyl)-4-methylbenzo[h]quinoline and the aldehyde (V) must be 2-(β-naphthyl)-benzo[h]quinoline-4-carboxaldehyde.



It is possible that the discrepancy in the melting point exhibited by compound VI and that reported in the literature of 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid might have been due to the use of a different method of purification.

Reaction of 2-(β-naphthyl)-4-methylbenzo[h]quinoline with gaseous hydrogen chloride in ether gave a yellow salt having a green fluorescence. Conversion of the base into the salt caused a bathochromic shift of about 30 mμ in the ultraviolet spectrum. On being heated, the salt decomposed slowly at 90–100° reforming the parent base. Titration of the salt in alcohol with standard potassium hydroxide gave a molecular weight of 314.

A crystalline methiodide salt was formed by prolonged heating of the base (I) with methyl iodide at 100°. Addition of picric acid in ethanol to the base immediately yielded the picrate.

Compound II was proven to be racemic 1-(β-naphthyl)ethylurea by direct comparison with an authentic sample[6] prepared by the condensation of 1-(β-naphthyl)ethylamine with urea. It is interesting to note that four of the bands (3435, 3350, 3230, and 1648 cm.$^{-1}$) in the infrared spectrum of compound II are similar to those of a monosubstituted urea.[7,8]

After compounds I and II were separated from the reaction mixture, the remaining residue when chromatographed on alumina using benzene-*t*-butyl alcohol as developer yielded impure compounds III and IV. Subsequent rechromatographic purification of III and IV on alumina using benzene–ethyl acetate as developer essentially freed compound III of impurities but failed to give an analytically pure sample of IV. Fractional crystallization of IV was unsuccessful, giving very low yields of a compound having a wide melting range.

On the bases of chemical and infrared analyses[2,9] (NH stretching at 3310 and lactam at 1690 cm.$^{-1}$), fraction III was assumed to be 3-methylbenzo[f]phthalimidine. Elemental analyses gave an empirical formula consistent with structure III. Support for the formation of the linear rather than an angular benzo[h]phthalimidine was deduced from the work of Murahashi[10] who found that 2-naphthaldehyde anil cyclized under similar conditions to yield the linear isomer.

On the bases of chemical and infrared analyses bands [at 3300, 1625, 1596 (sh), 1578 (sh), and 1562 cm.$^{-1}$], we suggest that compound IV is probably *sym*-di-1-(β-naphthyl)ethylurea formed by the condensation of 1-(β-naphthyl)ethylurea. Such condensations which are readily brought about by heating monosubstituted ureas are well known in the literature.[11] The similarity of the infrared spectra of IV with that of *sym*-dibenzylurea (3337, 1625, 1591, and 1575 cm.$^{-1}$) supports our assignment of structure IV.

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EXPERIMENTAL[12]

The equipment used was previously described.[2]

Reaction of 2-acetonaphthoxime (cis-methyl) with carbon monoxide and hydrogen. Into the glass liner contained in the high pressure bomb was introduced 100 ml. of thiophene-free anhydrous benzene, 2-acetonaphthoxime (15 g., 0.08 mole), and dicobalt octacarbonyl (10 g., 0.03 mole). The reactor was then closed and connected to a high pressure source (2140 p.s.i.) of mixed gas consisting of 98.5% carbon monoxide and 1.5% hydrogen. The bomb was rocked and heated at 210–235° for 50 min. After the vessel was cooled the pressure was 1950 p.s.i. Subsequent decomposition of the dicobalt octacarbonyl at 70–80° was followed by removal of the benzene under reduced pressure. Extraction of the residual wax with hot chloroform (Norit) gave a green solution which, upon evaporation, gave a brown wax; yield, 13.8 g. Crystallization of the wax from 100 ml. of chloroform at −15° for 1 day yielded product II (1.1 g., 8%) of white crystalline material having a melting point range of 170–205°. Essentially the same material could be obtained by partial crystallization of the product from benzene. Evaporation of the solvent left a residue which could be crystallized from ethanol yielding I.

A portion of the above residue (7.8 g.) was dissolved in 15 ml. of benzene and added to the top of a glass column containing a 150 × 70 mm. (diam.) adsorbent column of alumina. The following mixtures of developer were then added consecutively with the results as indicated. (1) 80 ml. of benzene–petroleum ether (b.p. 30–60°) (1:1/V:V) gave 0.16 g. of a sirup (showed no carbonyl in the infrared and did not fluoresce). (2) 700 ml. of the above developer yielded 3.15 g. (41%) of fluorescent I. (3) 500 ml. of same developer eluted a second fluorescent zone (0.23 g.). (4) 1000 ml. of benzene eluted 0.14 g. of nonfluorescent material. (5) 1750 ml. of benzene-*t*-butyl alcohol (98:2) eluted 2.30 g. of a mixture of III and IV. (6) 350 ml. of benzene-*t*-butyl alcohol (98:2) yielded 0.23 g. of III (compounds III and IV were difficult to separate with benzene-alcohol). (7) 450 ml. of benzene-ethanol (1:1) eluted 1.02 g. (13%) of material which was proved to be identical to compound II.

Compounds III and IV were rechromatographed on alumina using benzene–ethyl acetate (1:1) as developer. Compound IV had a faster rate of elution than compound III.

Characterization of fractions. Fraction I: *2-(β-naphthyl)-4-methylbenzo[h]quinoline.* Two recrystallizations of compound I from ethanol gave white needles, m.p. 123–124°.

Anal. Calcd. for $C_{24}H_{17}N$: C, 90.26; H, 5.33; N, 4.39; mol. wt., 319. Found: C, 90.07; H, 5.37; N, 4.48; mol. wt. (Rast), 288.

Infrared spectrum of I (potassium bromide): 3070(W), 2940(W), 2860(W), 1621(W), 1595(S), 1556(W), 1520(W), 1460(M), 1388(W), 1245(W), 1198(W), 829(S), 801(S), 763(S).

Ultraviolet spectrum of I in 95% ethanol showed maxima at 362, 345, 322, 315, 287, 276, 243, 312 mμ (log ε = 4.14, 4.16, 4.36, 4.31, 4.30, 4.50, 4.60, and 4.44, respectively).

Sodium hydroxide fusion for 6 hr. or prolonged hydrolysis of compound I with boiling concd. hydrochloric acid gave unchanged material. An attempted reduction of I with magnesium in methanol according to the procedure of Zechmeister and Truka[13] gave unchanged starting material.

Compound I did not react with maleic anhydride when heated according to the method of Johnson and Mathews.[3]

Oxidation of compound I with acidic permanganate completely degraded it. Oxidation with potassium dichromate in glacial acetic acid,[3] or with chromic acid–acetic acid–sulfuric acid,[14] gave a quinone in low yield which polymerized in the presence of air. Further oxidation of the isolated quinone with chromic acid or permanganate[3] completely degraded it.

2-(β-Naphthyl)-4-methylbenzo[h]quinoline hydrochloride. Hydrogen chloride was bubbled through a solution of 2-(β-naphthyl)-4-methylbenzo[h]quinoline in ether and the greenish yellow precipitated hydrochloride was recovered by filtration, followed by drying over potassium hydroxide pellets under vacuum; m.p. 90–100° with decomposition to yield the original compound.

Anal. Calcd. for $C_{24}H_{17}N \cdot HCl$; mol. wt., 340. Found: 341 (by titration with standard potassium hydroxide in ethanol using phenolphthalein as indicator.

Ultraviolet spectrum of the hydrochloride in 95% ethanol showed maxima at 392, 366, 346, 316, and 287 mμ (log ε = 4.23, 4.14, 4.04, 4.47, and 4.49, respectively).

Reaction of 2-(β-naphthyl)-4-methylbenzo[h]quinoline with methyl iodide to yield the methiodide salt. An amount of 0.083 g. of 2-(β-naphthyl)-4-methylbenzo[h]quinoline in 3 ml. of methyl iodide was heated in a sealed tube at 100° for 170 hr. The product was washed with diethyl ether; m.p. 182–186°.

Anal. Calcd. for $C_{25}H_{20}NI$: I, 27.6%. Found: I, 30.3%.

Reaction of 2-(β-naphthyl)-4-methylbenzo[h]quinoline with picric acid to yield the picrate. The picrate was prepared according to a usual procedure[15] and recrystallized from ethanol, m.p. 233–236°.

Anal. Calcd. for $C_{30}H_{20}N_4O_7$: N, 10.22. Found: N, 9.99.

2-(β-Naphthyl)-benzo[h] quinoline-4-carboxaldehyde (V). Oxidation of 2-(β-naphthyl)-4-methylbenzo[h]quinoline (0.25 g.) with selenium dioxide (0.09 g.) at 180–200° for 15 min.; according to the method of Burger and co-workers[16] gave thei mpure aldehyde. Pure crystalline 2-(β-naphthyl)-benzo[h]quinoline-4-carboxaldehyde was obtained by chromatographic fractionation of the ether extract (residue) of the product on alumina (150 × 35 mm. diam.) using benzene–petroleum ether (b.p. 30–60°) (1:3/V) as developer. The first 300 ml. of developer eluted the original unoxidized compound, whereas the next 1200 ml. gave a trace of unidentified material. A further 2000 ml. of the same developer yielded 0.05 g. of bright yellow crystals which were recrystallized from ligroin; m.p. 140–142°.

Anal. Calcd. for $C_{24}H_{15}NO$: C, 86.46; H, 4.54; N, 4.20; O, 4.80. Found: C, 86.26; H, 4.68; N, 4.18; O, 4.70.

Infrared spectrum (potassium bromide): 2940(S), 2870(M), 1700(S), 1685(W), 1655(W), 1647(W), 1585(W), 1560(W), 1547(W), 1525(W), 1510(W), 1460(W), 1365(W), 1325(W), 1212(W), 1197(W), 1157(W), 1135(W), 1122(W), 1090(W), 1025(W), 928(W), 883(M), 852(M), 827(W), 815(M), 798(W), 745(S), 712(W), 707(W).

The aldehyde gave a positive Tollen's and negative Fehling's test. Treatment of the aldehyde with hydroxylamine hydrochloride gave a crystalline oxime, m.p. 170–185°, without recrystallization.

2-(β-Naphthyl)-benzo[h]quinoline-4-carboxylic acid (VI). A solution of 2-(β-naphthyl)benzo[h]quinoline-4-carboxaldehyde in acetone was oxidized with potassium permanganate in acetone at 30° for 15 min. After the mixture was filtered, the acetone was removed by evaporation. Extraction of the residue with hot aqueous 2*N* potassium hydroxide was followed by acidification of the filtrate (Norit) with glacial acetic acid. The product was further purified by the method of Robinson and Bogert[5]; m.p. 248–250°. Oxidation of the aldehyde (V) with silver oxide according to the procedure of Burger and Modlin[16] also gave the carboxylic acid (VI). An

(12) All melting points were obtained on a Leitz heating stage and are corrected. The infrared analyses were done on a Perkin-Elmer spectrophotometer, Model 21, using a sodium chloride crystal. Microanalyses were done by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, im Max-Planck Institut fur Kohlenforschung, Mülheim (Ruhr), Germany.

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authentic sample of 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid was prepared by the condensation of α-naphthisatin with 2-acetonaphthone[4] and purified by the aforementioned method[5]; m.p. 248–250°; mixed m.p. of the authentic sample with compound VI 248–250°.

Fraction II: *racemic 1-(β-naphthyl)ethylurea.* Fraction II was thrice recrystallized from 3-pentanone, m.p. 198–200°; mixed m.p. with an authentic sample of racemic 1-(β-naphthyl)ethylurea, 198–200° (lit.,[6] m.p. 196–198°).

Infrared spectrum of II (potassium bromide): 3435(S), 3350(S), 3230(M), 3070(W), 2990(W), 2930(W), 1681(W), 1648(S), 1618(W), 1460(W), 1384(M), 1341(W), 1330(W), 1301(W), 1276(W), 1252(W), 1182(M), 1145(M), 1128(M), 1055(W), 1019(W), 968(W), 954(W), 909(W), 896(W), 878(W), 860(W), 825(S), 775(W), 750(S), 662(M).

The infrared spectrum of authentic 1-(β-naphthyl)ethylurea was identical with that of compound II.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08; O, 7.47. Found: C, 72.56; H, 6.62; N, 13.12; O, 7.81.

Fraction III: *3-methylbenzo[f]phthalimidine.* Fraction III was recrystallized from benzene-ethanol and from chloroform; m.p. 236–240°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 78.80; H, 5.65; N, 7.10. Found: C, 78.90; H, 6.23; N, 6.97.

Infrared spectrum of III(potassium bromide): 3310(W), 3050(W), 3005(W), 2960(W), 2905(W), 1708(M), 1690(S), 1598(W), 1550(W), 1535(W), 1505(W), 1455(W), 1378(W), 1345(W), 1273(W), 1216(S), 1127(W), 1016(W), 950(W), 887(W), 855(W), 817(M), 752(S), 663(W).

Fraction IV: *sym-di-1-(β-naphthyl)ethylurea.* Fraction IV was recrystallized from ethanol; m.p. 226–230°. Further purification by chromatography on alumina using benzene–ethyl acetate (1:1) as developer gave a pure compound, m.p. 229–231°.

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.51; H, 6.57; N, 7.61; mol. wt., 368. Found: C, 81.61; H, 6.89; N, 7.52; mol. wt. (Rast) 394.

Infrared spectrum of IV (potassium bromide); 3300(S), 3035(W), 2955(M), 1625(S), 1596(sh), 1578(sh), 1562(S), 1504(W), 1450(W), 1373(S), 1325(M), 1291(W), 1272(W), 1236(S).

VANCOUVER 8, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Psoralenes. III. Cyclization Studies of Certain Substituted Coumarins and Coumarans[1]

ROBERT C. ESSE AND BERT E. CHRISTENSEN

Received December 14, 1959

The synthesis of a series of new 5,6-dialkyl-2,3-dihydropsoralenes is described along with the dehydrogenation of these derivatives to the corresponding psoralenes. A compound which may be the 6-coumaranyl ester of 2,3-dihydro-5-carboxypsoralene was prepared. This compound was dehydrogenated and also converted to the free acid. The free acid was also synthesized directly by a Pechmann type reaction. This acid was simultaneously decarboxylated and dehydrogenated to psoralene. An isomer of xanthotoxin, 5-methoxypsoralene, was prepared from the corresponding 2,3-dihydro derivative. 5-Acetoxypsoralene was prepared; this compound was stable toward dehydrogenation in contrast to 5-hydroxypsoralene which has been reported to decompose under dehydrogenation operations. The synthesis of a number of coumarin derivatives which might serve as intermediates for the preparation of psoralenes was accomplished. Extensive attempts to cyclize two of these intermediates, 7-(2-oxoethoxy)-4-methylcoumarin and 7-(2-bromoethoxy)-4-methylcoumarin, were unsuccessful. In several of the cyclization experiments where a pure product was isolated it was found that ether cleavage to 4-methylumbelliferone rather than ring closure had taken place.

In recent years the furocoumarin xanthotoxin has received considerable attention, both in the scientific literature[2] and the popular press. As xanthotoxin (9-methoxypsoralene) is obtained from natural sources and the number of known psoralenes are limited, it was worthwhile to investigate the procedures for the synthesis of these potential drugs as well as to prepare a number of new psoralenes for research purposes.

The starting material for the synthesis of psoralene compounds is resorcinol or its 2- or 5-substituted derivative. Two routes are available either (1) *via* conversion to 6-hydroxycoumaran, I (2,3-dihydro-6-hydroxybenzofuran) or (2) by way of 7-hydroxycoumarin, II (umbelliferone) (see Fig. 1).

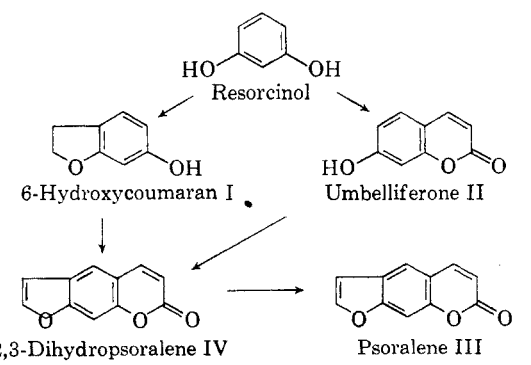

Fig. 1. Synthesis of psoralene from resorcinol

(1) This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 381, School of Science, Department of Chemistry.

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