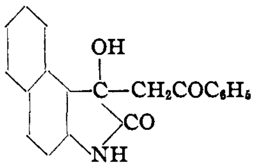
[CONTRIBUTION FROM NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

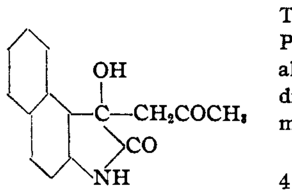
Synthesis of Certain Beta-Naphthoxindole Derivatives

BY EDWARD ZRIKE AND H. G. LINDWALL

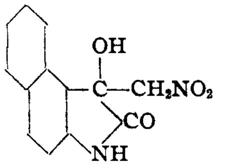
The condensation reactions of beta-naphthisatin with certain active methylene compounds have been studied for purposes of correlation with those of isatin. Acetophenone, acetone and nitromethane, when condensed with beta-naphthisatin by the Knoevenagel[1] method, yield, respectively, 3-hydroxy-3-phenacyl-beta-naphthoxindole (I), 3-hydroxy-3-acetonyl-beta-naphthoxindole (II), and 3-hydroxy-3-(nitromethyl)-beta-naphthoxindole (III).



I



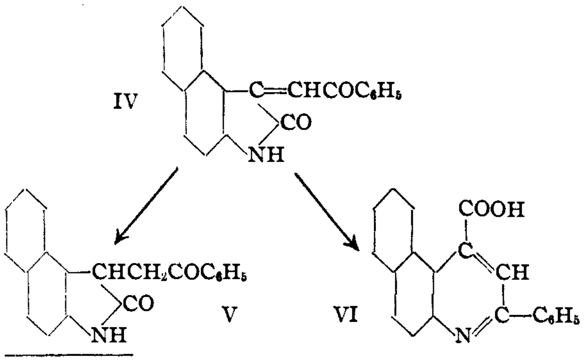
II



III

Compounds I, II and III have typical aldol characteristics, tending to dissociate in solution under the influence of heat into their original components. They behave like the oxindole analog of I[2] in this respect.

When I is warmed with hydrochloric acid, 3-phenacylidene-beta-naphthoxindole (IV) results, which can be reduced to yield 3-phenacyl-beta-naphthoxindole (V). Treatment of IV with hot hydrochloric acid yields beta-naphthcinchophen (VI). This behavior of IV is analogous to that of 3-phenacylideneoxindole.[3] The identity of VI with beta-naphthcinchophen, prepared by the Pfitzinger[4] and Döbner[5] methods, was shown by melting point methods.



Experimental Part

3-Hydroxy-3-phenacyl-beta-naphthoxindole (I).—A mixture of 1 g. of beta-naphthisatin, 0.7 g. of acetophenone, and 3 drops of diethylamine in 25 cc. of alcohol was allowed to stand for twenty-four hours at room temperature. The product which separated was in a good state of purity. Purification beyond washing of the crystals with ether and alcohol was not practicable because of the tendency for dissociation in hot solvent; yield, 75%; colorless crystals; m. p. 179–180°.

Anal. Calcd. for $C_{20}H_{15}NO_3$: C, 75.68; H, 4.77; N, 4.41. Found: C, 75.53; H, 4.14; N, 4.36.

3-Phenacylidene-beta-naphthoxindole (IV).—Compound I and a solution of 0.5 cc. of concd. hydrochloric acid in 10 cc. of glacial acetic acid were warmed until the solid dissolved and the solution was red. IV separated upon cooling as fine orange-red needles; m. p. 224–226° after recrystallization from alcohol; soluble in acetone, glacial acetic acid, and alcohol; yield, 64%.

Anal. Calcd. for $C_{20}H_{13}NO_2$: N, 4.68. Found: N, 4.59.

Beta-Naphthcinchophen (VI) from IV.—A mixture of 0.1 g. of IV, 10 cc. of concd. hydrochloric acid and 3 cc. of alcohol was refluxed until the solid had dissolved. The solution was then evaporated to crystallization and the product was recrystallized from alcohol as small pale yellow needles; m. p. 296°; yield, 70%. The product was identified by its melting point mixed with a known sample.

3-Phenacyl-beta-naphthoxindole (V).—Compound IV (0.5 g.) was reduced by treatment on a steam-bath with 1 g. of sodium hyposulfite in 10 cc. of water and 2 cc. of alcohol. When reduction was complete the solution was cooled and the product recrystallized from ethyl alcohol as colorless crystals; m. p. 233–235°; soluble in alcohol and acetone; yield 80%.

Anal. Calcd. for $C_{20}H_{15}NO_2$: N, 4.65. Found: N, 4.53.

3-Acetonyl-3-hydroxy-beta-naphthoxindole (II).—Beta-naphthisatin (3 g.), 15 g. of acetone and 0.5 g. of diethylamine were allowed to stand at room temperature for twenty-four hours. The product was recrystallized from acetone; higher boiling solvents tend to decompose it; yield, 75%; white plates; m. p. 204–205°, with darkening at about 170°.

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(1) Knoevenagel, *Ann.*, **281**, 25 (1894); **288**, 321 (1895); *Ber.*, **31**, 2585 (1898); **37**, 4464 (1904).

(2) Lindwall and Maclennan, THIS JOURNAL, **54**, 4739 (1932).

(3) DuPuis and Lindwall, *ibid.*, **56**, 471 (1934).

(4) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 583 (1888); **56**, 283 (1897).

(5) Döbner, *Ber.*, **20**, 277 (1887).

Anal. Calcd. for $C_{15}H_{13}NO_3$: N, 5.49. Found: N, 5.38.

Oxime of II.—This was prepared in the usual way; yield 80%; colorless needles, m. p. 241–242°, crystallized from alcohol.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: N, 10.37. Found: N, 10.21.

3-Hydroxy-3-(nitromethyl)-beta-naphthoxindole (III).—A mixture, cooled in ice, was made of 1.0 g. of beta-naphthisatin, 0.35 g. of nitromethane, 3 drops of diethylamine, and 10 cc. of absolute ethyl alcohol. After twenty-four hours at room temperature white needles separated, which were purified by precipitation from acetone by slow addition of ligroin. III is unstable toward heat in solution, making purification by recrystallization difficult; yield, crude, 84%; m. p. 246–248°, with decomposition.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: N, 10.85. Found: N, 10.76.

Summary

Beta-naphthisatin reacts with acetone, acetophenone, and nitromethane to yield the corresponding aldol-like condensation products. The acetophenone product is dehydrated in the normal manner by treatment with mineral acid; further acid treatment causes the formation of beta-naphthcinchophen.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Isomeric α-Cyano-α-methyl-β-phenylglutaric Acids and their Derivatives

BY S. AVERY AND FRANK C. McGREW

In the course of an investigation of substituted glutaric acids in general, with the aim of studying stereoisomerism in these and related compounds, Avery and Fossler[1] prepared α-methyl-β-phenylglutaric acid by Michael's reaction, linking methyl α-methylcinnamate with ethyl malonate in the presence of sodium ethoxide, subsequently saponifying, and decarboxylating the acid thus formed. The method, however, was unsatisfactory in that little of the pure product was obtained.

Carter and Lawrence[2] prepared this acid by a similar condensation using ethyl cinnamate and ethyl cyanoacetate, with subsequent methylation, hydrolysis and decarboxylation. Certain of the intermediate compounds were isolated and structures assigned to them; the isomerism noted was explained partly on stereochemical and partly on other structural grounds.

The present authors, in elaboration of the work of Carter and Lawrence, began with the same condensation. The product consisted of the two stereomeric esters, the initial substances which afford by hydrolysis under various conditions, two series of compounds, each member of which was found similar in constitution to the parallel substance of the other series, the only differences being those physical properties affected by different spatial configurations. In this communication the terms A and B series will be used instead of the α and β of Carter and Lawrence to avoid misunderstanding of the significance of the Greek letters. The conventional *trans* and *cis* terms are not used, since in the present work most of the spatial differences are not analogous to the type of isomerism exhibited by unsaturated compounds.

The A acid, prepared from the solid ethyl α-cyano-α-methyl-β-phenylglutarate by hydrolysis in absolute alcohol solution with potassium hydroxide, on treatment with acetyl chloride forms a compound melting at 111° which was shown by analysis to be not an acetylated imide, as supposed by Carter and Lawrence, but the anhydride of a dicarboxylic acid, stereomeric with the anhydride of the corresponding B cyano acid. From this fact and from the easy conversion of the A acid into the original 90° melting ester by esterification, it is established that the A acid is stereomeric with the B acid and has not the cyclic structure previously advanced.

The A and B cyano acids were subjected to resolution into their optically active enantiomorphs by fractional crystallization of the brucine salts. The A acid gave two isomers of melting point 185–187° (dec.) and $[\alpha]_D$ +7.4° and $[\alpha]_D$ −7.5°. The B acid was resolved into two isomers of melting point 164–165° (dec.) and $[\alpha]_D$ +32.4° and $[\alpha]_D$ −32.1°.

Efforts to prepare the tricarboxylic acid of Carter and Lawrence by alkaline hydrolysis gave only a tricarboxylic acid melting approximately at 188°, depending on the rate of heating,

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[1] Avery and Fossler, *Am. Chem. J.*, **20**, 516 (1898).

[2] Carter and Lawrence, *Proc. Chem. Soc.*, **16**, 178 (1900).