of labilizing groups will possess the same degree of reactivity. This is demonstrated by the quantitative reaction of ethyl phenylacetate and ethyl malonate as compared to the lack of reactivity of dibenzoylmethane under similar conditions and by the fact (*cf.* the first column of Table I) that ethyl malonate reacts quantitatively with piperidine as a catalyst while ethyl phenylacetate does not react.

Comparison of Enolization with Reactivity.—The reactivity of a compound in the Michael condensation may be considered as a criterion of the activity of the methylene group involved. Still another method of classifying such groups may be in the order of enolization of the compounds. It therefore was of interest to ascertain whether or not the reactivity of active methylene groups as measured by these two methods bore any relationship. For this particular study it would have been more desirable to compare the reactivity in the Michael condensation with the amount of enolization under the conditions of the experiment. However, since there was no satisfactory way of ascertaining the latter value, the reactivity of the methylene compound as indicated by its tendency to enolize in the pure state seemed to be the next best basis for comparison.

The data in Table I indicate that there is no such relationship between these two methods of measuring the reactivities. This is shown by the fact that there is such a wide difference in reactivity among the first eight compounds listed, although they can differ only minutely in their tendency to enolize. Furthermore, ethyl acetoacetate is enolized to a greater extent than ethyl α-ethylacetoacetate and less than dibenzoylmethane but is more reactive than either of these compounds.

Summary

A study of the addition of various compounds containing an active methylene group to benzalacetophenone has indicated that no conclusion concerning the reactivity of the addendum may be drawn from the number of activating groups upon the carbon of the active methylene or from the amount of enolization. In any given structure, however, the reactivity is decreased by the introduction of substituents and the influence of methyl is much less than that of the higher alkyl groups.

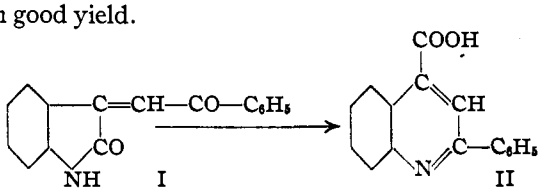
Ithaca, New York Received September 17, 1934

[Contribution from the Nichols Laboratory of New York University]

A Synthesis of 1,4-Dihydrocinchophens from 3-Phenacyloxindoles[1]

By R. N. DuPuis and H. G. Lindwall

It has been shown[2] that 3-phenacylideneoxindole (I) upon treatment with hydrochloric acid gives 2-phenylcinchoninic acid (cinchophen) (II) in good yield.



This reaction does not take place, evidently, when alkali is substituted for acid; an apparent mixture of products results and no recognizable amount of cinchophen is obtained.[3]

When 3-phenacyloxindole (III) (Chart I) is employed with hydrochloric acid as the reagent, a good yield of a (IV) chlorine-containing compound is obtained. By analogy to the case of 3-phenacylideneoxindole, and on the basis of its chemical behavior, the product was suspected of being a quinoline hydrochloride, and indeed it yielded a free base (V) upon treatment with alkali in the cold.

If the analogy to the case of the behavior of 3-phenacylideneoxindole is carried on to the extent of attempting to formulate a mechanism, such a sequence as that shown in Chart I may ensue.

It will be noted that an intermediate (not isolated) is indicated on the chart, having an hydroxyl at position 2 of the quinoline ring. Dimroth and Zoeppritz[4] were able to isolate such hydroxy derivatives in the course of the formation of a number of Schiff bases.

(1) Presented in part at the Cleveland meeting of the American Chemical Society, September, 1934.

(2) DuPuis and Lindwall, This Journal, **56**, 471 (1934).

(3) Lindwall and Maclennan, *ibid.*, **54**, 4739 (1932).

(4) Dimroth and Zoeppritz, *Ber.*, **35**, 984 (1902).

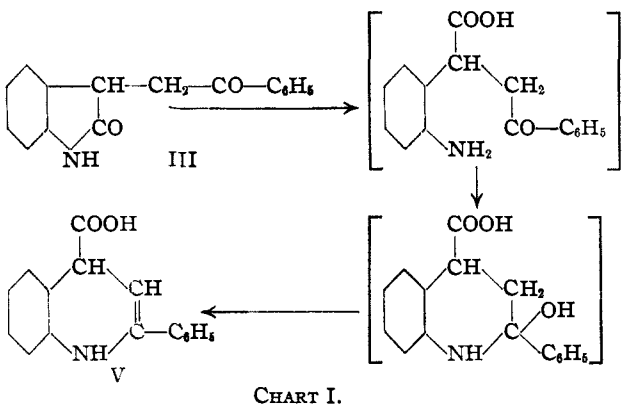
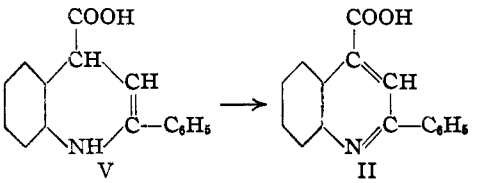


CHART I.

Other possible mechanisms would be enolization of the keto group with subsequent splitting out of water through reaction with the aryl amino group after ring opening, or direct condensation of the amino group with the keto followed by a bond shift to give 2,3 unsaturation.

Compound V is postulated as a dihydrocinchophen, more particularly as 1,4-dihydro-2-phenylquinoline-4-acid. That V is a quinoline derivative is shown most decisively by the action of certain oxidizing agents, especially nitrobenzene, upon it. When V is heated with nitrobenzene, cinchophen (II) is obtained



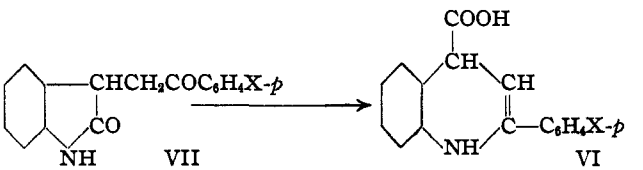
Cinchophen is also obtained, though in smaller yield, when V is heated with glacial acetic acid. Certain other media also seem to favor this oxidative effect, for example, if alcohol is present with the hydrochloric acid in the course of the hydrolytic rearrangement of the 3-phenacyloxindole, a quantity of cinchophen is obtained among the products. Compound V evidently has the quinoline ring as its essential structure.

Referring to structure V and the mechanism suggested for its formation, Chart I, there seems no logical reason for questioning the location of the hydrogen on the 4-position. To assume its presence elsewhere in the molecule would be to assume a shift of the hydrogen from the carbon on which it was originally present. In the formulation a secondary amino group is postulated. Compound V forms a hydrochloride and a sulfate, differing from cinchophen (with its tertiary nitrogen) in that respect; cinchophen may be crystallized from hydrochloric acid without reaction. Application of the Grignard reagent for the detection and determination of "active" hydrogens indicates that *two* hydrogens are reactive, the hydrogen of the carboxyl and the hydrogen of the nitrogen.

Notwithstanding this evident secondary nitrogen, attempts to acetylate, benzoylate or alkylate thus far have been fruitless. In the attempts made, tarry materials resulted, from which no single product could be isolated. In general the properties of compound V may be summarized as follows: a silver salt and a sodium salt have been prepared; their analyses agree with the postulated structure. The molecular weight shows the compound to be a monomer. It is slightly sensitive to light, becoming brown slowly upon exposure to sunlight. It is quite stable toward dry heat; it may be held at 80° for several days without change, although it is rather easily oxidized to the corresponding quinoline when heated in contact with certain wet agents already cited.

Attempts to reduce 1,4-dihydro-2-phenylcinchoninic acid to the tetrahydro-2-phenylcinchoninic acid of Skita and Brunner[5] using metals and acids or sodium and amyl alcohol have been without result. The catalytic reduction method used by Skita and Brunner for the production of their compound from cinchophen has not yet been tried.

To test the generality of the method for the formation of 1,4-dihydro 2-substituted cinchoninic acids (VI) from the corresponding 3-phenacyloxindoles, three 4′ substituted (VII) 3-phenacyloxindoles were subjected to treatment with hydrochloric acid.



In this manner the 4′-methyl, chloro and bromo analogs were prepared. A direct parallel to the case of the unsubstituted 1,4-dihydro-2-phenylquinoline-4-acid was found in each instance. Each of the dihydroquinoline derivatives formed was oxidized to the corresponding quinoline upon being heated with nitrobenzene. These products seem to be more susceptible to oxidation than is compound V.

(5) Skita and Brunner, *Ber.*, **49**, 1597 (1916).

Extending the study to an attempt to prepare 3-amino substituted dihydrocinchoninic acids by the same method, 3-(α-benzoylamino)-phenacyloxindole (VIII) (Chart II) was prepared. Benzoylphenacylamine, prepared according to Rupe,[6] was condensed with isatin under Knoevenagel[7] conditions and yielded 3-hydroxy-3-(α-benzoylamino)-phenacyloxindole (IX). Compound IX upon treatment with alcoholic hydrogen chloride gave 3-(α-benzoylamino)-phenacylideneoxindole (X). Compound X can also be obtained through the direct condensation of benzoylphenacylamine and isatin in the presence of piperidine, although the yield is not good. Reduction of X using zinc dust and acetic acid gives (VIII) 3-(α-benzoylamino)-phenacyloxindole.

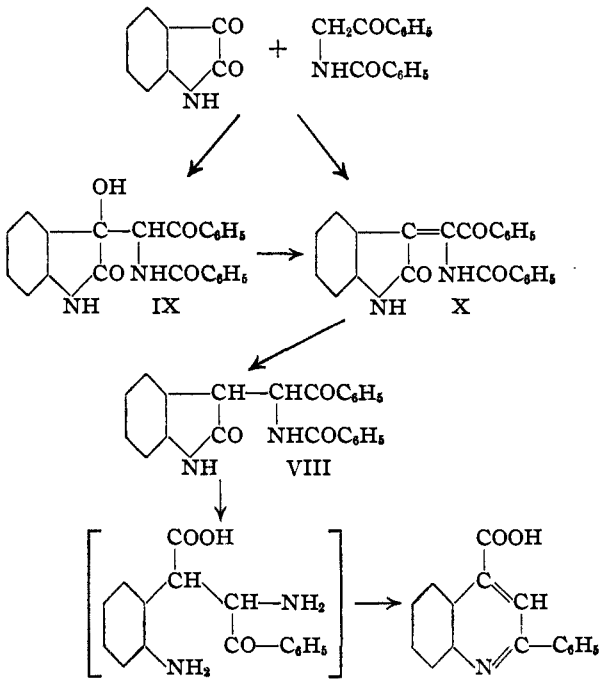


Chart II.

The actions of various hydrolytic agents upon compound VIII were studied. Alkaline agents produced no definite compounds. When mineral acid, especially hydrochloric acid, was used the action was definite; the product was 2-phenylcinchoninic acid (cinchophen) (Chart II). The production of cinchophen was surprising; its formation requires deaminization as one step of the reaction. No study has been made of the mechanism, but the reaction is probably, in its essentials, like the formation of cinchophen from the simpler 3-phenacylideneoxindole. The work is being continued.

(6) Rupe. *Ber.*, **28**, 254 (1895).

(7) Knoevenagel, *Ann.*, **281**, 25 (1894); **288**, 321 (1895); *Ber.*, **31**, 2585, 2596 (1898); **37**, 4464 (1904).

Experimental Part

3 - Hydroxy - 3 - (α - benzoylamino) - phenacyloxindole (IX).—One-half gram of benzoylphenacylamine and 0.3 g. of isatin were dissolved in 6.5 cc. of warm ethyl alcohol and the solution allowed to cool. Several drops of diethylamine (or piperidine) were then added and the mixture was allowed to stand at room temperature for fifteen hours with intermittent shaking. The product which separated was purified by washing with ether and recrystallized from cold acetone by the slow addition of water. The product obtained by this method was not completely pure; yield, 40%; needles, m. p. 144–147°. The compound is unstable toward heat; boiling alcohol or acetone will cause its dissociation into the original reactants.

Anal. Calcd. for $C_{23}H_{18}O_4N_2$: C, 71.5; H, 4.66; N, 7.25. Found: C, 70.0; H, 4.41; N, 6.56, 6.54.

3-(α-Benzoylamino)-phenacylideneoxindole (X)

Method A.—3-Hydroxy-3-(α-benzoylamino)-phenacyloxindole (3 g.) was suspended in 40 cc. of absolute alcohol previously saturated at room temperature with hydrogen chloride. The solid dissolved gradually and a bright yellow product separated slowly. The product was filtered off from time to time, the process requiring about five days for completion; yield, 90%.

Method B.—One-half gram of benzoylphenacylamine, 0.3 g. of isatin, 5.5 cc. of ethyl alcohol and a few drops of piperidine were heated under reflux for four hours. The green solution was allowed to cool and crystals of yellow product separated during the course of several days. The yield was very poor. The product was identical with that formed by Method A. It crystallizes in bright yellow needles from hot glacial acetic acid or from hot alcohol, m. p. 252–253°.

Anal. Calcd. for $C_{23}H_{16}O_3N_2$: N, 7.61. Found: N, 7.50, 7.30.

3-(α-Benzoylamino)-phenacyloxindole (VIII).—3-(α-Benzoylamino)-phenacylideneoxindole (1.2 g.) was dissolved in 20 cc. of boiling glacial acetic acid. Zinc dust was added in small portions with continued heating until the yellow color disappeared. The product was isolated after filtration by the addition of water. It may be crystallized from 75% acetic acid or from alcohol; yield, 58%; white needles, m. p. 209–211°.

Anal. Calcd. for $C_{23}H_{18}O_3N_2$: N, 7.57. Found: N, 7.29, 7.46.

Cinchophen (II) by the Hydrolysis of 3-(α-Benzoylamino)-phenacyloxindole. With Acid.—1.5 grams was suspended in 15 cc. of ethyl alcohol, 15 cc. of concd. hydrochloric acid and 10 cc. of water and the mixture refluxed in a bath at 110–120° for nine hours. The product after crystallization from alcohol melted at 209–210°. Its identity with cinchophen was shown by a mixed melting point with a known sample.

Anal. Calcd. for $C_{16}H_{11}O_2N$: N, 5.62. Found: N, 5.46, 5.29.

With Alkaline Agents.—Neither 10% sodium hydroxide nor 50% barium hydroxide produced cinchophen. Tars resulted.

1,4-Dihydro-2-phenylquinoline-4-acid (V)

The Hydrochloride (IV).—3-Phenacyloxindole (12 g.) was wetted with a few cc. of glacial acetic acid. To this was added 50 cc. of concd. hydrochloric acid and 40 cc. of water, and the mixture was refluxed for one hour; yield 98%; yellow cubes, m. p. 213–217° with the evolution of gas. The compound may also be prepared by treatment of the acetone solution of the free base with hydrogen chloride.

Anal. Calcd. for $C_{16}H_{14}O_2NCl$: N, 4.86; neut. equiv., 144. Found: N, 4.46, 4.37; neut. equiv., 149, 151.

The Sulfate.—3-Phenacyloxindole (5 g.) was heated under reflux for six hours with 10 cc. of acetic acid and 40 cc. of 18% sulfuric acid. The product was crystallized from acetic acid; yield, 67%; m. p. 198–200° with evolution of gas.

The Free Base (V).—A sample of the hydrochloride or of the sulfate was dissolved in slightly more than the necessary amount of dilute alkali and filtered. Acetic acid was added to the alkaline solution in small amounts with stirring. The white precipitate was dissolved in cold acetone and an equal amount of water added. Upon standing, the base is deposited in crystalline form; soluble in alcohol, m. p. 165°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58; neut. equiv., 251; active hydrogens, 2; mol. wt., 251. Found: N, 5.32, 5.35; neut. equiv., 266; active hydrogens (Grignard), 2; mol. wt., 253.

Silver Salt.—*Anal.* Calcd. for $C_{16}H_{12}O_2NAg$: Ag, 30.17. Found: Ag, 30.33.

4′-Bromo-, 4′-Chloro- and 4′-Methyl-1,4-dihydro-2-phenylquinoline-4-acids (VI).—These compounds were prepared from the corresponding para-substituted 3-phenacyloxindoles by methods similar to that indicated above. No attempt was made to isolate the hydrochlorides or sulfates in pure form; the crude materials were neutralized with alkali directly. The products are difficult to purify, evidently tending to be oxidized (Table I).

TABLE I

Derivative	Formula	M. p., °C.	Analyses, % Calcd.		Found
4′-Bromo-	$C_{16}H_{12}O_2NBr$	153–155	N	4.24	4.14
4′-Chloro-	$C_{16}H_{12}O_2NCl$	145	N	4.9	5.0
4′-Methyl-	$C_{17}H_{15}O_2N$	150	N	5.28	5.15
Silver salt of 4′-methyl-	$C_{17}H_{14}O_2NAg$	...	Ag	29.0	28.6

Oxidation of 1,4-Dihydro-2-phenylquinoline-4-acid and 4′-Substituted Derivatives.—These compounds were in each case heated in a small amount of boiling nitrobenzene for about three hours. Upon cooling, cinchophen, or the corresponding 4′-substituted cinchophen, resulted. The products were identified by melting point determinations. mixed with known samples (Table II).

TABLE II

Reactant	Product	M. p. of product, °C.	M. p. of known sample, °C.	Mixed m. p., °C.
1,4-Dihydro-2-phenylquinoline-4-acid	2-Phenylquinoline-4-acid	208	208	208
4′-Bromo-	4′-Bromo-	237	238–240	238–239
4′-Chloro-	4′-Chloro-	233	237	235–237
4′-Methyl-	4′-Methyl-	203–206	208–210	206–208

Summary

Mineral acids act upon 3-phenacyloxindole to form a compound the properties of which indicate it to be 1,4-dihydro-2-phenylquinoline-4-acid. Similarly certain 4′-substituted 3-phenacyloxindoles yield corresponding 4′-substituted 1,4-dihydro-2-phenylquinoline-4-acid derivatives.

When 3-(α-benzoylamino)-phenacyloxindole is treated with hydrochloric acid, the product is 2-phenylquinoline-4-acid, and not an aminodihydroquinoline compound.

NEW YORK, N. Y. RECEIVED SEPTEMBER 19, 1934