The same process was repeated using 3.33 g. of α-bromodiethylacetyl chloride. In this case the removal of hydrogen bromide was not as complete, the product, 2.1 g., obtained analyzing for 29.75% bromine, 35.85% being the theoretical for $C_8H_{15}O_2Br$.

Reaction of Unsaturated Acid Chlorides with Sodium Azide.—The unsaturated acids were prepared from α-bromo esters by heating with dimethylaniline at 175–180° for one to two hours and subsequent hydrolysis. Thus prepared, tetrahydrobenzoyl chloride, b. p. 90–2° at 14–15 mm., and α-ethylcrotonyl chloride, b. p. 54–57° at 14–15 mm., reacted with sodium azide in benzene to yield cyclohexanone (60%) and diethyl ketone (56%).

Examination of Cyclopentylmethanal and Cyclohexanone for Rearrangement Products.—The cyclopentylmethanal from several runs was united and distilled. One gram of the highest boiling fraction, 136–137°, was dissolved in acetone and an excess of finely powdered potassium permanganate was added. After standing at room temperature for three days, the manganese dioxide was removed and the neutral fraction extracted with ether. Since no appreciable residue was obtained on removal of the ether, cyclohexanone was proved absent in the original mixture, for when an authentic mixture of cyclopentylmethanal and cyclohexanone was treated in the same way, cyclohexanone was demonstrable.

The cyclohexanone from several runs was united and distilled. One gram of the lowest boiling fraction was tested for the presence of aldehyde. No color developed with fuchsin-sulfur dioxide reagent and no dimedon condensation product was obtained.

Isolation of α-Bromobenzyl Isocyanate.—Thirty grams of α-bromophenylacetyl chloride in 100 cc. of benzene was treated with 9 g. of sodium azide. After heating for ten minutes, the benzene was removed *in vacuo* and the residue distilled. The second fraction, b. p. 110–120° at 18–19 mm., was redistilled and the portion of b. p. 114–116° at 18–19 mm. analyzed.

Anal. Calcd. for C_8H_6ONBr: N, 6.61; Br, 37.70. Found: N, 5.63; Br, 39.85.

On hydrolysis with dilute acid, 3.84 g. yielded 1.74 g. (90%) of benzaldehyde.

Formation of Benzylidene Diurethan.—The α-bromobenzyl isocyanate was dissolved in dry ether and added slowly to absolute alcohol. The ether was removed with a current of dry air and the alcohol in a vacuum desiccator. The residue was triturated with hexane and the crystals filtered and washed with cold water and alcohol to remove all traces of hydrobromic acid. The product was recrystallized from alcohol by the addition of water and was identical with benzylidene diurethan, m. p. and mixed m. p. 179–180°.[6]

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.61; H, 6.82; N, 10.53. Found: C, 58.65; H, 6.9; N, 10.51.

The author takes this opportunity to thank Dr. H. T. Clarke for his interest in this work, and Mr. W. Saschek for the microanalyses.

Summary

1. Application of the Curtius rearrangement to α-bromo acids has been shown to lead to the formation of carbonyl compounds.

2. α-Bromocyclopentylacetic acid and α-bromohexahydrobenzoic acid yielded cyclopentylmethanal and cyclohexanone, respectively, no rearrangement of the cyclic structure taking place.

3. The preparation of uniformly active sodium azide is described.

NEW YORK, N. Y. RECEIVED JANUARY 21, 1935

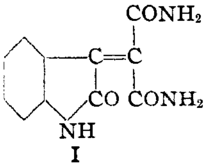
[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY AND THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Condensation Reactions of Cyclic Ketones. III. Oxindole-malonic Acid Derivatives

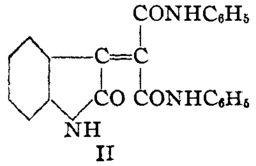
BY H. G. LINDWALL AND ARTHUR J. HILL

The previous paper[1] of this series dealt with the behavior on hydrolysis of the reduced products of the indigoids derived from the condensation of isatin with diketopiperazine and hydantoin; quinolones were obtained. This investigation involves further syntheses of oxindole derivatives for the purpose of studying their hydrolytic products.

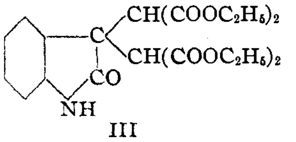
Isatin has been condensed with ammonium malonate, malonamide, and malonanilide by the use of ammonia as a catalyst and with diethyl malonate under the influence of diethylamine. The characteristics of the ammonium malonate product have been studied. Malonamide and malonanilide yield 3-(diformamido)-methylene-oxindole (I) and 3-(diformanilido)-methylene-oxindole (II), respectively. Diethylmalonate



I



II



III

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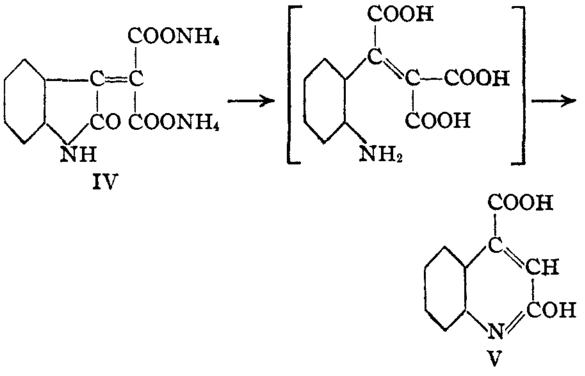
[1] Hill, Schultz and Lindwall, THIS JOURNAL, **52**, 769 (1930).

gave the tetra-ethyl ester of 3,3-bis-(methane di-acid)-oxindole (III).

In a manner analogous to the formation of I and II, ammonium malonate might be expected to yield the ammonium salt of 3-(methylene-di-acid)-oxindole (IV). A product was obtained, but difficulties were encountered when attempts were made to free the acid from its salt; the acid was not obtained in pure form, but the properties of its ammonium and silver salts suggest structure IV.

Treatment of IV with hydrochloric acid gave 2-hydroxycinchoninic acid (V) through evident hydrolytic ring opening, decarboxylation and ring closure. Esterification of IV, using absolute ethyl alcohol and dry hydrogen chloride, yielded the ethyl ester of V. Treatment of IV with hydriodic acid and red phosphorus gave 1,2,3,4-tetrahydro-2-quinolone-4-carboxylic acid, which can also be obtained from V by similar treatment.



Evidence was found for the oxindole and di-acid nature of IV. A di-silver salt of IV was obtained, though isolation of the free acid from this salt again presented difficulties; treatment with carbonic acid was ineffective, and sulfuric acid caused the formation of V with the loss of carbon dioxide equivalent to one carboxyl group. However, hydrogen sulfide, when passed through the aqueous suspension of the silver salt, yielded a white product, although in poor yield and with no definite crystalline structure. The formation of isatin from this product through oxidation with hydrogen peroxide was significant, for it showed that IV has the oxindole ring; 2-hydroxycinchoninic acid (V) is stable under the same oxidative conditions.

Experimental Part

3-(Di-formamido)-methyleneoxindole (I).—Ten grams of isatin and 8 g. of malonamide, in 60 cc. of 3% ammoniacal absolute alcohol, were heated at 70° for ten hours with vigorous stirring. A pale yellow solid formed gradually. The product was recrystallized from nitrobenzene; yellow plates, m. p. 245°; yield, 76%; soluble in alcohol and benzene.

Anal. Calcd. for $C_{11}H_9O_3N_3$: N, 18.20. Found: N, 18.10, 18.45.

3-(Di-formanilido)-methyleneoxindole (II).—The procedure described above was repeated, using malonanilide. Twenty hours of heating and stirring were required. The product was recrystallized from nitrobenzene: yield, 70%; yellow needles; m. p. above 320°.

Anal. Calcd. for $C_{23}H_{17}O_3N_3$: N, 10.95. Found: N, 11.15.

Tetra-ethyl Ester of 3,3-Bis-(methane di-acid)-oxindole (III).—A mixture of 5 g. of isatin, 5 g. of diethylmalonate, and 50 drops of diethylamine in 30 cc. of absolute alcohol was allowed to stand at room temperature for three weeks. The pale yellow product was obtained when the solution, after concentration, was poured into water. Recrystallization from 50% alcohol yielded pale yellow hexagonal plates; m. p. 152°; yield, 57%.

Anal. Calcd. for $C_{22}H_{27}O_9N$: C, 58.77; H, 6.07; N, 3.12. Found: C, 59.20; H, 6.20; N, 2.93, 3.05.

Ammonium 3-(Methylene di-acid)-oxindole (IV).—Ten grams of isatin and 8 g. of malonic acid, in 25 cc. of 10% ammoniacal absolute alcohol, were heated at 60° for one hour, with vigorous stirring. At first crystals of ammonium malonate were formed; later, a suspension of the pale yellow product appeared. The yield, crude, was almost quantitative.

Anal. Di-silver salt. Calcd. for $C_{11}H_5O_6NAg_2$: Ag, 48.27; N, 3.13. Found: Ag, 47.81; N, 3.08, 3.26.

Conversion of IV to Quinolones. (A) 2-Hydroxycinchoninic Acid (V).—An aqueous solution of the ammonium salt (IV) was acidified with hydrochloric acid at room temperature and the product was recrystallized from hot water; long white needles, m. p. above 300°, resulted. Compound V was identified by conversion to the ethyl ester which melted at 203° when mixed with a known sample.

(B) **Ethyl-2-hydroxycinchoninate.**—Esterification of IV, using absolute ethyl alcohol and dry hydrogen chloride, was carried out in the usual manner. The product was identified by melting point methods.

(C) **1,2,3,4-Tetrahydro-2-ketocinchoninic Acid.**—Five grams of IV and 5 g. of red phosphorus in 60 cc. of hydriodic acid (sp. gr. 1.7) were heated at 140° for five hours. After removing hydriodic acid under diminished pressure, the residue was extracted with hot water. Recrystallization from 40% alcohol gave white needles, m. p. 218°, yield 75%; mixed with a known sample, m. p. 218°.

Action of Sulfuric Acid upon the Silver Salt of IV.—A mixture of 2.73 g. of the silver salt and 50 cc. of 7% sulfuric acid was heated until completion of the evolution of carbon dioxide, which was collected in barium hydroxide solution. This procedure made possible a rough estimation of the amount of carbon dioxide, which was 8.05%, whereas the theoretical yield is 9.86% calculated on $C_{11}H_6O_6Nag_2$, and on the loss of one molecule of carbon dioxide. The product, 2-hydroxycinchoninic acid (V), was obtained in 70% yield, and was identified by crystal form and conversion to the ethyl ester.

Action of Hydrogen Sulfide upon the Silver Salt of IV.—A suspension of 10 g. of powdered silver salt in 50 cc. of water was agitated and saturated with hydrogen sulfide for five hours at 40°. After removal of silver sulfide, the filtrate was concentrated at 30° in an atmosphere of hydrogen, and 1 g. of a white amorphous product (VI) separated. Purification of this white product was not practicable because of ease of decomposition. Product VI melted at about 122°, though not sharply; further heating caused color change to a bright red, with evolution of a gas.

Isatin, by the Oxidation of VI.—A suspension of 0.4 g. of product VI (obtained above) in 25 cc. of 3% hydrogen peroxide was agitated and warmed gently for three hours. The color changed from pale yellow to red. After cooling, acidification caused the slow separation of a red-brown substance which crystallized from alcohol in red needles, yield 80%, and was identified as isatin by melting point methods.

Summary

Isatin condenses with malonamide and with malonanilide, mole for mole, to give the corresponding iso-indigoid compounds. Diethyl malonate, however, yields the tetra-ethyl ester of 3,3-bis-(methane di-acid)-oxindole.

Malonic acid and isatin react in the presence of ammonia to give a product for which the formula of ammonium-3-(methylene di-acid)-oxindole, is suggested. Acid treatment of this compound causes the formation of known quinolones, but oxidation to yield isatin demonstrated its essential oxindole configuration.

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

The Cleavage of Unsymmetrical Ketones by Potassium Hydroxide. I

BY W. E. BACHMANN

A considerable number of two-way reactions have been investigated in order to obtain comparisons of chemical reactivities; these reactions have received ample discussion from von Braun,[1] Schönberg,[2] Adkins[3] and others. Among the methods is the cleavage of unsymmetrical ketones by potassium hydroxide; thus, a ketone R_1—CO—R_2 can react with the alkali in two ways

$$R_1\text{—CO—}R_2 \xrightarrow{\text{KOH}} \begin{array}{l} \nearrow R_1COOK + R_2H \\ \searrow R_1H + R_2COOK \end{array}$$

By determining the proportions of the two acids in the mixture that is produced the amount of cleavage at each of the two bonds, R_1—CO and R_2—CO, can be ascertained. Since the reactions are irreversible no equilibrium is attained; the relative rates at which two competing reactions take place are measured. As far as can be learned, no quantitative study of the cleavage of a single unsymmetrical aromatic ketone has been made. We have now undertaken an investigation of this reaction and at this time report the results obtained on eleven aromatic ketones. The method is simple, rapid and gives reproducible results; the method possesses a number of advantages over that of Schönberg, who employed sodamide to cleave unsymmetrical aromatic ketones.

Procedure.—A mixture of 0.005 gram mole of ketone and 1.5 g. of solid potassium hydroxide (85%) is heated in a 15-cm. Pyrex test-tube in a direct flame. During the heating the mixture is shaken in order to obtain an emulsion and the heating is carried out cautiously in order to avoid a violent reaction which occurs if the temperature is allowed to go too high. When the mixture thickens it is stirred with a glass rod as it is being heated; after five to ten minutes the reaction is at an end. The potassium salts of the acids are separated from the neutral products by solution in water and the proportion of each acid in the mixture is determined.[4] The results of several runs checked each other; thus, four runs on *p*-tolyl *p*-biphenyl ketone gave for the ratio of *p*-toluic acid to *p*-phenylbenzoic acid values of 53:47, 54:46, 53:47 and 52:48. With a little experience one can cleave the ketone to the extent of 90–100%; since the remainder was found to be unchanged ketone, the yields of acids were practically quantitative, an indication that the reaction RCOOK + KOH $\longrightarrow$ RH + K_2CO_3 did not take place under the conditions of the experiment. It is considered that the results are accurate within a few per cent.

Discussion of Results.—The results of the experiments are summarized in Table I.

On the basis of phenyl as unity, the groups can be assigned values which represent what might be termed the relative tenacity with which the groups are held to the carbonyl group; these values are shown in Table II.

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(1) Von Braun, *Ber.*, **56**, 1573 (1923).

(2) Schönberg, *Ann.*, **436**, 205 (1924); *Ber.*, **58**, 580 (1925).

(3) Adkins, *J. Chem. Educ.*, **9**, 1865 (1932).

(4) The methods of analysis were those employed in the study of the pinacol–pinacolone rearrangement; see Bachmann and Moser, THIS JOURNAL, **54**, 1124 (1932); Bachmann, *ibid.*, **54**, 2112 (1932); Bachmann and Sternberger, *ibid.*, **56**, 170 (1934); Bachmann and Ferguson, *ibid.*, **56**, 2081 (1934).