[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. XIII. Oxindole-3-propionic Acid

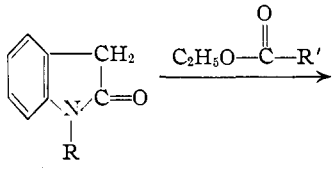
BY PERCY L. JULIAN AND HELEN C. PRINTY

RECEIVED APRIL 24, 1953

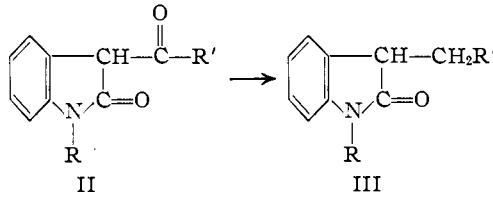
Oxindole-3-propionic acid has been obtained by reduction of the condensation product of oxindole and ethyl malonate. In the course of this series of reactions, interesting intermediates for the synthesis of dioxindole-3-alanine have been secured. Of the two products formerly described in the literature, only that of Kendall is authentic oxindole-3-propionic acid. Previous attempts to prepare oxindole-3-propionic acids by Michael condensation between oxindoles and acrylic ester are discussed and proof is given that such condensation products are the oxindole-3,3-dipropionic acids.

Over a span of several years our studies on the alkylation of oxindoles at the 3-position—the initial phases of which led to the first successful synthesis of physostigmine[1]—have been intermittently resumed, as circumstances permitted, with results that indicate the flexibility of this approach. Thus, for example, the introduction of the N-tetrahydroisoquinolylethyl group into the 3-position of 1-methyloxindole led to a surprisingly simple synthesis of the basic ring structure of yohimbine.[2] Moreover, our observation that certain oxindoles are rather smoothly reduced by lithium aluminum hydride to the corresponding indoles[3] opened up the intriguing possibility that several difficultly accessible indole derivatives might be prepared from readily available oxindoles.

Among our suggested 3-alkylation procedures of oxindoles was the condensation of an oxindole (Ib) with aliphatic esters and reduction of the resulting 3-acyloxindole (II) to the desired 3-alkyl derivative (III).[4] In our earlier experiments we employed only 1-methyloxindoles. Horner,[5] who later attempted this mode of alkylation with oxindole itself, reported failure in attempts to reduce compounds like II (R = H) to the desired alkyl derivatives III (R = H). Sumpter[6] has interpreted Horner's observations as implying that 3-acyloxindoles without substituent groups on nitrogen cannot be reduced to 3-alkyl derivatives.

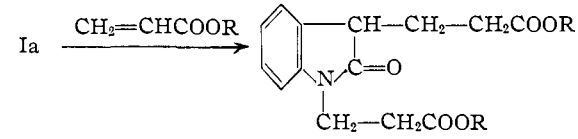


Ia, R = H
Ib, R = CH_3



II III

The immediate objective of Horner appeared to be the synthesis of oxytryptophan (oxindole-3-alanine). It was therefore to be expected that he would investigate the condensation of oxindole with appropriate derivatives of malonic ester.[7] When he was unable to effect these condensations, he attempted the synthesis of oxindole-3-propionic acid, presumably as possible starting material for the synthesis of oxindole-3-alanine. Among these attempted syntheses of oxindole-3-propionic acid was a Michael condensation of oxindole (Ia) with acrylic ester, whereupon a dipropionic acid, to which he assigned the structure IVa, was obtained.

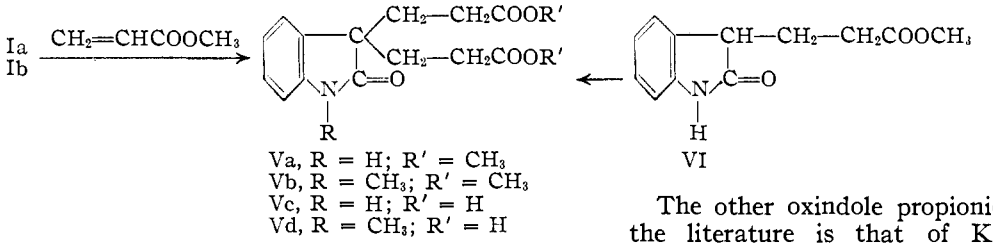


IVa, R = H
IVb, R = C_2H_5

Such a result was exceedingly surprising to us because, despite the fact that isatin is reported to add to acrylonitrile to produce an N-propionitrile,[8] our earlier observations on the remarkable activity of the hydrogen at the 3-position of a 3-alkylated oxindole[9] made it appear strange indeed that the Michael condensation with excess acrylate should so readily stop at the introduction of one, rather than two propionic residues, into the 3-position. Since his was a dipropionic acid, we suspected that Horner's product was the 3,3-dipropionic acid (Vc) and not the 1,3-dipropionic acid (IVa) as he reported. Our suspicions were further strengthened by the fact that 1-methyloxindole (Ib), subjected to this condensation, yielded a dipropionic acid, for which the only structure that can be envisaged is Vd. Further proof that the Horner acid has the constitution Vc rather than IVa came with the methylation of Horner's condensation product (Va) with methyl sulfate. Hydrolysis of this methylated product gave 1-methyloxindole-3,3-dipropionic acid (Vd) identical with that obtained from the condensation of 1-methyloxindole (Ib) with acrylic ester. Finally when an authentic specimen (to be described below) of the methyl ester of oxindole-3-propionic acid (VI) was subjected to the Michael condensation with methyl acrylate, the acid secured on hydrolysis was identical with the Horner acid (Vc).

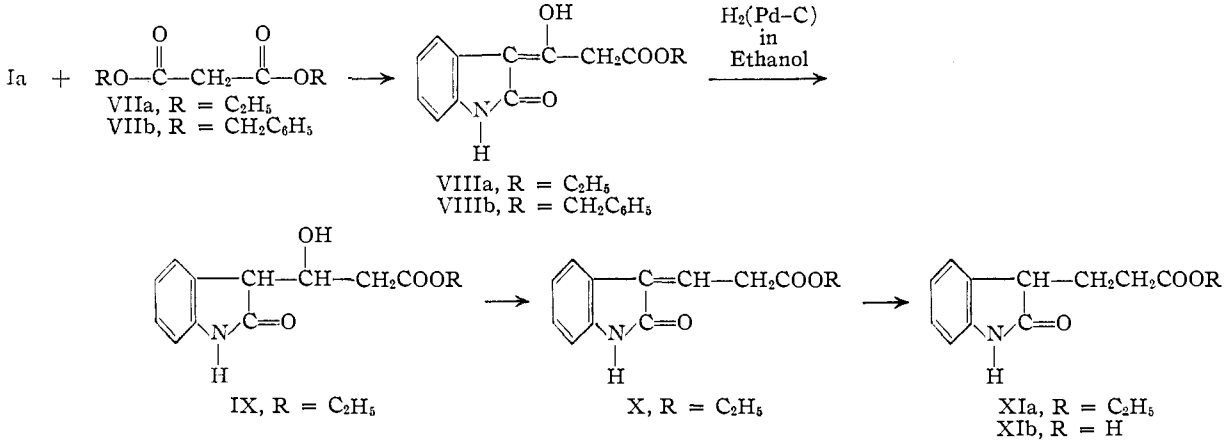
Despite several efforts we have ourselves been unable to stop the Michael condensation between oxindole and acrylic ester at the bimolecular stage, so that this condensation in our hands could not be

(1) P. L. Julian and J. Pikl, THIS JOURNAL, **57**, 563, 755 (1935).
(2) (a) P. L. Julian, A. Magnani, J. Pikl and W. Karpel, *ibid.*, **70**, 174 (1948); (b) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949).
(3) P. L. Julian and H. Printy, *ibid.*, **71**, 3206 (1949).
(4) P. L. Julian, J. Pikl and F. E. Wantz, *ibid.*, **57**, 2026 (1935).
(5) L. Horner, *Ann.*, **548**, 117 (1941).
(6) W. C. Sumpter, *Chem. Revs.*, **37**, 443 (1945).
(7) *Cf.* ref. 4, p. 2027.
(8) F. J. DiCarlo and H. G. Lindwall, THIS JOURNAL, **67**, 199 (1945).
(9) P. L. Julian and J. Pikl, *ibid.*, **57**, 539 (1935); ref. 1, p. 756.



Va, R = H; R′ = CH_3
Vb, R = CH_3; R′ = CH_3
Vc, R = H; R′ = H
Vd, R = CH_3; R′ = H

employed for the preparation of oxindole-3-propionic acid. Interesting also for the chemistry of the Michael condensation is the fact that we could not effect the Michael condensation between the highly enolic 3-acetyloxindole or 1-methyl-3-acetyloxindole and acrylic ester. This recalls to mind Connor's observation[10] that diethyl phenylmalonate failed to undergo the Michael condensation with acrylic esters, while ethyl malonate and ethyl phenylacetate readily undergo this condensation. Likewise Connor and Andrews[11] found that 100% enolic dibenzoylmethane also failed to undergo the Michael condensation, at least to any perceptible extent. Although these investigators could find no relationship between degree of enolization and reactivity in the Michael condensation, their data show that the compounds which might be expected to exhibit 100% enolization under the conditions of the experiment behaved poorly in the Michael condensation. Considering the ease with which 1,3-dimethyloxindole and oxindole-3-propionic acid undergo the Michael condensation, and the failure with 3-acyloxindoles, it would appear that the particular enolic character of the latter is responsible for the lack of reactivity in the Michael condensation.



Up to this writing there are only two described preparations of oxindole-3-propionic acid in the literature. One of these is described by Schoeller and Schmidt who gave a melting point of 208° and claimed to secure this acid by reduction of the condensation product of oxindole-3-aldehyde with malonic acid.[12] We have repeated their preparation and find that the product of melting point 208° is not oxindole-3-propionic acid. *Indeed the product is unchanged oxindole aldehyde*, and Schoeller and Schmidt, unaware of the solubility of this highly enolic aldehyde in aqueous sodium bicarbonate—a solubility which we have found to be characteristic of 3-acyloxindoles—apparently assumed that they had a new acid.

The other oxindole propionic acid described in the literature is that of Kendall.[13] Sumpter[6] doubts that the Kendall acid has the constitution assigned it and suggests that the acid of Schoeller and Schmidt is the authentic substance. Unable to secure from Dr. Kendall a specimen of his acid,[14] we were forced to repeat this laborious, albeit interesting preparation. Our findings show that the Kendall acid is authentic oxindole-3-propionic acid and has the structure he assigned to it. Proof of this is its condensation to the Horner acid described above and its identity with a new preparation which we ourselves have recently consummated.

Returning to our earlier suggestion[4] that compounds like oxindole-3-propionic acid can be prepared by condensation of the appropriate oxindole with malonic esters, followed by catalytic reduction, we have found that contrary to Horner's observations and more recent observations by Behringer,[15] the condensation of oxindole (Ia) with malonic ester to produce the enol VIIIa proceeds very smoothly indeed and the catalytic reduction of VIIIa in the presence of palladium-on-charcoal is as easy as can be imagined. Thus by the procedures outlined in formulas Ia → XIb, we have obtained oxindole-3-propionic acid in excellent yields.

That the condensation product (VIIIa) of oxindole with ethyl malonate is practically 100% enolic is shown by its decided acidity, evidenced by ready solubility in sodium bicarbonate. Thus VIIIa behaves like a true carboxylic acid and may be considered a vinylog of the latter.[15] Further support for assigning the structure VIIIa to this enol, rather than one of the other possible structures, XII or XIII, resides in the marked similarity between its ultraviolet spectrum (Fig. 1) and that of isatin

(10) R. Connor, THIS JOURNAL, **55**, 4597 (1933).
(11) R. Connor and D. B. Andrews, *ibid.*, **56**, 2713 (1934).
(12) German Patent 451,957; U. S. Patent 1,656,239.
(13) E. C. Kendall, A. E. Osterberg and B. F. MacKenzie, THIS JOURNAL, **48**, 1384 (1926).
(14) One week before our request, Dr. Kendall, in moving into his new laboratory at the Mayo Clinic, had discarded all the old oxindole preparations.
(15) H. Behringer and H. Weissauer, *Ber.*, **85**, 774 (1952).

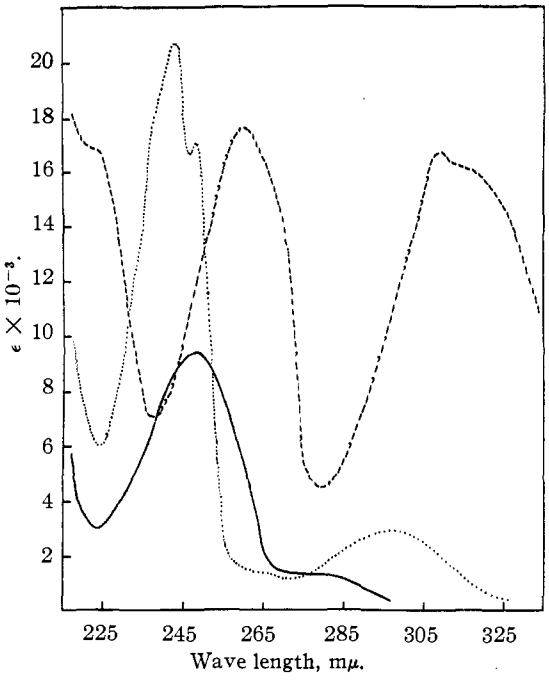


Fig. 1.—Ultraviolet absorption spectra in methanol of oxindole, —; ethyl β-isatylidene-β-hydroxypropionate, - - -; and isatin, ...

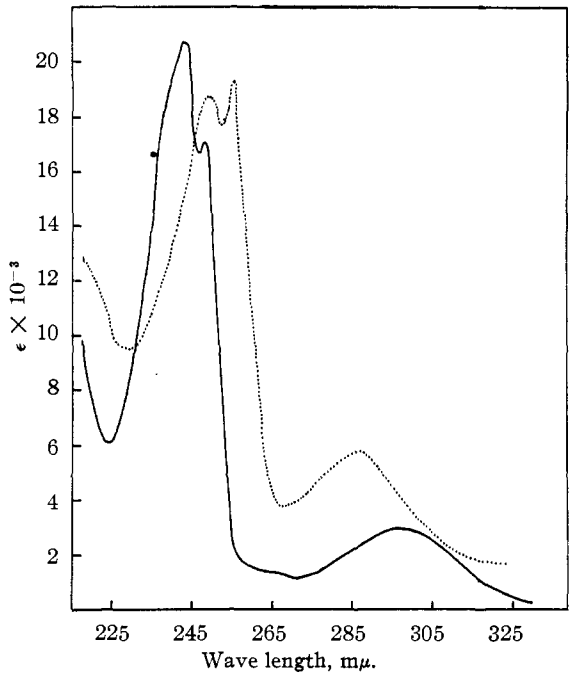
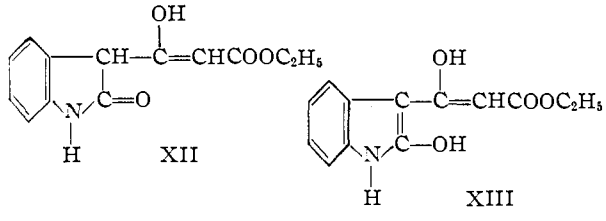


Fig. 2.—Ultraviolet absorption spectra in methanol of ethyl β-isatylidenepropionate, ...; and isatin, —.

(Fig. 1). Fig. 1 shows the spectrum of oxindole, which is quite different.



When the catalytic reduction of ethyl β-isatylidene-β-hydroxypropionate (VIIIa) is carried out in ethanol solution in the presence of palladium-on-charcoal, the reaction stops when one mole of hydrogen has been consumed and the product is ethyl β-hydroxy-β-oxindole-3-propionate (IX). Taken up in glacial acetic acid containing a small amount of sulfuric acid, IX readily loses water and is converted into ethyl β-isatylidenepropionate (X). The assignment of structure X to this compound is further strengthened by the similarity between its ultraviolet spectrum (Fig. 2) and that of isatin.

When the reduction of the enol VIIIa is carried out in glacial acetic acid containing a small amount of sulfuric acid, the product is ethyl oxindole-3-propionate (XIa). When VIIIb, the product of the condensation of benzyl malonate with oxindole is similarly reduced the product is oxindole-3-propionic acid itself (XIb).

Also interesting for these catalytic reductions is the fact that we could not effect them with our present samples of palladium oxide catalyst though years ago[4] this catalyst afforded us the desired product. Whether a situation similar to that described by Hartung and Chang[16] is responsible, we did not investigate since palladium-on-carbon has appeared to be so uniformly excellent for the purposes of this investigation.

It is obvious that the enol VIIIa and likewise the isatylidene ester X represent attractive starting material for the synthesis of dioxindole-3-alanine, a substance much discussed recently as a possible intermediate in the metabolism of tryptophan.[17] Experiments in this direction will be the subject of a forthcoming communication.

Acknowledgment.—The authors are indebted to Dr. Edwin W. Meyer and Mr. Francis A. Taylor for technical assistance. They are also indebted to Messrs. Robert Doone, Roger Ketcham and Robert Morgan, formerly of Antioch College, for preparing sizable quantities of Kendall's oxindole-3-propionic acid.

Experimental[18]

1-Methyloxindole-3,3-dipropionic Acid (Vd) from 1-Methyloxindole (Ib).—Fourteen and seven-tenths grams of 1-methyloxindole was dissolved in a solution containing 2.3 g. of sodium in 100 ml. of absolute ethanol, then 17.6 g. of methyl acrylate was added through a condenser. The reaction was refluxed under nitrogen for six hours, then a solution of 2.3 g. of sodium in 100 ml. of 90% ethanol was added, and the reaction refluxed under nitrogen for 1.5 hours. The solvent was removed *in vacuo*, the residue dissolved in 500 ml. of water and extracted with two 50-ml. portions of chloroform. The aqueous layer was acidified with 100 ml. of 10% hydrochloric acid. A nicely crystalline yellow product came out; this was collected by filtration, washed with water and dried. The material, 21.2 g. (92.5% yield, corrected for 4.3 g. of recovered methyloxindole) melted at 122°, then solidified and remelted at 165–168°. Recrystallization from hydroxylic solvents led to solvated products; the analytical sample was obtained by refluxing crude acid for 30 minutes with xylene, then crystallizing the material from acetone–xylene. Fine white needles, m.p. 169–170°, were obtained.

(16) W. H. Hartung and V. T. Chang, THIS JOURNAL, **74**, 5927 1952).

(17) (a) A. Ek. H. Kissman, J. B. Patrick and B. Witkop, *Experientia*, **8**, 36 (1952); (b) H. Hellmann and E. Renz, *Ber.*, **84**, 901 (1951); (c) H. Behringer and H. Weissauer, *ibid.*, **85**, 743 (1952).

(18) Analyses are by Micro-Tech Laboratories, Skokie, Illinois.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 67.73; H, 5.97; calcd. for $C_{15}H_{17}O_5N$: C, 61.84; H, 5.88. Found: C, 62.05; H, 5.96.

Confirmatory evidence for the formulation of the crude product as a dipropionic acid dihydrate lies in the neutralization equivalent of the crude acid.

Anal. Calcd. for $C_{12}H_{13}O_3N$: neut. equiv., 219; $C_{15}H_{17}O_5N$; neut. equiv., 146; $C_{15}H_{17}O_5N\cdot 2H_2O$: neut. equiv., 164. Found: neut. equiv., 161.

The acid Vd was converted *via* the Curtius degradation to a diphthalimide which crystallized from aqueous ethanol in fine white needles, m.p. 209°.

Anal. Calcd. for $C_{29}H_{23}N_3O_3$: C, 70.57; H, 4.69. Found: C, 70.34; H, 4.53.

The di-*p*-phenetidide, prepared from the acid chloride, was recrystallized from aqueous ethanol as fine white needles, m.p. 197.5–198.5°.

Anal. Calcd. for $C_{31}H_{35}O_5N_3$: C, 70.29; H, 6.66. Found: C, 70.25; H, 6.51.

1-Methyl-3,3-dipropionic Acid (Vd) from the Horner Ester (Va).—The condensation of oxindole with methyl acrylate was carried out as described by Horner.[5] A 2.16-g. portion of the neutral condensation product (dimethyl oxindole-3,3-dipropionate) (Va) was reserved before hydrolysis, and this was dissolved in 25 ml. of methanol. The refluxing solution was treated with 2 g. of dimethyl sulfate and 2.6 g. of 42% sodium hydroxide solution added alternately, and was refluxed an additional two hours. The solution was diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was concentrated to a red oil, which was hydrolyzed by refluxing it with 0.5 g. of sodium in 25 ml. of 95% ethanol. The solution was diluted with water, extracted with ether and the acid precipitated from the aqueous phase with hydrochloric acid. The product, 1.3 g., melted at 165–169°, and was identical with 1-methyloxindole-3,3-dipropionic acid (Vd). The *p*-phenetidide prepared from the methylated acid melted at 196–198° and gave no depression when melted with the di-*p*-phenetidide from 1-methyloxindole-3,3-dipropionic acid.

Kendall Acid (XIb) and Methyl Oxindole-3-propionate (VI).—Oxindole-3-propionic acid (XIb), prepared according to the directions of Kendall,[13] was recrystallized for analysis from water. The acid was obtained as white needles, m.p. 169–170°, lit. 174°.[13]

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.27; H, 5.26; N, 6.67.

The acid XIb, 6.57 g., was converted *via* the acid chloride to the methyl ester VI in 90% yield. The ester crystallized from ether–petroleum ether (b.p. 35–65°) in white prisms, m.p. 79–80°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.73; H, 5.97; N, 6.38. Found: C, 66.00; H, 6.07; N, 6.40.

Oxindole-3,3-dipropionic Acid (Vc) from Methyl Oxindole-3-propionate (VI).—One gram of methyl oxindole-3-propionate (VI) and 0.43 g. of methyl acrylate were refluxed under nitrogen with a solution of 0.12 g. of sodium in 5 ml. of ethanol for three hours. One milliliter of 15% sodium hydroxide solution was added to the reaction, and refluxing was continued an additional two hours. The solution was then diluted with water, extracted with ether and the chilled aqueous phase acidified with hydrochloric acid. The solution deposited 0.98 g. of white crystals, m.p. 150–155°, which gave no depression when melted with a sample of the Horner acid (Vc).

Ethyl β-Isatylidene-β-hydroxypropionate (VIIIa).—To a stirred solution of 9 g. of sodium in 140 ml. of absolute ethanol, 60 g. of distilled ethyl malonate was added, then a solution of 13.3 g. of oxindole (Ia) in 60 ml. of ethanol was added dropwise during two hours. The reaction was stirred and refluxed under nitrogen for six hours, during which time 120 ml. of ethanol was distilled. The tan slushy product (sodium salt) was dissolved in ice-water and the solution extracted with ether. The aqueous portion was acidified with cold concentrated hydrochloric acid, and a heavy creamy precipitate formed. This was collected on a funnel, washed with water and dried. The yield of material, m.p. 150–152°, was 22.19 g. (90%). This product was crystallized for analysis from ether, then from benzene, in creamy needles, m.p. 155–156°.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.40; H, 5.20; N, 5.72.

Ethyl β-Hydroxy-β-oxindole-3-propionate (IX) from Ethyl β-Isatylidene-β-hydroxypropionate (VIIIa).—Ethyl β-isatylidene-β-hydroxypropionate (VIIIa), 4.94 g., was hydrogenated with 2 g. of 10% palladium-on-charcoal catalyst[19] in 200 ml. of ethanol at 3–4 atm. The hydrogenation proceeded rapidly until one mole had been consumed, then stopped. The catalyst was removed by filtration and the filtrate, which gave no color with ferric chloride, was concentrated *in vacuo* to a solid. A total of 4.13 g. (83%) of material, m.p. 135–142°, was obtained in two crops from ethanol. Upon recrystallization from ethanol, the product was obtained as white needles, m.p. 147–148°.

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.63; H, 6.06; N, 5.61. Found: C, 62.88; H, 6.05; N, 5.86.

Ethyl β-Isatylidenepropionate (X) from Ethyl β-Hydroxy-β-oxindole-3-propionate (IX).—Two grams of ethyl β-hydroxy-β-oxindole-3-propionate (IX) was suspended in 50 ml. of glacial acetic acid containing 0.1 ml. of concentrated sulfuric acid. The solid went into solution during one hour and a deep orange solution was formed. The solution was kept at room temperature for 15 hours. Careful addition of cold water to the solution resulted in the separation of a yellow crystalline solid. This was filtered and washed with water. This material, 1.16 g., melting at 140–152°, crystallized from methylene chloride–hexane as yellow prisms, m.p. 144–145°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.51; H, 5.66; N, 6.05. Found: C, 67.05; H, 5.59; N, 6.33.

Ethyl Oxindole-3-propionate (XIa) from Ethyl β-Isatylidenepropionate (X).—A solution of 1.16 g. of unsaturated ester X in 50 ml. of ethanol was hydrogenated in the presence of 0.5 g. of 10% palladium-on-charcoal catalyst. After the absorption of one mole of hydrogen, the solution was filtered, concentrated, and the residue crystallized from ether–petroleum ether (b.p. 35–65°). One gram of white needles, m.p. 66–69°, was obtained.

Ethyl Oxindole-3-propionate (XIa) from Ethyl β-Isatylidene-β-hydroxypropionate (VIIIa).—A solution of 2.47 g. of ethyl β-isatylidene-β-hydroxypropionate (IX) in 100 ml. of acetic acid containing 1 ml. of concentrated sulfuric acid was hydrogenated in the presence of 1 g. of 10% palladium-on-charcoal catalyst. The compound absorbed two moles of hydrogen rapidly. The catalyst was removed by filtration; 4 g. of sodium bicarbonate was added to the filtrate and the solvent removed *in vacuo* with gentle heating. The residual slush was dissolved in ether, the ethereal solution washed with 10% sodium bicarbonate solution and water, and dried over sodium sulfate. The dried solution was concentrated, and upon the addition of petroleum ether (b.p. 35–65°), 1.26 g. of white crystals, m.p. 65–67°, was obtained. Further concentration yielded an additional 0.42 g. of material, m.p. 60–65° (72%). A sample recrystallized from ether had m.p. 73–74°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.34; H, 6.51; N, 6.24.

Oxindole-3-propionic Acid (XIb) from Ethyl β-Isatylidene-β-hydroxypropionate (VIIIa).—Two and forty-seven hundredths grams (0.01 mole) of ethyl β-isatylidene-β-hydroxypropionate (VIIIa) was shaken in an atmosphere of hydrogen with 2 g. of 10% palladium-on-charcoal catalyst in 100 ml. of glacial acetic acid containing 1 ml. of concentrated sulfuric acid until two moles of hydrogen was absorbed. The solution was then filtered to remove the catalyst and the solvents removed *in vacuo*. The residue was refluxed for one hour with 25 ml. of water, the resulting solution treated with 1 g. of Darco G-60, filtered and cooled. From the solution, 1.70 g. (83%) of white crystals, m.p. 164–168°, which gave no depression when melted with the Kendall acid, was obtained.

Benzyl β-Isatylidene-β-hydroxypropionate (VIIIb).—To 2.3 g. of powdered sodium suspended in 25 ml. of dry, thiophene-free benzene, stirred under nitrogen, a solution of 9 g. of dibenzyl malonate[20] in 20 ml. of benzene was added, followed during the course of one hour by the addition of a solution of 4.43 g. of oxindole and 19.4 g. of dibenzyl malonate in 150 ml. of benzene. The reaction was stirred at room temperature for five hours while a slushy precipitate formed.

(19) Obtained from The American Platinum Works, Newark, N. J.

(20) R. E. Bowman, *J. Chem. Soc.*, 325 (1950).

The reaction mixture was dissolved in ice-water, extracted with ether and the aqueous phase acidified with cold concentrated hydrochloric acid. The oily enolic product was extracted with ether–methylene chloride, the extract dried and concentrated. The solid residue was crystallized from ether; 6.2 g. of material, m.p. 130–134°, was obtained. The analytical sample, white needles from acetone, melted at 137–138°.

Anal. Calcd. for $C_{18}H_{15}O_4N$: C, 69.89; H, 4.88; N, 4.52. Found: C, 70.00; H, 4.94; N, 4.62.

Oxindole-3-propionic Acid (XIb) from Benzyl β-Isatylidene-β-hydroxypropionate (VIIIb).—Three and nine-hundredths grams (0.01 mole) of benzyl β-isatylidene-β-hydroxypropionate (VIIIb) was shaken with 2 g. of 10% palladium-on-charcoal catalyst in 100 ml. of glacial acetic acid containing 1 ml. of concd. sulfuric acid in an atmosphere of hydrogen until three moles of hydrogen had been absorbed. The catalyst was then removed by filtration and the filtrate concentrated *in vacuo* to a heavy sirup. Upon the addition of 20 ml. of water, the product solidified and was collected by filtration. An 82% yield of crystals, 1.65 g., m.p. 163–165°, was obtained. The product gave no depression with the Kendall acid.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE RESERCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. XIV. Oxindole-3-acetic Acid

BY PERCY L. JULIAN, HELEN C. PRINTY, ROGER KETCHAM AND ROBERT DOONE

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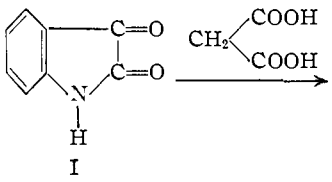
The synthesis of oxindole-3-acetic acid has been achieved for the first time. All previous attempts to isolate this substance involved vigorous hydrolysis procedures which resulted in the formation of 2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid. The present successful synthesis had its origin in the observation that acetaminoacrylic acid, in its tautomeric imino modification, condenses smoothly with oxindole in the absence of hydroxyl ions to produce stable α-isatylidene-α-methylacetic acid. Its reduction product, α-oxindolylmethylacetic acid, is likewise stable and is converted into the corresponding quinolonecarboxylic acid only on vigorous hydrolysis. Following this observation it was, therefore, not surprising that we successfully achieved the synthesis of oxindole-3-acetic acid by reduction of the condensation product of oxindole with dibenzyl oxalate.

Oxindole-3-acetic acid (IV) has enjoyed a long history in the literature but has, up to the present, eluded all attempts at its synthesis. Even its precursor in certain condensation reactions, namely, isatylideneacetic acid (II), has likewise never been secured. Thus Borsche and Jacobs[1] condensed isatin (I) with malonic acid in acetic acid solution and obtained 2-oxo-1,2-dihydroquinoline-4-carboxylic acid (III) instead of the expected isatylideneacetic acid (II).



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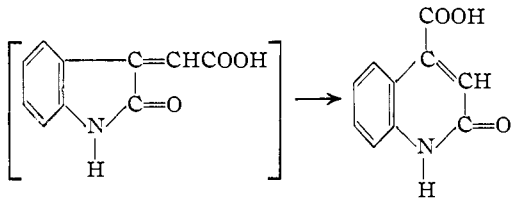
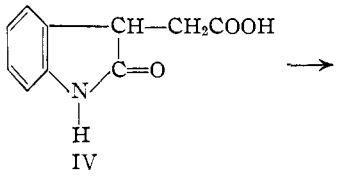


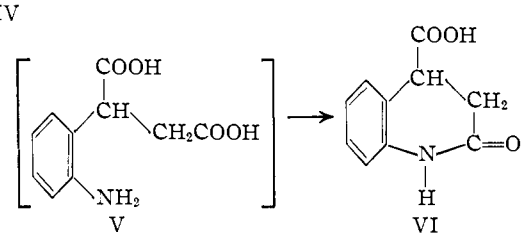
II III

Aeschlimann[2] demonstrated that the constitution III was to be assigned to the acid of Borsche and Jacobs and further that the condensation I → III took place even in the absence of solvents at 200°, followed by recrystallization of the products from non-aqueous solvents to avoid the possibility of isomerization during purification. Such a result would indicate that isatylideneacetic acid (II) is an extremely labile substance and hardly capable of existence.

Gränacher and Mahal[3] reported the preparation of "oxindole-3-acetic acid" by reduction of "oxindole-3-α-thiolacetic acid," which was obtained by alkaline hydrolysis of 3-rhodanylideneoxindole. Aeschlimann,[2] however, showed that their product was not oxindole-3-acetic acid (IV), but instead 2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (VI), formed by hydrolytic rupture of the oxindole



IV



V VI

ring to produce *o*-aminophenylsuccinic acid (V), which, in its turn, underwent ring closure to produce VI. Indeed, Aeschlimann was so impressed with this comparative instability of the oxindole as over against the quinolone ring structure that he even proposed the constitution X for oxindole-3-aldehyde (VII), prepared first by Friedlander and Kielbasinski[4] by alkaline hydrolysis of Thioindigo Scarlet R. His conclusion was based upon the observation that oxindole-3-aldehyde (3-formyloxindole) (VII) is a relatively strong acid and behaved more like indolecarboxylic acid (X) than like an aldehyde. Accordingly, he represented the mechanism of its transformation, during the hydrolysis of Thioindigo Scarlet R, in a manner indicated by formulas VII → X. It is true indeed that oxindole-

(1) W. Borsche and W. Jacobs, *Ber.*, **47**, 354 (1914).
(2) J. A. Aeschlimann, *J. Chem. Soc.*, 2902 (1926).
(3) Ch. Gränacher and A. Mahal, *Helv. Chim. Acta*, **6**, 467 (1923).
(4) P. Friedlander and S. Kielbasinski, *Ber.*, **44**, 3098 (1911).