A schematic mechanism for the ethanol–DPN reaction is presented in Fig. 1. It allows for electrostatic binding of the oxygen to the positively charged nitrogen of the pyridinium ring, for the stereospecificity of the reaction and for possible charge-transfer complex formation between DPNH and acetaldehyde.

Acknowledgment.—I would like to thank Dr. Robert West of this Department for helpful discussion.

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[CONTRIBUTION FROM THE JULIAN LABORATORIES, INC.]

Studies in the Indole Series. XV.[1] Dioxindole-3-propionic Acid

BY PERCY L. JULIAN, HELEN C. PRINTY AND EARL E. DAILEY

RECEIVED DECEMBER 30, 1955

Dioxindole is condensed with dihydropyran to yield the crystalline tetrahydropyranyl ether (VIII). Michael condensation of the latter with ethyl acrylate, followed by alkaline and then acid hydrolysis, gives dioxindole-3-propionic acid (XII), identical with the product secured several years ago by Kendall by oxidizing oxindole-3-propionic acid with iodine in sodium hydroxide solution.

As part of our long-pursued interest in providing 3-alkylated indole derivatives for use in the syntheses of substances related to natural products, our attention turned to the possibility of alkylating dioxindoles at the 3-position. The present paper describes the preparation of dioxindole-3-propionic acid.

The impetus to this endeavor resided in the still existing necessity for demonstrating experimentally a plausible mechanism for the metabolic pathway by which oxidative rupture of the indole nucleus of tryptophan (I) produces N-formylkynurenine (II).

While Witkop[2] believes that "the actual intermediate" in this biological transformation is 3-hydroxyindolenine-3-alanine (III), he at the same time recognizes the almost practical impossibility of preparing such a substance because of the expected ease with which intramolecular ring closure of III to the eserine-like ring system (VI or VIa) would take place. He, therefore, suggests that III might undergo hydration to the glycol IV, which can either go to II *via* oxidative rupture, or might be converted into dioxindole-3-alanine (V). The latter may be considered an acyloin produced by internal condensation of N-formylkynurenine (II).

Of all these speculations it appears that the one which lends itself to probable immediate experimental verification is the route V → II, since the synthesis of V should be realized from a study of C_3-alkylation of dioxindoles. Although the literature records no such alkylations, it appeared that a synthesis of authentic dioxindole-3-propionic acid might well be the most appropriate starting point.

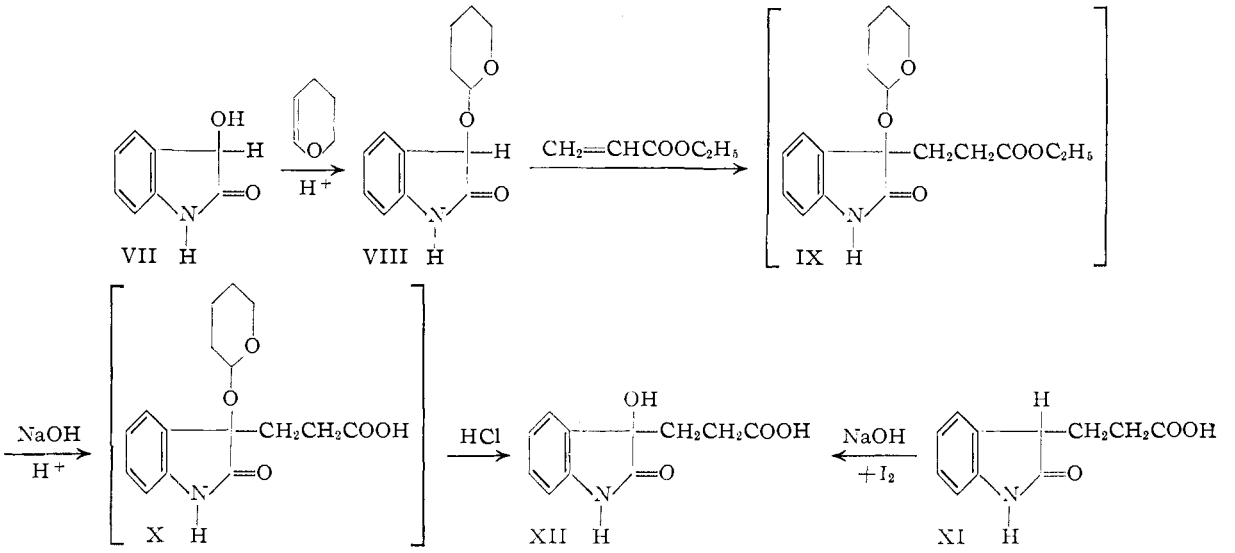
It should be expected that the electron induction of the C_3-hydroxyl group of dioxindole (VII) would so increase the acidity of the C_3-hydrogen atom that dioxindole might well alkylate as readily as or more readily than 3-alkyloxindoles.[3] Any alkali-induced condensations, however, must reckon with the possible enediol character of dioxindole. Also it must be recalled that in the Michael condensation, for example, indole gives with ethyl acrylate indole-1-propionic ester.

Actual attempts to condense dioxindole with ethyl acrylate in the presence of alkali alcoholates led to deeply colored mixtures and finally to intractable tars. It was obvious that suitable replacement of the hydrogen of the C_3-hydroxyl had to be provided. The tetrahydropyranyl ethers of dioxindoles were found to be the best derivatives

(1) For paper XIV in this series see THIS JOURNAL, **75**, 5305 (1953).

(2) A. Ek, H. Kissman, J. B. Patrick and B. Witkop, *Experientia*, **8**, 36 (1952).

(3) P. L. Julian, J. Pikl and D. Boggess, THIS JOURNAL, **56**, 1797 (1934); P. L. Julian and J. Pikl, *ibid.*, **57**, 539, 563, 755 (1935); E. C. Horning and M. W. Rutenberg, *ibid.*, **72**, 3534 (1950).



for study of C_3-alkylation of dioxindoles. While their exhaustive chemistry will be the subject of a later communication, it may be stated here that they are obtained as crystalline derivatives in good yield; they readily form soluble sodio derivatives in benzene and thus provide promising new reagents for obtaining C_3-alkylated indole derivatives.

When ethyl acrylate was added carefully to a solution of 3-(tetrahydropyran-2-yloxy)-oxindole (VIII) in alcoholic sodium ethylate, an oily ester IX was obtained which could not be induced to crystallize, or distil without deep-seated decomposition. Alkaline hydrolysis and careful acidification of the crude ester gave X as a mobile oil which also could not be induced to crystallize. The crude oily acid X was, however, dissolved in ether and treated with a few drops of 18% hydrochloric acid, whereupon the tetrahydropyranyl ether (X) was cleaved and crystalline dioxindole-3-propionic acid (XII) was obtained in 57% yield based upon VIII.

A substance reported to be dioxindole-3-propionic acid was prepared several years ago by Kendall, Osterberg and MacKenzie.[4a]

Its constitution has been accepted until now with reservations, primarily because of doubt as to the authenticity of Kendall's oxindole-3-propionic acid (XI) from which the supposed XII was prepared. Recently we reported[5] a novel and simple synthesis of oxindole-3-propionic acid (XI), and found it identical with the compound given this structure and synthesized by Kendall, *et al.*,[4] by a very involved procedure.

In this work Kendall and Osterberg called special attention to the ease with which the C_3-hydrogen of their oxindole-3-propionic acid was replaced by hydroxyl,[6] indeed with molecular oxygen. Later Julian and Pikl,[7] having overlooked the work of Kendall, rediscovered this same susceptibility to oxidation on the part of 3-monoalkyloxindoles, and were able to convert 1,3-dimethyloxindole almost quantitatively into 1,3-dimethyldioxindole by bubbling moist air through an ethereal suspension of the sodio derivative of the former.

Kendall suggested that the oxidation product of his oxindole-3-propionic acid (XI) was dioxindole-3-propionic acid (XII) and indeed prepared a crystalline product, m.p. 199°, having presumably this constitution, by treating his oxindole-3-propionic acid with iodine in excess sodium hydroxide solution. While his attempt at structural proof led him into a maze of yet untangled observations and deductions, the characteristically excellent experimental work of his school is again attested by the correctness of the structure assigned to this acid. A repetition of Kendall's iodine–sodium hydroxide oxidation of our synthetic oxindole-3-propionic acid (XI) gave dioxindole-3-propionic acid (XII) identical with the product reported in this paper by a synthesis which leaves no doubt as to its constitution.

Experimental[8]

3-(Tetrahydropyran-2-yloxy)-oxindole (VIII).—Twenty nine and eight-tenths grams of finely powdered dioxindole (m.p. 168–171°) was slurried with 60 g. of purified dihydropyran (the dihydropyran was purified by refluxing over sodium and then distilling over calcium hydride, b.p. 84–86°) and 500 ml. of anhydrous ether. To this suspension was added 3 ml. of concentrated hydrochloric acid and the resulting mixture was agitated until solution ensued (12–18 hours). The solution was made alkaline by the addition of 10% sodium bicarbonate, then was washed exhaustively with water. The ethereal extract was dried over anhydrous potassium carbonate and the ether was removed by distillation. (Excess heating of the residual red oil resulted in a poor yield.) The residual red mobile sirup was then slurried with 50 ml. of anhydrous ether, whereupon a heavy crystalline precipitate of the tetrahydropyranyl ether separated rapidly. The product was chilled, filtered and washed with ether. A first crop of 30 g., m.p. 120–122°, was obtained. The mother liquor was concentrated and a second crop of material, 3 g., m.p. 119–121°, was obtained from ether–petroleum ether (yield 70%). For analysis, the product was recrystallized from methanol–ether and white prisms, m.p. 119–120°, were obtained.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.10; H, 6.40; N, 6.14.

(4) (a) E. C. Kendall, A. E. Osterberg and B. F. MacKenzie, THIS JOURNAL, **48**, 1384 (1926); (b) E. C. Kendall and A. E. Osterberg, *ibid.*, **49**, 2047 (1927).

(5) P. L. Julian and H. C. Printy, *ibid.*, **75**, 5301 (1953).

(6) See reference 4b, especially footnote, page 2054.

(7) P. L. Julian and J. Pikl, THIS JOURNAL, **57**, 539 (1935). See particularly page 542.

(8) All melting points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

3-(Tetrahydropyran-2-yloxy)-oxindole-3-propionic Acid (X) from VIII.—Nine and thirty-two hundredths grams (0.04 mole) of the tetrahydropyranyl ether of dioxindole (VIII) was added to a solution of 1 g. of sodium in 30 ml. of absolute ethanol. This mixture was warmed gently in a nitrogen atmosphere to effect solution. To this solution was carefully added 5 ml. of ethyl acrylate (exothermic reaction). The reaction mixture was then refluxed for 2 hours. The solution was refluxed an additional hour under nitrogen after the addition of 2.6 g. of sodium hydroxide in 20 ml. of water. The solution was then concentrated to remove the alcohol, acidified with concentrated hydrochloric acid and extracted with two 50-ml. portions of methylene chloride. The methylene chloride solution was concentrated to a mobile oil (12.85 g.). Attempts to isolate the 3-(tetrahydropyran-2-yloxy)-oxindole-3-propionic acid (X) were unsuccessful.

Dioxindole-3-propionic Acid (XII) from X.—The yellow oil X was dissolved in 50 ml. of anhydrous ether and 10 drops of 18% hydrochloric acid was added. This solution precipitated an oil which crystallized on chilling and swirling. The product was filtered and washed with ether. Five and two-hundredths grams of dioxindole-3-propionic acid (XII) was obtained, m.p. 176–180°, with some effervescence, which gave no depression when mixed with the Kendall preparation. A 57% yield was obtained from 3-(tetrahydropyran-2-yloxy)-oxindole (VIII). The analytical sample was recrystallized from water and a fine powder, m.p. 195–196°, was obtained.

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01. Found: C, 59.98; H, 4.78.

Kendall's Preparation of Dioxindole-3-propionic Acid (XII) from Oxindole-3-propionic Acid (XI).—Two and five-hundredths grams (0.01 mole) of oxindole-3-propionic acid (XI) was dissolved in 10 ml. of 1.0 *N* sodium hydroxide and cooled to 10°. Two equivalents (2.54 g.) of finely divided iodine was added; 6 ml. of 5 *N* sodium hydroxide was then added slowly with swirling. The solution was allowed to come to room temperature and 8 ml. of 5 *N* sulfuric acid was added followed by 0.71 g. of iodic acid in 10 ml. of water. The mixture was then warmed gently to coagulate the iodine, filtered, and the filtrate was concentrated *in vacuo* until crystallization began. The crystals which separated on cooling were filtered and washed with water. Two grams of dioxindole-3-propionic acid (XII), m.p. 178–180°, (yield 90%) was obtained. The product when recrystallized from water gave a fine crystalline powder, m.p. 195–196°.

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[CONTRIBUTION FROM THE JULIAN LABORATORIES, INC.]

Studies in the Indole Series. XVI.[1] Oxindole-3-alanine and Dioxindole-3-alanine

BY PERCY L. JULIAN, EARL E. DAILEY, HELEN C. PRINTY, HYMAN L. COHEN AND SHINICHI HAMASHIGE[2]

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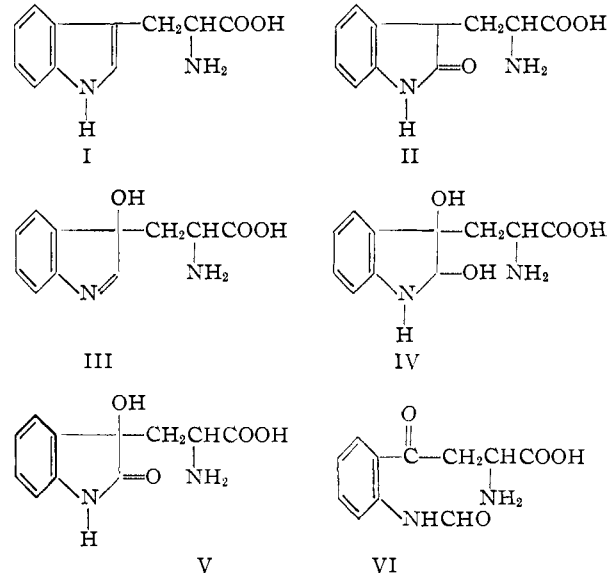
A new synthesis of oxindole-3-alanine is devised and three distinct improvements and safeguards are suggested for the Cornforth synthesis of this substance, thus making this amino acid a readily available material for further syntheses of substances related to natural products. Dioxindole-3-alanine, suggested as a possible intermediate in the metabolic transformation of tryptophan into formylkynurenine, also has been synthesized. Condensation of the tetrahydropyranyl ether (VII) of dioxindole with methoxymethylmalonic ester, hydrolysis, nitrosylation of the resulting lactone XI of α-carboxy-β-dioxindolyl-3-propionic acid (X) and catalytic hydrogenolysis of the obtained lactone XII of α-oximino-β-dioxindolyl-3-propionic acid (XVII) lead, on the one hand, to oxindole-3-alanine, while catalytic reduction of the oximino acid XVII itself gave dioxindole-3-alanine in two diastereomeric forms, separated and characterized by several derivatives and by use of the Dakin–West reaction.

The search for the missing chemical link, or links, between tryptophan (I) and formylkynurenine (VI) in the metabolic transformation of the former,[1] has been the subject of numerous endeavors over the past two decades. The literature contains several recent summaries[3] of this work. Four potential intermediates have been suggested for this metabolic pathway: oxindole-3-alanine (II), 3-hydroxyindolenine-3-alanine (III), 2,3-dihydroxyindoline-3-alanine (IV) and dioxindole-3-alanine (V). The synthesis of the first of these (II) has recently been reported from six laboratories.[4] It has been eliminated as an intermediate because of its inactivity in the oxidase–peroxidase system of Knox and Mehler,[5] as well as with the tryptophan-



(1) For paper XV in this series, see THIS JOURNAL, **78**, 3501 (1956).

(2) Antioch College Cooperative student, March to August, 1952.

(3) (a) C. E. Dalgliesh, *Quart. Revs. (London)*, **5**, 227 (1951); (b) P. L. Julian, E. W. Meyer and H. C. Printy in Elderfield's "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 63, 182; (c) A. Ek, H. Kissman, J. B. Patrick and B. Witkop, *Experientia*, **8**, 36 (1952); (d) A. H. Mehler in "Amino Acid Metabolism," edited by William McElroy and Bentley Glass, The Johns Hopkins Press, Baltimore, Md., 1955, p. 882.

(4) (a) B. Witkop, *Ann.*, **558**, 98 (1947); (b) M. Kotake, T. Sakan and T. Miwa, THIS JOURNAL, **72**, 5085 (1950); (c) J. W. Cornforth, R. H. Cornforth, C. E. Dalgliesh and A. Neuberger, *Biochem. J.*, **48**, 591 (1951); (d) H. Behringer and H. Weissauer, *Chem. Ber.*, **85**, 743 (1952); (e) H. Rinderknecht, H. Koechlin and C. Niemann, *J. Org. Chem.*, **18**, 971 (1953); (f) T. Wieland, O. Wieberg and W. Dilger, *Ann.*, **592**, 69 (1955).

(5) (a) W. E. Knox and A. H. Mehler, *J. Biol. Chem.*, **187**, 419 (1950); (b) A. H. Mehler and W. E. Knox, *ibid.*, **187**, 431 (1950); (c) C. E. Dalgliesh, W. E. Knox and A. Neuberger, *Nature*, **168**, 20 (1951).