the catalyst washed with benzene and the combined filtrates were evaporated *in vacuo* at 100°. The residue crystallized spontaneously; yield 0.29 g.; m.p. 172–176°. Recrystallization from acetic acid and then from alcohol gave colorless, elongated rods of the correct m.p. 177–178°.

The trinitrobenzene complex crystallized in yellow leaflets, m.p. 136–137°.

Anal. Calcd. for $C_{28}H_{17}N_3O_6$: C, 68.5; H, 3.5. Found: C, 68.9; H, 3.4.

(b) A mixture of 280 mg. of (IX) and 70 mg. of sulfur was heated for 20 minutes at 250–280°. Sublimation at 170° (0.1 mm.) gave pale yellow crystals of m.p. 176–177°; yield 150 mg. Recrystallization from acetic acid gave pure material of m.p. 177–178°.

Anal. Calcd. for $C_{22}H_{14}$: C, 95.0; H, 5.0. Found: C, 94.8; H, 4.9.

(c) The dihydro-compound (IX) (280 mg.), N-bromosuccinimide (200 mg.), benzoyl peroxide (10 mg.) and carbon tetrachloride (15 cc.) were refluxed for 45 minutes. Hydrogen bromide was evolved throughout the reaction. The reaction mixture was cooled to room temperature, filtered and evaporated *in vacuo*. The residue (m.p. 130–140°) was dissolved in 10 cc. of glacial acetic acid. One gram of anhydrous potassium acetate was added and the whole refluxed for one hour. The solvent was evaporated *in vacuo*, water added and the precipitate filtered and washed with water; m.p. 140–145°. After three crystallizations from acetic acid the material melted at 176–177° (50 mg.), and the trinitrobenzene complex at 136–137°. Both products showed no depression in melting point in mixture with the materials obtained by methods (a) and (b).

DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, ISRAEL

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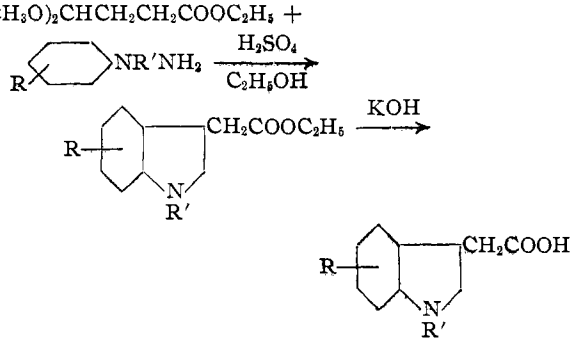
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

A Convenient Synthesis of Indole-3-acetic Acids[1]

BY MILON W. BULLOCK AND SIDNEY W. FOX[2]

A convenient synthesis of indole-3-acetic acids from ethyl γ,γ-dimethoxybutyrate and a phenylhydrazine or phenylhydrazine hydrochloride has been described. By this procedure it is possible to prepare the intermediate ethyl succinaldehydate phenylhydrazone and to cyclize the intermediate to the corresponding indole-3-acetic acid in one operation. Several indole-3-acetic acids have been prepared by this method. The method has also been applied to the preparation of 2-methylindole-3-acetic acid from levulinic acid and to the preparation of 3-ethylindole from butyraldehyde.

The phytologically important indole-3-acetic acid and derivatives with substituents in the benzene ring have recently been made available through the Fischer ring closure of the succinaldehydic acid phenylhydrazones obtained indirectly from glutamic acid.[3] A more direct method has now been developed for the synthesis of these compounds. It has been found possible to prepare the intermediate phenylhydrazones and to carry out the cyclization reaction in one operation. This procedure employs as the starting materials ethyl γ,γ-dimethoxybutyrate[4] and a phenylhydrazine or a phenylhydrazine hydrochloride.



To prepare the indole-3-acetic acid it is necessary only to reflux a solution of the acetal and a phenylhydrazine in a solution containing a suitable catalyst, similarly to the direct ring closure of cyclohexanone phenylhydrazone.[5] In the indole-3-acetic acid series a solution of sulfuric acid in ethanol is employed to catalyze the phenylhydrazone formation and to effect the cyclization. The yields obtained by this method parallel those in which the succinaldehydic acid phenylhydrazones were used as starting material,[3] a fact which suggests that the limiting factor is the cyclization reaction and that the formation of the phenylhydrazone from the acetal occurs in good yield.

The method has been applied to the synthesis of 5-fluoroindole-3-acetic acid, 5,7-dichloroindole-3-acetic acid and 1-methylindole-3-acetic acid as well as to indole-3-acetic acid itself. The products were in most experiments obtained from the saponification reaction in a nearly pure state. The 5,7-dichloro derivative was an exception. An unidentified by-product was formed in large amounts and was separated from the desired product with some difficulty.

In order to determine whether carbonyl compounds could be substituted for acetals, experiments were conducted with levulinic acid and butyraldehyde. A 79% yield of 2-methylindole-3-acetic acid was obtained by refluxing equimolar quantities of levulinic acid and phenylhydrazine hydrochloride in ethanolic sulfuric acid. Only traces of impure 3-ethylindole were obtained from butyraldehyde and phenylhydrazine in ethanolic sulfuric acid; however, a 15% yield of 3-ethylindole was obtained with boron trifluoride in benzene.[6] It is not surprising that no 3-ethylindole was obtained from the sulfuric acid solution, as Korczynski and co-workers[7] have reported that the

(1) Journal Paper No. J-1925 of the Iowa Agricultural Experiment Station, Project 1110, Preparation of Chemicals for Agricultural Utility.

(2) Author to whom inquiries should be addressed.

(3) S. W. Fox and M. W. Bullock, THIS JOURNAL, **73**, 2756 (1951).

(4) Ethyl γ,γ-dimethoxybutyrate apparently has not been described in the literature; however, the closely related ethyl γ-oxobutyrate and ethyl γ,γ-diethoxybutyrate have been described and are readily available through the hydroformylation of ethyl acrylate; *cf.*, H. Adkins and G. Krsek, *ibid.*, **71**, 3051 (1949).

(5) C. U. Rogers and B. B. Corson, *ibid.*, **69**, 2910 (1947).

(6) H. R. Snyder and C. W. Smith, *ibid.*, **65**, 2452 (1943).

(7) A. Korczynski, W. Brydowna and L. Kierzek, *Gazz. chim. ital.*, **56**, 903 (1926).

preparation of 3-ethylindole by the cyclization of butyraldehyde phenylhydrazone with ethanolic hydrogen chloride was not successful. These acidic cyclization agents polymerized the indole derivative.

Experimental[8]

Indole-3-acetic Acid.—A solution of 20.0 g. (0.135 mole) of ethyl γ,γ-dimethoxybutyrate,[9] 16.6 g. (0.135 mole) of phenylhydrazine hydrochloride, 360 ml. of absolute ethanol, and 40 ml. of concentrated sulfuric acid was refluxed under a nitrogen atmosphere for 8 hr. The cooled reaction mixture was poured into 1 l. of ice-water and the oil extracted with 350- and 250-ml. portions of ether. The combined ether extracts were washed with half-saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the ether left 21 g. of a yellow oil. This crude ester was purified by vacuum distillation through a short vacuum-jacketed Vigreux column to give 6.0 g. distilling 150–155° at 0.1–0.25 mm. The ester was saponified by refluxing for 20 minutes with 30 ml. of 10% methanolic potassium hydroxide. Some of the potassium indole-3-acetate separated in plates during the saponification. The salt was filtered off and dissolved in water. Acidification of the aqueous solution gave 3.0 g. of almost pure indole-3-acetic acid; m.p. 166–167° (dec.). The mother liquor from which the salt was filtered was diluted with 30 ml. of water and distilled until the temperature of the vapor was 90°. The cooled solution was extracted with 30 ml. of ether, the distillation of which left a trace of crystalline product having the odor of skatole. Acidification of the aqueous solution with 10% hydrochloric acid gave a white crystalline product, which was filtered off and washed with water. This sample m.p. 166° (dec.); total yield 4.9 g., 21%. A recrystallization from water (Norit A) gave pure indole-3-acetic acid; m.p. 166–168° (dec.), mixed m.p. with authentic indole-3-acetic acid 166–168°.

5-Fluoroindole-3-acetic Acid.—A solution of 20.0 g. (0.135 mole) of ethyl γ,γ-dimethoxybutyrate, 17.6 g. (0.108 mole) of *p*-fluorophenylhydrazine hydrochloride,[10] 360 ml. of absolute ethanol and 40 ml. of concd. sulfuric acid was refluxed in a nitrogen atmosphere for 8 hr. The cooled solution was poured into 1 l. of ice-water and the oil extracted with 350-, 250- and 150-ml. portions of ether. The combined ether extracts were washed with half-saturated sodium bicarbonate solution, dried over sodium sulfate and distilled. The oily residue was vacuum distilled through a short vacuum-jacketed stillhead to give 14.2 g., b.p. 150–175° at 0.4 mm. The ester was saponified by refluxing 20 min. with 60 ml. of 10% methanolic potassium hydroxide. The alkaline solution was diluted with 50 ml. of water and distilled until the temperature of the vapor was 96°. The cooled solution was extracted with 30 ml. of ether, the distillation of which left no residue. The aqueous solution was heated to boiling with 0.5 g. of Norit A and filtered. Acidification of the filtrate with 10% hydrochloric acid gave 11.0 g., 53%, from the *p*-fluorophenylhydrazine hydrochloride, of almost pure acid, m.p. 138–139°. After one recrystallization from water (Norit A) the acid m.p. 138–140°.

Anal. Calcd. for $C_{10}H_8O_2NF$: neut. equiv., 193.2; N, 7.24. Found: neut. equiv. (potentiometric), 192; N, 7.01, 7.12.

5,7-Dichloroindole-3-acetic Acid.—A solution of 31.2 g. (0.146 mole) of 2,4-dichlorophenylhydrazine hydrochloride[11] 23.0 g. (0.155 mole) of ethyl γ,γ-dimethoxybutyrate, 360 ml. of absolute ethanol and 40 ml. of concentrated sulfuric acid was refluxed under nitrogen for 8 hr. The cooled solution was poured into 1.5 liters of ice-water and the ester extracted with 350- and two 250-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and vacuum distilled through a short vacuum-jacketed stillhead. The product distilled over a wide range. The fraction distilling 110–240° at 0.15 mm. and weighing 17 g. was collected. This crude ester was saponified by refluxing 30 min. with 60 ml. of 10% methanolic potassium hydroxide. The solution was diluted with an equal volume of water and distilled until the temperature of the vapor was 97°. The cooled solution was extracted with two 40-ml. portions of ether, the distillation of which left a trace of oil. The aqueous solution was heated to boiling with 1 g. of Norit A and filtered. Careful acidification of the filtrate with 10% hydrochloric acid gave a brown tar, which was recovered by decantation and dried. Extraction of the tar with 20 ml. of chloroform left 4.0 g. (0.0164 mole), 11%, of almost white crystals; m.p. 181–188°. Three recrystallizations from 50% ethanol gave a product m.p. 192–196°; mixed m.p. with an authentic sample of 5,7-dichloroindole-3-acetic acid, 194–197°,[3] was 193–196°. The yield of the purified acid was only 7% of the 5,7-dichlorophenylhydrazine hydrochloride used as starting material. The chloroform-soluble fraction could not be obtained in a satisfactory condition for analysis.

1-Methylindole-3-acetic Acid.—A solution of 15.0 g. (0.085 mole) of ethyl γ,γ-dimethoxybutyrate, 10.4 g. (0.085 mole) of α-methyl-α-phenylhydrazine,[12] 180 ml. of absolute ethanol and 20 ml. of concentrated sulfuric acid was refluxed in a nitrogen atmosphere for five hours. The cooled solution was poured into 500 ml. of ice-water and the oily ester extracted with four 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate containing a small amount of sodium bicarbonate and distilled. The oily residue was purified by distillation through a short vacuum-jacketed Claisen stillhead. The ester distilled 155–160° at 0.4 mm. The crude ethyl 1-methylindole-3-acetate (13.0 g.) was saponified by refluxing 40 min. with 90 ml. of 10% methanolic potassium hydroxide. Fifty ml. of water was added and the methanol distilled off. More water was added from time to time so that the volume of the solution remained above 70 ml. The basic solution was extracted with 60 ml. of ether. The aqueous layer was heated with 0.5 g. of Norit A and filtered. Acidification with 10% hydrochloric acid gave 10.4 g., 64%, of crude 1-methylindole-3-acetic acid, m.p. 117°. Extraction of the crude material with chloroform gave a pure product, but was not entirely satisfactory because of the moderate solubility of the product in the solvent. The acid remaining in the chloroform was recovered by extraction with 30 ml. of *N* NaOH, and separated from a tarry contaminant by recrystallization from water (Norit A). The combined crops from the chloroform extraction and the recrystallization from water were recrystallized from a 50% solution of Skellysolve B in benzene. The yield of pure acid, m.p. 127–129°,[13] was 8.2 g., 51%.

2-Methylindole-3-acetic Acid.—A solution of 28.8 g. (0.248 mole) of levulinic acid, 36 g. (0.248 mole) of phenylhydrazine hydrochloride, 180 ml. of absolute ethanol and 20 ml. of concentrated sulfuric acid were refluxed for 3.5 hours. A solid separating from the refluxing solution was filtered off after the solution had cooled and washed with absolute ethanol. This salt weighed 10.5 g. and m.p. 332–335° (dec.) after softening from 180°. The identity of this product was not established.

The ethanol solution from which the salt was filtered was poured into 1 liter of ice-water and the precipitated oil was extracted with three 250-ml. portions of ether. The combined ether extracts were washed with 150 ml. of half-saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the ether solution left a dark oil which was purified by vacuum distillation. This distillation gave 45 g., 89%, of ethyl 2-methylindole-3-acetate,[14] b.p. 158–160° at 0.15 mm.

The ester was saponified by refluxing 30 min. with 160 ml. of 10% methanolic potassium hydroxide. The solution was diluted with 200 ml. of water and the methanol distilled off. The cooled solution was extracted with 50 ml. of ether, the distillation of which left a trace of oil. The aqueous layer was heated to boiling with 0.5 g. of Norit A and filtered. Acidification of the filtrate with 10% hydrochloric acid gave a crystalline product. After the solution had cooled the crystals were collected by filtration and washed with water.

(8) Melting points are corrected. Nitrogen was assayed by the micro Dumas method.

(9) Kindly furnished by the Rohm and Haas Company, Philadelphia, Pa. The material used in these experiments was a purified sample, b.p. 102–103° at 20 mm.

(10) G. Schiemann and W. Winkelmüller, *Ber.*, **66**, 729 (1933).

(11) F. D. Chattaway and C. F. B. Pearce, *J. Chem. Soc.*, **107**, 32 (1915).

(12) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 418.

(13) H. R. Snyder and E. L. Eliel, THIS JOURNAL, **70**, 1703 (1948).

(14) T. Hoshino and K. Shimodaira, *Ann.*, **520**, 19 (1935).

This gave 34.7 g. of pure acid; m.p. 197–199° (dec.).[6] An additional 2 g. of pure product was recovered from the mother liquor; total yield of pure product 36.7 g. (87% based on the ester, or 79% on the levulinic acid).

3-Ethylindole.—Thirty-nine and four-tenths gram (0.28 mole) of boron trifluoride etherate was slowly poured down the condenser into a solution of 20 g. (0.28 mole) of butyraldehyde and 32.8 g. (0.28 mole) of phenylhydrazine in 90 ml. of benzene. The solution refluxed a few minutes from the heat of reaction and separated into two phases. The mixture was refluxed for two hours and the benzene distilled off. The residue was triturated with water and the oily product extracted with ether. A small amount of unidentified solid insoluble in ether or water was filtered off and discarded. Distillation of the ether extract left an oil which was vacuum distilled to give 6.0 g. (15%) distilling at 138–139° at 6 mm. This product could not be crystallized from Skellysolve B, but was identified by the picrate with m.p. 114–115°[15] after one recrystallization from a benzene–Skellysolve B solution.

(15) G. Plancher and O. Carrasco, *Atti. Accad. Lincei*, [5] **14**, II, 31 (1905).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Raney Nickel Desulfuration

BY CHARLES D. HURD AND BERNARD RUDNER[1]

Three modifications of Raney nickel were investigated in the desulfuration of three compounds containing the thiocarbonyl group, five thiazoles, and one thiophene derivative. From *o*-tolyl isothiocyanate or *o*-tolylthiourea the product obtained was *o*-toluidine. Thiobenzanilide gave rise to N-benzylaniline. Aniline was the major product from 2-mercaptobenzothiazole, with lesser quantities of *o*-aminothiophenol and benzothiazole. Acetophenone was formed in quantity from both 2-mercapto- and 2-amino-4-phenylthiazole; other products from the latter were methylamine and 1-phenylethylamine, and from the former 4-phenylthiazole. Acetamide and acetaldehyde were the chief products, respectively, from 2-amino- and 2-mercapto-4-hydroxythiazole. 2-Thienyl methyl ketone underwent desulfuration into 2-hexanone, but small quantities of acetaldehyde and ethyl alcohol were formed also.

The numerous recent reports on desulfuration of organic compounds[2,3] have prompted us to summarize our findings in this field. This paper reports new data regarding desulfuration by Raney nickel.

Three generally similar methods were used for preparing the nickel from its alloy $NiAl_2$: (A) the second procedure described by Mozingo[4]; (B) a procedure somewhat similar to that used for the Adkins–Pavlic W-4 nickel[5]; and (C) a procedure similar to that used by Ralls, Dodson and Riegel.[6] It was found that the hydrogenolytic activity of the nickels increased in the order (A), (B), (C). Nickel-C appeared to have a much greater amount of adsorbed hydrogen than the other two.

Three types of carbocyclic compounds and two heterocyclic systems were chosen for study. Each of the carbocyclics contained a nitrogen–carbon–sulfur triad: *o*-tolyl isothiocyanate, *o*-tolylthiourea and thiobenzanilide. Mozingo nickel in refluxing benzene converted *o*-tolyl isothiocyanate into *o*-toluidine in 64% of the theoretical yield. *o*-Tolylthiourea, with five times its weight of nickel-C, gave an 82% yield of *o*-toluidine. In neither reaction mixture could secondary amines or single-carbon compounds be detected. In spite of the report by Bougault and his co-workers that benzylthiourea yielded toluene rather than benzylamine on desulfuration,[7] Ashworth[8] only obtained an unidentifiable basic liquid from *p*-chlorophenylthiourea. Thiobenzanilide was reduced with seven to eight times its weight of nickel-B in benzene, producing an 86% yield of benzylaniline but no aniline.

2-Mercaptobenzothiazole (Captax) was readily cleaved by nickel-C to yield 2.9% of benzothiazole, 20.7% of *o*-aminothiophenol and 54.6% of aniline. Nickel-A under similar conditions gave 31% of *o*-aminothiophenol, 12% of aniline and 36% of *o*-aminophenyl disulfide. The facile rupture of the heterocyclic ring was surprising in view of the report[9] that mercaptobenzothiazole is not altered by hydrogenation over Raney nickel.

2-Mercapto-4-phenylthiazole was considerably more resistant to cleavage than "Captax." Prolonged heating with eight to ten times its weight of nickel converted the thiazole to a tar and 15% of the theoretical yield of 4-phenylthiazole. From the tar acetophenone was obtained, both free and in a combined, acid-labile form, totalling 48% of the theoretical amount. A small quantity of unidentified basic tar was formed as well, and an even smaller quantity of starting material was recovered. 2-Amino-4-phenylthiazole proved even more resistant to hydrogenolysis. By prolonged heating with nickel-C, it was converted to acetophenone (45%), *dl*-phenylethylamine (9%) and methylamine (11.5%). An appreciable quantity of starting material was recovered. The ease of cleavage of thiazoles by Raney nickel is apparently dependent on the nature and position of the thiazole substituents. Heilbron and his co-workers[10] showed that although 2-hydroxy-4-phenyl-5-aminothiazole underwent cleavage and rearrangement to yield (phenylethylene)-urea, 2-mercapto-4-phenyl-5-aminothiazole formed only 4-phenyl-5-aminothiazole. Marrian[11] reported that desulfuration of substituted 2-amino-4-hydroxy-5-thiazoleacetamides gave sub-

(1) The Texas Company fellow, 1948–1949.

(2) Cook, Heilbron and Hunter, *J. Chem. Soc.*, 1797 (1949); Blicke and Sheets, THIS JOURNAL, **71**, 4010 (1949).

(3) Rylander and Campaigne, *J. Org. Chem.*, **15**, 24 (1950).

(4) Mozingo, THIS JOURNAL, **66**, 1015 (1943).

(5) Adkins and Pavlic, *ibid.*, **69**, 3039 (1947).

(6) Ralls, Dodson and Riegel, *ibid.*, **71**, 3320 (1949).

(7) Bougault, Cattelain and Chabrier, *Compt. rend.*, **208**, 657 (1939).

(8) Ashworth, *J. Chem. Soc.*, 1716 (1948).

(9) Blomquist and Diuguid, *J. Org. Chem.*, **12**, 723 (1947).

(10) Cook, Heilbron and Levy, *J. Chem. Soc.*, 1598 (1947); Cook Heilbron and Hunter, *ibid.*, 1443 (1949).

(11) Marrian, *ibid.*, 1797 (1949).