[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

APPLICATION OF REFORMATSKY AND GRIGNARD REAGENTS TO 1,2-DISUBSTITUTED INDOXYLS

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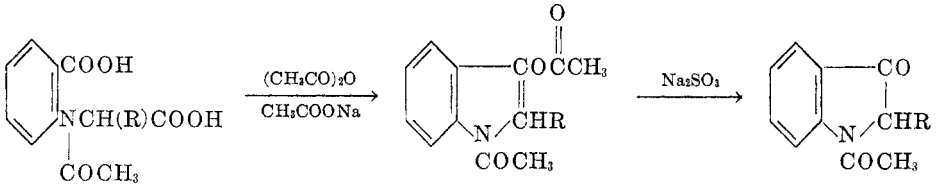
Vorlander (1) has reported the formation of 1,3-diacetylindoxyl by the cyclization of the N-acetyl derivative of phenylglycine-*o*-carboxylic acid using acetic anhydride and dry sodium acetate. This has been transformed into 1-acetylindoxyl by selective hydrolysis (2) using sodium sulfite, sodium bisulfite, or disodium hydrogen phosphate. Now, by similar reactions, there have been prepared 1-acetyl-2-methylindoxyl (IA) and 1-acetyl-2-phenylindoxyl (IB) from the respective 1,3-diacetyl derivatives described by van Alphen (3).

CHART I



IA, IB

IA. R = CH_3 IB. R = C_6H_5

Compounds IA and IB were subjected to treatment with zinc and ethyl bromoacetate, yielding respectively compounds IIA and IIB which appear to be the normal Reformatsky products resulting from reaction of the carbonyl group of each substituted indoxyl derivative. This was indicated by the subsequent results: dehydration of the individual β-hydroxy ester, followed by hydrolytic removal of the ester and acetyl groups gave the respective 2-substituted-indoleacetic acids (IVA and IVB).

Further, the substituted indoleacetic acids (IVA and IVB) were prepared from the corresponding 2-substituted-gramines by the method of Snyder and co-workers (4, 5) and the products from the two sources were identical.

The Grignard reaction was applied to compounds IA and IB since this suggested a flexible method of preparation of a number of substituted indoles (See Chart III). Methylmagnesium iodide and phenylmagnesium bromide yielded respectively 1-acetyl-2,3-dimethylindole (VIII) and 1-acetyl-2,3-diphenylindole (XII) from IA and IB, after dehydration of the initial tertiary alcohol products.

Acetylation of 2,3-dimethylindole (IX), obtained by the Fischer indole synthesis, yielded 1-acetyl-2,3-dimethylindole (VIII) identical with that obtained from IA.

The identity of XII was shown by its preparation independently by the method of Japp and Murray (6) as modified by Fennel and Plant (7).

CHART II

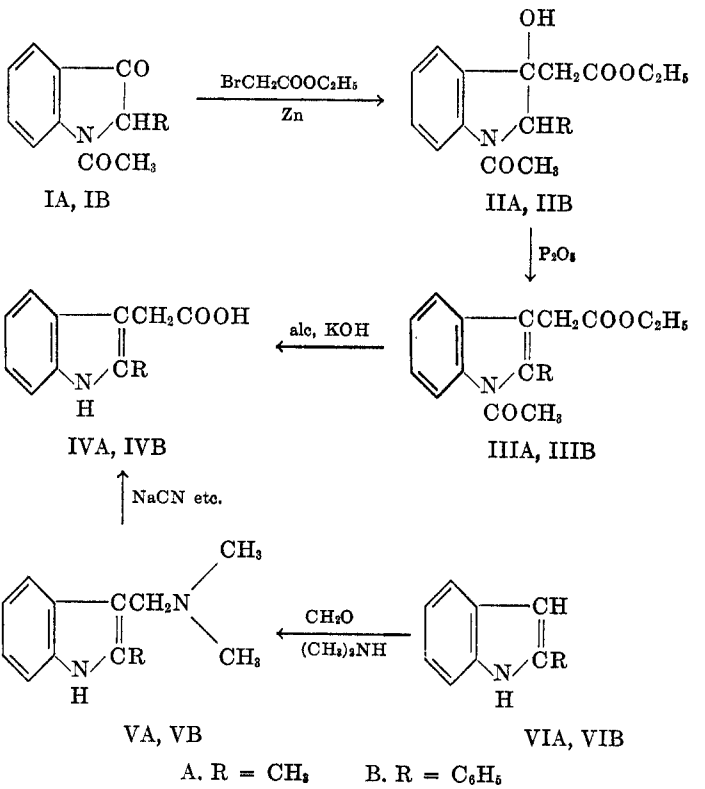
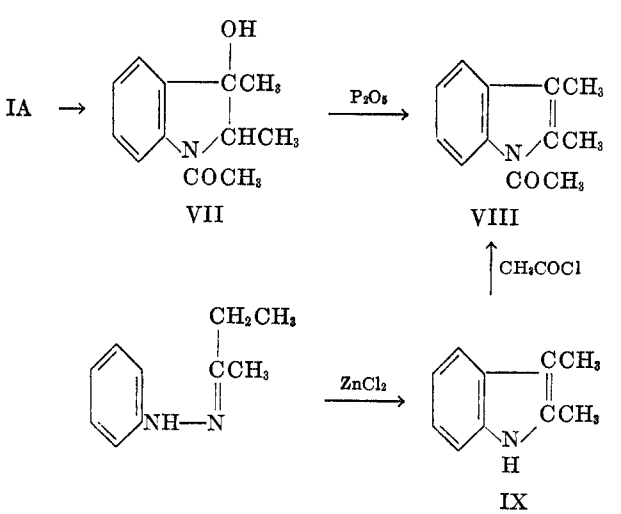


CHART III



EXPERIMENTAL

α-(o-Carboxyanilino)propionic acid. To a solution of 250 g. (2.36 moles) of anhydrous sodium carbonate in 350 ml. of water, was added 68 g. (0.5 mole) of anthranilic acid with stirring. When the solid material had dissolved, 55 g. (0.51 mole) of α-chloropropionic acid was added with stirring. The solution was heated over a steam-bath for four hours. Treatment with Norit, hot filtration, and acidification with conc'd hydrochloric acid followed. Cooling overnight yielded a solid product; this was washed with water, pressed nearly dry, and was dried at 85°. The light gray crude (m.p. 190–200°; yield 68.5 g., 66%) was used without further purification in the next step. The melting point reported by van Alphen (3) is 216°.

N-Acetyl-α-(o-carboxyanilino)propionic acid. To a solution of 159 g. (3.98 moles) of sodium hydroxide in 1590 ml. of water, 318 g. (1.52 moles) of α-(o-carboxyanilino)propionic acid was added and the mixture was stirred until solution was complete. Acetic anhydride (3.4 moles) was added all at once without cooling and the mixture was stirred for 20 minutes. A second portion of acetic anhydride was added (3.4 moles) and stirring was continued for 20 minutes without cooling. This was followed by one-half hour of heating on a steam-bath. The hot solution was made acidic with conc'd hydrochloric acid, cooled, and left in a refrigerator overnight. The crude product was filtered, washed rapidly with water, air-dried, and finally it was dried under a vacuum over phosphorus pentoxide. The crude material was a white crystalline powder, m.p. 184–195°, yield 344 g. (90%). This was used as such in the next step. A small sample of the crude material was purified by successive crystallizations from 5% hydrochloric acid and from 95% ethyl alcohol; m.p. 205.3–205.6°.

Anal. Calc'd for $C_{12}H_{13}NO_5$: N, 5.58. Found: N, 5.46.

1,3-Diacetyl-2-methylindoxyl. A 500-ml. flask, three-necked, was equipped with a mercury-sealed stirrer, a condenser with a drying-tube, and a system for providing an atmosphere of nitrogen. To the flask was added 250 ml. (2.65 moles) of acetic anhydride, 50 g. (0.2 mole) of N-acetyl-α-(o-carboxyanilino)propionic acid, and finally 50 g. (0.61 mole) of freshly fused sodium acetate. The vigorously stirred mixture was heated in an oil-bath (bath temperature 165°) for one-half hour. Then the flask contents were cooled to about 100°, and 75 ml. of water was added dropwise. The acetic anhydride decomposition was completed by heating several minutes on the steam-bath. The acetic acid so-formed was removed by vacuum-distillation (20 mm.). The residue was triturated successively with 200 ml. of water, 200 ml. of 5% aqueous sodium carbonate, and 200 ml. of water. The crude product was a light yellow, m.p. 125–126°; yield, 13.1 g. (28%). The reported (3) melting point is 134°. This material was used in the next step without further purification.

1-Acetyl-2-methylindoxyl (IA). A mixture of 73 g. (0.32 mole) of 1,3-diacetyl-2-methylindoxyl, 110 g. of anhydrous sodium sulfite, 365 ml. of dioxane, and 1100 ml. of water was refluxed over a steam-bath for three hours. Most of the water and the dioxane were removed at 20 mm., in a nitrogen atmosphere. The residue was triturated with several portions of water, filtered, pressed, and air-dried. The crude product was a pale yellow solid; m.p. 85–98°; yield 54 g. (91%).

This crude product 57.8 g. (0.30 mole) was recrystallized from 100 ml. of 95% ethyl alcohol, with Norit treatment. Crystallization seemed fairly complete after several hours in the refrigerator. Filtration, pressing, air-drying, and vacuum-drying yielded a first batch of product amounting to 44.8 g. or 75%. The melting point of this material was 95–98°. The mother liquor yielded further material (6.3 g; m.p. 93–97°). The combined yield was 86%. Four recrystallizations of a small sample from 95% ethyl alcohol gave white crystals, m.p. 98.3–99.3°.

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.78; H, 5.82; N, 7.41.
Found: C, 69.72; H, 6.13; N, 7.39.

Phenyl hydrazone of IA. Light yellow crystals from ethyl alcohol, m.p. 184.9–185.3°.

Anal. Calc'd for $C_{17}H_{17}N_3O$: N, 15.05. Found: N, 14.99

α-Chlorophenylacetic acid was prepared by the conventional method from mandelic

acid (8). It was condensed with anthranilic acid to form *α-(o-carboxyanilino)phenylacetic acid* (m.p. *circa* 195°; the literature reports 222° (3). The crude product was used for the preparation of *N-acetyl-α-(o-carboxyanilino)phenylacetic acid* (m.p. 193°) which was analyzed for check purposes.

Anal. Calc'd for $C_{17}H_{15}NO_5$: N, 4.47. Found: N, 4.35.

1,3-Diacetyl-2-phenylindoxyl. The same procedure was used as for the preparation of the corresponding 2-methyl derivative (*vide supra*). This is a light yellow, yield 47%; m.p. crude, 116–124°. The literature reports 126° for the pure product (3).

1-Acetyl-2-phenylindoxyl (IB). This was prepared by a method identical with that for Compound IA. This is a light yellow compound, as obtained from 95% ethyl alcohol crystallization. The yield was 68%, and additional less pure material was isolated from the mother liquor. M.p. 135–139°. Seven recrystallizations from ethyl alcohol did not change the melting range.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58.
Found: C, 76.01; H, 5.27; N, 5.47.

2-Methyl-3-indoleacetic acid (IVA). (*Using the Reformatsky reaction.*) A flask was equipped with a stirrer and a condenser protected with a calcium chloride tube. Into the flask was introduced 2 g. (0.0106 mole) of 1-acetyl-2-methylindoxyl (IA), 25 ml. of dry ether, 25 ml. of dry thiophene-free benzene, 5 g. of clean 20-mesh granular zinc, 0.15 g. of iodine, and finally 1.6 ml. of dry ethyl bromoacetate. The mixture was refluxed with stirring for 45 minutes. Five more additions of zinc and iodine were made at 45-minute intervals and two more additions of ethyl bromoacetate were made after 1½- and 3-hour intervals. The mixture was refluxed for a total of four hours with continuous stirring. The gray addition product was dissolved by adding 2 ml. of methanol-acetic acid solution (1:1 volume ratio) and the solution was decanted from the zinc into 50 ml. of ice-water. The zinc residue in the flask was rinsed with 20 ml. of fresh ether containing a few drops of methanol-acetic acid solution, and this was added to the above. The mixture was acidified with acetic acid (7 ml.) to Congo Red paper. After shaking thoroughly, the aqueous layer was separated and extracted with 50 ml. of ether. The combined organic extracts were washed with two 50-ml. portions of 5% aqueous ammonium hydroxide, finally with 50 ml. of water. The solution was dried over calcium chloride, then the solvents were removed by distillation, finally removing the last traces under a vacuum. This yielded 3.1 g. of a yellow, non-crystallizable oil (IIA). This was used in the next step without further purification.

The above crude (IIA) was dissolved in 10 ml. of dry benzene,3 g. of phosphorus pentoxide was added, and the mixture was refluxed over a steam-bath for three hours. The excess phosphorus pentoxide was destroyed by adding 10 ml. of water and stirring and cooling. To the mixture, 50 ml. of ether was added, then it was filtered to separate the small amount of purple solid from the two-liquid system. The aqueous layer was separated and extracted with 50 ml. more of ether. The combined organic extracts were washed with 20 ml. of 5% aqueous sodium bicarbonate solution, finally with 20 ml. of water. The organic solvents were removed by distillation over a steam-bath, finally under a vacuum. Approximately 2 g. of brown, non-crystallizable oil (IIIA) was obtained. This was used in the next step without further purification.

A mixture of the above crude (IIIA), 13 ml. of water, 5 ml. ethanol, and 2 g. sodium hydroxide was refluxed one hour over a steam-bath. The mixture was cooled, a small amount of undissolved, purple solid was filtered off, and the filtrate was treated with 0.5 g. of Norit for ten minutes over a steam-bath, then filtered. The dark red solution was acidified by concentrated hydrochloric acid, and cooled in ice for 30 minutes. The light brown precipitate was filtered, washed thoroughly with water, and dried under a vacuum. The crude product (IVA) was a brown granular solid, yield 0.95 g. (47% based on the amount of IA used), m.p. 158–170° with decomposition. Two recrystallizations from acetic acid yielded 0.42 g. (21%) of light tan crystals, m.p. 195–200° with decomposition. This melting point agreed with that reported by Fischer (9).

Anal. Calc'd for $C_{11}N_{11}NO_2$: N, 7.41. Found: N, 7.48.

2-Methylindole. (*By the Fischer method*). To a filtered solution of 20 g. (0.14 mole) of phenylhydrazine hydrochloride and 30 g. of sodium acetate in 200 ml. of water was added 5.8 g. (0.1 mole) of acetone with vigorous shaking. The product separated immediately as a yellow oil. After ½ hour, 100 ml. of ether was added, the mixture was shaken, and the aqueous layer was separated. The organic layer was washed three times with 50-ml. portions of water. The ether solution was dried over calcium chloride, and the ether was distilled from a steam-bath; the last traces of solvent were removed under a vacuum. This yielded 14.3 g. (96%) of light red oil. The crude phenylhydrazone was used immediately in the next step.

An intimate mixture of 5 g. (0.034 mole) of acetone phenylhydrazone and 25 g. of dry, powdered zinc chloride was heated with stirring over a Wood's metal bath at 180° for ten minutes. The dark brown mixture was cooled, 50 ml. of water was added, and it was heated over a steam-bath until the liquid and solid phases became separable. The mixture was cooled, acidified with conc'd sulfuric acid (4 ml.), transferred to a separatory-funnel, and extracted with 100 ml. of ether. The organic extract was washed with 50 ml. of water, the ether was distilled, and the residue was steam-distilled. The product came over as a colorless oil which quickly solidified into a white crystalline solid. The steam-distillate was cooled several hours in the refrigerator, and the product was filtered, washed with a little water, air-dried overnight, and finally under a vacuum. The 2-methylindole (VIA), which had become light yellow on standing, weighed 4 g. (91%), m.p. 56–60°. This was used in the next step without further purification. The reported melting point is 60° (9).

2-Methylgramine (VA). A solution of dimethylamine (4.10 g. of 33% aqueous solution, 0.03 mole) was cooled to 5°. While maintaining the temperature at 5°, the following components were added in order: 4.1 g. glacial acetic acid, formaldehyde (2.42 g. of 36% aqueous solution, 0.029 mole) with slight agitation, finally 3.8 g. (0.029 mole) of 2-methylindole (VIA). The mixture was shaken for 20 minutes, then set aside at room temperature overnight. The undissolved solid was filtered off, the filtrate was diluted with 60 ml. of water, and unreacted VIA was filtered off. The light yellow filtrate was made slightly alkaline with 10% sodium hydroxide, causing the precipitation of the white solid product. The mixture was cooled in ice for 20 minutes, and the solid was filtered, washed thoroughly with water, dried at room temperature, and finally under a vacuum. This yielded 1.99 g. (36.5%) of white powder (VA), m.p. 117–121°. This was used in the next step without further purification. The reported melting point is 120–121° (10).

2-Methyl-3-indoleacetic acid (IVA). A mixture of 1.99 g. (0.0106 mole) of 2-methylgramine (VA) 3.50 g. of sodium cyanide, 28 ml. of ethanol, and 7 ml. of water was refluxed 80 hours over a steam-bath. The mixture was cooled, filtered, and the filtrate was treated by boiling ten minutes with 0.50 g. of Norit. The clear solution was concentrated under a vacuum until all the alcohol had been removed, sufficient water added to bring the total volume to about 7 ml., then the mixture was cooled in an ice-bath. The white solid which separated was filtered off and discarded. The cold filtrate was acidified with concentrated hydrochloric acid, causing a light brown oil to separate. This oil solidified in the refrigerator after several hours. The crude product (IVA) was filtered, washed thoroughly with water, and dried at room temperature, finally under a vacuum. The crude, 2-methyl-3-indoleacetic acid, was a light brown powder, yield 1.27 g. (64%), m.p. 94–165°. Two recrystallizations from glacial acetic acid gave a light pink powder, m.p. 182–195°, with decomposition. An additional recrystallization from the minimum of acetone gave a nearly white product, m.p. 195–200°, with decomposition.

The mixture melting point of products obtained from IA and VA showed no depression.

2-Phenyl-3-indoleacetic acid (IVB). (From IB). The reaction proper was carried out in exactly the same way as described above for the 2-methyl derivative (IA), using 2.0 g. of compound IB (0.008 mole). At the end of the refluxing period, 6 ml. of a 1:1 volume solution of methanol and acetic acid was added, but the gray addition product was incompletely dissolved. The reaction mixture was cooled in ice and 50 ml. of ice-water was added rapidly with stirring. All the solid material dissolved except the unreacted zinc. The mixture was

made acidic to Congo Red with acetic acid (10 ml.) and the clear solution was decanted from the zinc into a separatory-funnel. The remaining residue was washed with 20 ml. of ether containing a few drops of the methanol-acetic acid solution, and this was combined with the bulk of solution. The aqueous layer was separated and extracted with 50 ml. of fresh ether. The combined organic extracts were washed with two 100-ml. portions of cold, 5% aqueous ammonium hydroxide, and finally with 50 ml. of water. The solution was dried over calcium chloride, the solvents were removed by distillation, and finally the last traces were removed under a vacuum. The non-crystallizable oil (IIB) was used in the next step without further purification.

The above crude was dissolved in 10 ml. of dry benzene, 4 g. of phosphorus pentoxide was added, and the mixture was refluxed (protected by a calcium chloride tube) over a steam-bath for three hours. After destroying the excess phosphorus pentoxide with 20 ml. of water, the mixture was worked up in exactly the same way as in the dehydration of IIA. The crude product was a reddish-brown, non-crystallizable oil (IIIB). This was used in the next step without further purification.

The above crude (IIIB) was refluxed one hour over a steam-bath in a solution of 4.00 g. of potassium hydroxide in 20 ml. of 95% ethanol; 40 ml. of water was added, and the ethanol removed by heating under a vacuum. The medium-brown aqueous solution was heated ten minutes over a steam-bath with 1.0 g. of Norit, filtered, and Norit was washed with 5 ml. of hot water, and this was combined with the bulk of the aqueous solution. The solution was cooled in ice and acidified with concentrated hydrochloric acid. This caused the precipitation of a light brown, oily semi-solid. After cooling in the refrigerator overnight, the crude material had solidified. This was filtered, washed thoroughly with water, and dried at room temperature, finally under a vacuum. The crude product was a light tan powder, yield 1.44 g. (72%), m.p. 166–177°, with decomposition. The crude substance was dissolved in 40 ml. of acetone, the small amount of black undissolved material was filtered off, and then the solution was boiled one-half hour over a steam-bath with 2.0 g. of Norit. The charcoal was filtered and washed with 20 ml. of fresh acetone. This treatment gave a nearly water-white solution. The solvent was evaporated at room temperature and the last traces were removed under a vacuum. This yielded 1.21 g. (61%) of nearly white crystalline solid (IVB), m.p. 170–175°. A small sample was recrystallized twice with glacial acetic acid, yielding nearly white crystals, m.p. 174–176°. The reported melting point is 174° (11).

Anal. Calc'd for $C_{16}H_{13}NO_2$: N, 5.58. Found: N, 5.37.

2-Phenylindole (VIB). This was prepared by Fischer's method (9, 12), and was recrystallized from ethanol, m.p. 187–188°.

2-Phenylgramine (VB). At 5° the following components were mixed in the following order with agitation: 1.9 ml. (0.014 mole) of 33% aqueous dimethylamine, 6 ml. of glacial acetic acid, 1.0 ml. (0.012 mole) of 36% aqueous formaldehyde, and finally 2.26 g. (0.012 mole) of 2-phenylindole (VIB). The mixture was shaken vigorously for 20 minutes, then set aside at room temperature overnight. The undissolved material was filtered off, and the filtrate was diluted with 100 ml. of water, cooled, and filtered. The colorless filtrate was made alkaline with 10% aqueous sodium hydroxide, causing the precipitation of a white solid. The mixture was cooled in ice for one-half hour, and the crude product was filtered, washed thoroughly with water, and dried at room temperature under a vacuum over phosphorus pentoxide. The crude material was a nearly white powder, m.p. 128–131°, yield 0.84 g. (29%). After two recrystallizations from ethanol, there was no further change in melting point range. The pure product (VB) was a white crystalline solid (small needles), m.p. 130.0–130.8°.

Anal. Calc'd for $C_{17}H_{18}N_2$: C, 81.60; H, 7.21; N, 11.19.
Found: C, 81.70; H, 7.46; N, 11.07.

2-Phenyl-3-indoleacetic acid (IVB). (From VB). A mixture of 0.95 g. (0.004 mole) of crude 2-phenylgramine (VB), 1.0 g. of sodium cyanide, 9 ml. of 95% ethanol, and 2 ml. of water was refluxed 80 hours over a steam-bath. The mixture was cooled, undissolved solids (0.58 g.) were filtered off, and the filtrate was decolorized by boiling ten minutes with a

small amount of Norit. The clear solution was concentrated under a vacuum until all the alcohol was removed, and sufficient water was added to make the total volume 2 ml.; then the mixture was cooled in an ice-bath. The white solid (0.26 g.) which separated was filtered off. The cold filtrate was acidified with concentrated hydrochloric acid with stirring, causing a white powder to precipitate. The mixture was cooled in the refrigerator several hours, and the solid was filtered, washed thoroughly with water, and dried at room temperature, finally under a vacuum over phosphorus pentoxide. The yield of crude 2-phenyl-3-indole acetic acid (IVB) was 0.06 g. (6%) of a light pink solid, m.p. 174–176°. Sufficient product was not obtained for purification by recrystallization.

The melting point of mixed samples of IVB obtained from IB and VB show no depression.

1-Acetyl-2,3-dimethylindole (VIII). A 100-ml., 3-necked flask was equipped with a condenser, calcium chloride drying tube, mercury-sealed stirrer, a dropping-funnel, and a system for maintaining a dry, carbon dioxide-free, nitrogen atmosphere. Into the flask was introduced 0.78 g. (0.032 mole) of clean, dry magnesium turnings, also a small iodine crystal, and 4 ml. of ether. To this was added, with stirring, at a rate sufficient to maintain refluxing, a solution of 4.52 g. (0.032 mole) of methyl iodide in 10 ml. of ether. When the addition was complete, the funnel was rinsed with 2 ml. of fresh ether, then the mixture was refluxed with stirring until all the metal had reacted (45 minutes). To this was added dropwise with vigorous stirring, 2.0 g. (0.0106 mole) of 1-acetyl-2-methylindoxyl (IA) dissolved in 4 ml. of dry thiophene-free benzene (five minutes), then the addition funnel was rinsed with 4 ml. more of hot benzene. A gray addition product precipitated out immediately. The mixture was refluxed one hour over a hot water-bath with stirring, cooled in an ice-bath, 50 ml. of ether was added, and then the whole was poured with stirring into an ice-cold solution of 3.6 ml. of conc'd sulfuric acid in 60 ml. of water. The reaction flask was rinsed with a small amount of water, and the rinsings were combined with the above. The water layer was drawn off and extracted with 50 ml. of ether. The combined ether extracts were washed with 20 ml. of water, 20 ml. of 5% sodium bicarbonate, and finally with 20 ml. of water. The organic solvents were distilled and last traces were removed under a vacuum. This yielded 1.87 g. of a viscous, yellow semi-solid with an indole odor. (Crude VII).

Part of the above crude VII (0.52 g.) was dissolved in 3 ml. of benzene, 2 g. of phosphorus pentoxide was added, and the mixture was refluxed (protected by a calcium chloride tube) for three hours. The excess phosphorus pentoxide was decomposed with 10 ml. of water with cooling. Ether (15 ml.) was added and the mixture was shaken thoroughly. The undissolved residue was filtered off, and the aqueous layer was separated. The aqueous layer was extracted with 15 ml. more of ether. The combined organic extracts were washed with 10 ml. of water, 10 ml. of 5% aqueous sodium bicarbonate, and finally with 10 ml. of water. The organic solvents were distilled and the last traces were removed under a vacuum to give a dark brown, completely solid residue (0.45 g.). This was steam-distilled, the distillate cooled in the refrigerator overnight, and the white crystalline solid was filtered, dried at room temperature, and finally under a vacuum. The yield of 1-acetyl-2,3-dimethylindole (VIII) was 0.33 g. (60%), m.p. 73–74°. Two recrystallizations from ethanol gave white crystals, melting sharply at 74°. The reported melting point is 74° (13).

Anal. Calc'd for $C_{12}H_{13}NO$: N, 7.48. Found: N, 7.42.

2,3-Dimethylindole (IX). *By the Fischer method* (9). Purification was by steam-distillation and repeated recrystallizations from ligroin; m.p., 105–106°.

1-Acetyl-2,3-dimethylindole (VIII). (From IX). A solution of 0.56 g. (0.004 mole) of IX in 3 ml. of acetyl chloride was refluxed four hours over a hot water-bath. The excess acetyl chloride was removed under a vacuum. The remaining dark brown oil was washed with water, then was steam-distilled. The steam-distillate was cooled in the refrigerator for several hours, and the white crystals were filtered, dried at room temperature, and finally under a vacuum. The crude yield of 1-acetyl-2,3-dimethylindole was 0.34 g. (47%), m.p. 71–76°. This crude was recrystallized once from 1 ml. of ethanol, washed with a few drops of fresh alcohol, and dried under a vacuum. This gave white needles, m.p. 73–76.5°.

The melting point of mixed samples of VIII from IA and IX showed no depression.

2,3-Diphenylindole (XII). A sample was prepared by a previously known method: that of Japp and Murray (6) as modified by Fennel and Plant (7). Recrystallization was from ethanol followed by recrystallization from glacial acetic acid, m.p. 126–126.5°.

2,3-Diphenylindole (XII). (From IB). The apparatus for preparing VIII was used for this preparation. Into the flask was introduced 0.29 g. (0.012 mole) of clean, dry magnesium turnings, then a small iodine crystal, and 2 ml. of ether. To this was added with stirring and at a rate sufficient to maintain refluxing, a solution of 1.88 g. (0.012 mole) of dry bromobenzene in 8 ml. of ether. When addition was complete, the dropping-funnel was rinsed with 2 ml. of fresh ether, and then the mixture was refluxed with stirring until all the metal had reacted (ten minutes). To this was added dropwise with vigorous stirring, 1.0 g. (0.004 mole) of 1-acetyl-2-phenylindoxyl (IB) dissolved in 4 ml. of dry, thiophene-free benzene, then the addition funnel was rinsed with 2 ml. more of hot benzene. A white addition product precipitated at once. The mixture was refluxed one hour over a hot water-bath with stirring. The flask contents were cooled, 30 ml. of ether was added, and then the mixture was poured with stirring into an ice-cold solution of 2 ml. of conc'd sulfuric acid in 30 ml. of water. The water layer was drawn off, neutralized with 5% aqueous sodium hydroxide, and extracted with 50 ml. of ether. The combined ether extracts were washed with 20 ml. of water, 20 ml. of 5% sodium bicarbonate solution, and finally with 20 ml. of water. The organic solvents were distilled, and the last traces were removed under a vacuum. The crude was dried under a vacuum. This yielded 1.30 g. of light brown solid (X), m.p. 56–72°. It was found difficult to purify X by ordinary crystallization methods; it is postulated to be N-acetyl-3-hydroxy-2,3-diphenylindoline.

A portion of crude X (0.50 g.) was dissolved in 2 ml. of dry benzene, 1.2 g. of phosphorus pentoxide was added, and the mixture was refluxed (protected by a calcium chloride tube) for three hours. The excess phosphorus pentoxide was decomposed with 5 ml. of water with cooling. Ether (15 ml.) was added, the mixture was shaken thoroughly, the undissolved residue was filtered, and the aqueous layer was separated. The aqueous layer was extracted with 15 ml. more of ether. The combined organic extracts were washed with 10 ml. of 5% aqueous sodium bicarbonate, and finally with 10 ml. of conc'd sodium chloride solution. The organic solvents were distilled, the last traces being removed under a vacuum. This procedure yielded 0.50 g. of a non-crystallizable oil (XI) which was used in the next step without further purification.

Hydrolysis of XI. Part of crude XI (0.35 g.) was dissolved in 5 ml. of ethanol, then 1 g. of potassium hydroxide was added and the solution was refluxed over a steam-bath for 20 minutes. Water (10 ml.) was added, and the ethanol was removed under a vacuum over a steam-bath. The oil-water mixture remaining was neutralized with concentrated hydrochloric acid, and then was extracted with 15 ml. of ether. The ether extract was washed with 10 ml. of water, and the solvents were removed by evaporation, finally under a vacuum. The reddish oil was dissolved in 5 ml. of ethanol, boiled several minutes with a little Norit until the solution was a light yellow color, and then was filtered, and the Norit washed with 5 ml. of hot ethanol. The combined ethanol solutions were evaporated slowly at room temperature, giving light-brown rosettes, m.p. 104–119°, yield 0.23 g. The crude product was recrystallized from 2.5 ml. of ligroin containing a few drops of benzene. A light granular crystalline solid gradually separated. After standing at room temperature overnight, the product was centrifuged off, washed with ligroin, and dried at room temperature, finally under a vacuum. This yielded a light tan granular solid (XII) m.p. 124–126°. A second recrystallization from glacial acetic acid produced white crystals, m.p. 125.2–126.0°. The reported melting point is 123–124° (14).

A sample of XII (prepared from IB) mixed with a known sample of 2,3-diphenylindole showed no depression of the melting point.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.20. Found: N, 5.11.

SUMMARY

1. 2-Substituted-indole-3-acetic acid derivatives have been prepared by the use of the Reformatsky reaction on 1-acetyl-2-substituted-indoxyl derivatives.

2. 2,3-Disubstituted indoles have been prepared by the action of Grignard reagents with 1-acetyl-2-substituted indoxyl derivatives.

NEW YORK 53, N. Y.

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