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4- And 6-Halogeno-2-methylindoles

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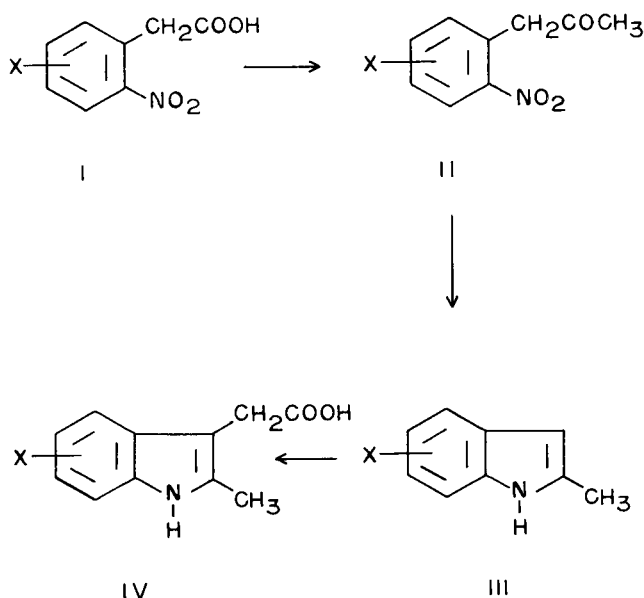
The lack of descriptions of 2-alkyl-4- and 6-halogenoindoles in the chemical literature is partially due to the problems of isomer separation and ambiguity accompanying application of the Fischer indole synthesis to *m*-substituted phenylhydrazones. Further, the Madelung synthesis, in which ambiguity is precluded through formation of the pyrrole moiety by reactions that occur external to the benzene ring, has been shown to fail in attempted preparations of halogeno-substituted indoles (2). But at least two other classical indole syntheses, namely reduction of 2,β-dinitrostyrenes (3) and reduction of *o*-nitrobenzyl carbonyl compounds (4), appear suitable for preparing 2-alkyl-4- and 6-halogenoindoles. This note describes the preparation of 4-chloro-2-methyl-, 6-chloro-2-methyl-, 4-bromo-2-methyl-, and 6-bromo-2-methylindole (IIIa-d respectively) by reduction of appropriately substituted derivatives of (*o*-nitrophenyl)-2-propanone and the isolation of both IIIa and IIIb following application of the Fischer synthesis to acetone *m*-chlorophenylhydrazone.

The appropriate halogen-substituted (*o*-nitrophenyl)-2-propanones (IIa-d) were prepared from the corresponding halogen-substituted (*o*-nitrophenyl)acetic acids (Ia-d) by the facile methyl ketone synthesis described by Hauser and coworkers (5). Reduction of the group II compounds with zinc dust and acetic acid afforded the indoles (IIIa-d).

Plieninger has noted the lack of the characteristic indole odor in the liquids 4-chloroindole and 4-bromoindole (6). Both IIIa and IIIc are liquids, and neither possesses the characteristic indole odor; but the solids IIIb and IIId do possess the characteristic odor.

Other marked differences in the properties of IIIa and IIIb, particularly the relatively difficult solubility of IIIb in benzene-ligroin solution and of IIIa picrate in ethanol, suggested a means of separating the mixture of IIIa and IIIb that would be expected to result from application of the Fischer synthesis to acetone *m*-chlorophenylhydrazone. And indeed, when a benzene solution of the product mixture resulting from the zinc chloride-promoted cyclization of acetone *m*-chlorophenylhydrazone was diluted with ligroin, pure IIIb separated readily; and pure IIIa was easily prepared from the remaining mixture. Regeneration of IIIa from its picrate was achieved by treatment with sodium bicarbonate solution.

The properties of the bromo compounds IIIc and IIId closely parallel those of the corresponding chloro compounds, and it therefore seems likely that a mixture of IIIc and IIId could be separated through similar methods. This was not verified however.



4- And 6-halogeno-2-methylindole-3-acetic acids (IVa-d) were prepared via their ethyl esters which were obtained by reaction of the indoles (IIIa-d) with ethyl diazoacetate in the presence of cuprous halide (7, 8). The samples of IVa and IVb obtained in this manner were identical (with respect to melting points, mixture melting points, and infrared spectra) with the samples of these compounds that we prepared earlier via the Reformatsky reaction applied to the appropriate chloro-substituted derivatives of 1-acetyl-2-methylindoxyl (9).

EXPERIMENTAL

(2-Chloro-6-nitrophenyl)acetic Acid (Ia), (4-Chloro-2-nitrophenyl)acetic Acid (Ib), and (4-Bromo-2-nitrophenyl)acetic Acid (Id).

Following condensation of diethyl oxalate with the appropriate halogen-substituted derivative of *o*-nitrotoluene (1.00 molar scale) according to the instructions of Uhle (10), the red ethanolic reaction mixture was diluted with water (400 ml.) and distilled with steam until the distillate became clear (approximately 4 l. of distillate). The filtrate obtained following clarification of the residual aqueous mixture was cooled to 20°, and cold 10% sodium hydroxide solution (100 ml.) was added followed by six additions, at 5-minute intervals, of 20-ml. portions of 30% hydrogen peroxide solution. The solution was left at room temperature for about 15 hours and was then acidified with 20% sulfuric acid solution. The yellow solid that precipitated was recrystallized from aqueous ethanol. The yield of Ia, m.p. 194-195° (lit. (11,12) m.p. 195° and 196-197°), was 38%; Ib, m.p. 166.5-167° (lit. (12) m.p. 166-168°), 42%; and Id, m.p. 167-167.5°, 35%. *Anal.* Calcd. for C₈H₆BrNO₂: N, 5.39. Found: N, 5.39.

TABLE I
Experimental Results

No.	Position-Substituent	Yield, %	B. p., °C (mm.)	M. p., °C (a)	Formula	Nitrogen	
						Calcd.	Found
IIa	2-Cl-6-NO ₂	85	124-127 (0.5)	35-35.5	C ₉ H ₈ ClNO ₃	6.56	6.63
IIb	4-Cl-2-NO ₂	85		79.5-80	C ₉ H ₈ ClNO ₃	6.56	6.43
IIc	2-Br-6-NO ₂	90	125-127 (0.15)	50-50.5	C ₉ H ₈ BrNO ₃	5.43	5.22
IId	4-Br-2-NO ₂	83		91-91.5	C ₉ H ₈ BrNO ₃	5.43	5.50
IIIa (b)	4-Cl	91	99-101 (0.02)		C ₉ H ₈ ClN	8.46	8.57
IIIb	6-Cl	70		128	C ₉ H ₈ ClN	8.46	8.63
IIIc (c)	4-Br	51	102 (0.01)		C ₉ H ₈ BrN	6.67	6.41
IIId	6-Br	55		134	C ₉ H ₈ BrN	6.67	6.49
IVa	4-Cl	27		210-215 (dec.) (d)	C ₁₁ H ₁₀ ClNO ₂	6.26	--
IVb	6-Cl	37		205-210 (dec.) (d)	C ₁₁ H ₁₀ ClNO ₂	6.26	--
IVc	4-Br	16		188-189 (dec.)	C ₁₁ H ₁₀ BrNO ₂	5.22	5.29
IVd	6-Br	47		190-192 (dec.)	C ₁₁ H ₁₀ BrNO ₂	5.22	5.05

(a) Melting points were taken on a Fisher-Johns block and are uncorrected. (b) n_D^{20} 1.6208. (c) n_D^{20} 1.6466. (d) Ref. (9).

(2-Bromo-6-nitrophenyl)acetic Acid (Ic) and (4-Bromo-2-nitrophenyl)acetic Acid (Id).

(2-Bromo-6-nitrophenyl)pyruvic acid was prepared along with (4-bromo-2-nitrophenyl)pyruvic acid by the instructions of Plieninger (6) from the mixture of isomers obtained on bromination of *o*-nitrotoluene. Degradative oxidation of the sodium salts of these acids with hydrogen peroxide in the manner described for similar compounds (12,13) afforded Ic and Id. The sample of Id obtained in this manner was identical with the sample obtained from pure 4-bromo-2-nitrotoluene. Pure Ic, m. p. 196.5-197°, was ultimately obtained by recrystallization from chloroform after two prior recrystallizations from aqueous ethanol.

Anal. Found: N, 5.55.

(2-Chloro-6-nitrophenyl)-2-propanone (IIa), (4-Chloro-2-nitrophenyl)-2-propanone (IIb), (2-Bromo-6-nitrophenyl)-2-propanone (IIc), and (4-Bromo-2-nitrophenyl)-2-propanone (IId).

A mixture of the appropriate compound from group I (0.371 mole) and thionyl chloride (100 ml.) was stirred overnight at room temperature and was then heated at 40-45° for 5 hours. Excess thionyl chloride was removed by evaporation under reduced pressure with the aid of a warm water bath not allowed to exceed 45° (14), and the red oil residue was freed of volatile substances by the addition and subsequent evaporation under reduced pressure of portions of benzene (3 x 100 ml.) and ether (3 x 100 ml.). The residual oil was then dissolved in ether (200 ml.), and the solution was added dropwise during 45 minutes to a stirred solution of the magnesium-methoxy derivative of diethyl malonate (5b) (0.412 mole) in ether (200 ml.).

The mixture was refluxed 2 hours longer and was then chilled in an ice bath while cold 10% sulfuric acid solution (100 ml.) was slowly added with stirring. The ether layer, to which was added an ether extract of the aqueous phase, was washed with water. Removal of the ether left an orange oil to which was added a solution of glacial acetic acid (100 ml.), concentrated sulfuric acid (14 ml.), and water (75 ml.). The mixture was refluxed with stirring for 6 hours.

Purification of IIa and IIc.

The reaction mixture was poured onto crushed ice (200 g.), and the resultant mixture was chilled in an ice-salt bath while being made barely alkaline with cold 20% sodium hydroxide solution. The mixture was extracted with ether (3 x 200 ml.), and the ether solution was washed with water (2 x 200 ml.) and dried (sodium sulfate). Removal of the ether left a dark oil that was purified by distillation *in vacuo*. The distillate, initially a yellow oil, crystallized on standing in the cold.

Purification of IIb and IId.

The reaction mixture was poured over crushed ice, and the crystalline product that separated was recrystallized from aqueous ethanol.

Group II *p*-nitrophenylhydrazones (molecular formula C₁₅H₁₃N₄O₄) were recrystallized from 95% ethanol.

No. of parent ketone	M. p., °C	Nitrogen, %	
		Calcd.	Found
IIa	175-176	16.07	15.81
IIb	154-155	16.07	15.80
IIc	167-168	14.25	14.33
IId	171-172	14.25	14.13

4-Chloro-2-methylindole (IIIa), 6-Chloro-2-methylindole (IIIb), 4-Bromo-2-methylindole (IIIc), and 6-Bromo-2-methylindole (IIId).

A solution of the appropriate group II compound (70.0 mmoles) in 80% acetic acid solution (100 ml.) was heated in a water bath at 70-75° while zinc dust (30 g. total) was added in portions during 30 minutes. The temperature of the bath was raised to 85-90°, and heating was continued 30 minutes longer. The hot mixture was filtered, and the excess zinc was washed with a little ethanol and ether. The filtrate was diluted with water (100 ml.) and extracted with ether (4 x 100 ml.). The ether solution was washed successively with water (3 x 100 ml.), 5% ammonium hydroxide solution (100-ml. portions) until the washings remained basic and again with water (100 ml.) and was then dried (sodium sulfate).

Purification of IIIa and IIIc.

Removal of the ether left a red oil that was purified by distillation *in vacuo*. The pure product was a pale yellow oil.

Purification of IIIb and IIId.

The pink solid remaining following removal of the solvent was recrystallized from aqueous ethanol as nearly colorless platelets. Further recrystallization from benzene-ligroin afforded a colorless product.

The picrates of IIIa and IIIc (molecular formula C₁₅H₁₁N₄O₇) were recrystallized from ethanol and those of IIIb and IIId from benzene.

No. of parent indole	M. p., °C	Nitrogen, %	
		Calcd.	Found
IIIa	168-169	14.20	14.12
IIIb	119.5-120	14.20	14.39
IIIc	167.5-168	12.76	12.47
IIId	113-114	12.76	12.72

IIIa and IIIb by the Fischer Indole Synthesis.

Acetone *m*-chlorophenylhydrazone was prepared in a nitrogen atmosphere by treating a stirred solution of *m*-chlorophenylhydrazine hydrochloride (15) (22.0 g., 0.123 mole) in warm water (50–60°) water (250 ml.) with acetone (12.0 ml., 0.164 mole) and a warm solution of sodium acetate trihydrate (17.0 g., 0.125 mole) in water (50 ml.). After the warm mixture had been stirred for 10 minutes, it was chilled in an ice bath with continued stirring for 45 minutes. The precipitate that formed was pulverized under the supernatant liquid; and the air-sensitive product was collected under nitrogen, covered with a rubber dam, and pressed as dry as possible on the funnel. After being dried *in vacuo* for 3 hours, the white product was used immediately in the Fischer ring closure.

A stirred (Teflon paddle) mixture of anhydrous zinc chloride (16) (approximately 30 g.) and the sample of acetone *m*-chlorophenylhydrazone described above was heated under nitrogen by means of an oil bath. The bath temperature was gradually raised to 150° during about 50 minutes. Slow heating from 150 to 165° during at least 20 minutes resulted in a smooth, almost indiscernible reaction. (More rapid heating through this range caused a rather violent reaction at bath temperature 160° with copious gas evolution and extensive resinification.) Heating was continued until the bath temperature reached 180°. The mixture was then allowed to cool, and, when stirring became difficult, the stirrer was raised clear of the thick mixture. After the mixture had cooled to room temperature, a mixture of ether (150 ml.) and 3 *N* hydrochloric acid solution (150 ml.) was added. Vigorous stirring for about 30 minutes dissolved the reaction mixture. The ether layer, to which was added an ether extract of the aqueous phase, was washed with water (2 x 75 ml.), 5% ammonium hydroxide solution (3 x 75 ml.), and again with water (2 x 75 ml.). Removal of the solvent from the dried (sodium sulfate) solution left an orange wax-like residue. Distillation afforded a pale yellow distillate, b.p. 133–137° (1.0–1.5 mm.), in 68% yield (13.9 g.) that formed a waxy semisolid.

Isolation of IIIb.

The distilled mixture of isomers was dissolved in warm benzene (15 ml.), and the solution was diluted with ligroin (b.p. 30–60°) (120 ml.). The white crystalline precipitate that formed was collected and washed on the funnel with ligroin (35 ml.). The sample of IIIb obtained amounted to 39% (5.4 g.) of the distilled mixture of isomers and had melting point, mixture melting point, and infrared spectrum identical with the sample obtained by reduction of IIb.

Isolation of IIIa.

The red oil (8.5 g.) remaining after removal of the solvents from the filtrate from IIIb was dissolved in boiling ethanol (50 ml.), and the solution was combined with a boiling solution of picric acid (13.5 g.) in ethanol (75 ml.). The resultant dark red solution was boiled for 5 minutes. The cooled solution afforded crimson needles of pure IIIa picrate with melting point and mixture melting point identical with the sample of IIIa picrate prepared following reduction of IIa. The pure IIIa picrate obtained (12.8 g., corresponding to 39% of the distilled mixture of isomers) was stirred for 4 hours in 5% sodium bicarbonate solution (200 ml.) at room temperature. Some yellow solid that formed was dissolved by dilution with water, and the mixture was extracted with ether (3 x 75 ml.). The ether solution was washed with 5% sodium bicarbonate solution (100-ml. portions) until the washings were no longer yellow. The ether was removed from the dried (sodium sulfate) solution, and the red oil residue was distilled *in vacuo*.

Pure IIIa, b.p. 108–110° (0.03 mm.) was obtained as a virtually colorless oil in 92% recovery from its picrate and had infrared spectrum and refractive index identical with the sample prepared by reduction of IIa.

4-Chloro-2-methylindole-3-acetic Acid (IVa).

The following description of the preparation of IVa is illustrative for the group IV compounds. A stirred mixture of IIIa (9.94 g., 60.0 mmoles) and cuprous chloride (8) (1.0 g.) in benzene (60 ml.)

was heated to reflux. The heat source was removed, and a solution of ethyl diazoacetate (17) (7.52 g., 66.0 mmoles) in benzene (12 ml.) was added dropwise at a rate that caused gentle reflux throughout the addition period (approximately 50 min.). The mixture was refluxed one hour longer and was then filtered through a Celite mat. The dark residue remaining following removal of the solvent from the filtrate was distilled *in vacuo*. Unchanged IIIa was collected as forerun, but no effort was made to effect fractionation. The ethyl ester of IVa was obtained as a viscous orange oil, b.p. 165–170° (1.0–1.5 mm.). The total distillate was mixed with 10% sodium hydroxide solution (60 ml.), and the stirred mixture was refluxed for 4 hours. The cooled mixture was extracted with ether (3 x 60 ml.), and workup of the ethereal phase afforded a recovery of 40% unchanged IIIa. The clear aqueous phase was treated with Norite while being warmed to expel residual ether. The mixture was filtered through Celite; and the filtrate, chilled to 0–5°, was treated dropwise with 3 *N* hydrochloric acid solution until precipitate stopped forming. The mixture was chilled 30 minutes longer; and the crude IVa, a yellow crystalline powder, was collected and washed thoroughly with cold water. Recrystallization from aqueous ethanol afforded a virtually pure product. A final recrystallization from acetone-chloroform gave colorless crystals of pure IVa identical with the sample prepared by another route (9).

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