Short Communications

Preparation of Chlorinated 3-Indolylacetic Acids

K. C. ENGVILD

Agricultural Research Department and Department of Chemistry, Research Establishment Risø, DK-4000 Roskilde, Denmark

The interest in chlorinated 3-indolylacetic acids as plant hormones has increased since 4-chloro-3-indolylacetic acid ¹ (I), its methyl ester,^{2,3} its aspartic acid amide,⁴ and two derivatives of 4-chlorotryptophan ⁵ were isolated from immature green pea seeds. Many other plants may contain similar hormones. When fed ³⁵Cl[−] at least

ten cultivated species incorporate radioactivity into compounds migrating close to 4-chloro-3-indolylacetic acid methyl ester on thin layer chromatograms.⁶

Published procedures of preparation are tedious or require rare chemicals or equipment.^{7–10} Therefore, simplified procedures giving similar or better yields were adopted. Five new compounds were synthesized. 4-Chloro-3-indolylacetic acid and 6-chloro-3-indolylacetic acid were made from the corresponding indoles by refluxing 3-diethylaminomethyl-chloroindoles with sodium cyanide overnight instead of four days.^{9,11} The other compounds were prepared by a two-step Fischer indole synthesis from 3-formylpropionic acid (from glutamic acid) and the appropriate phenylhydrazine in pyridine/HCl¹² avoiding distillation and saponification of the ethyl esters.^{7,8} A few compounds could also be prepared in one step from a phenylhydrazine and α -oxoglutaric acid in pyridine/HCl,¹³ but this method was not generally applicable. The results are shown in Table 1.

All new compounds showed satisfactory elemental analyses (Novo microanalytical laboratory). Infra-red spectra (Perkin Elmer Spectrophotometer 221, KBr) were very similar to the spectra of 5-bromo- and 5-fluoro-3-indolylacetic acids.¹⁴ The electron impact mass

spectra (Varian MAT CH5) gave the following values of m/e for chloro-3-indolylacetic acids: 209 (M⁺), 164 (100 %), 128, 129 and 101; for 7-bromo-3-indolylacetic acid: 253 (M⁺), 208 (100 %), 128, 129 and 101; for dichloro-3-indolylacetic acids: 243 (M⁺), 198 (100 %), 162, 163, 127, 128 and 99; for 5-chloro-7-methyl-3-indolylacetic acid: 223 (M⁺), 178 (100 %), 142 and 115; all in good agreement with the mechanism of fragmentation proposed for 4-chloro-3-indolylacetic acid methyl ester.¹⁵

4-Chloro-3-indolylacetic acid. To a solution in ethanol (225 ml) of crude 3-diethylaminomethyl-4-chloroindole ¹⁶ (22.2 g) prepared from 4-chloroindole (15 g, 0.1 mol; Zion Chemical Products, POB 51 Yavne, Israel) was added a solution of NaCN (0.5 mol) in water (50 ml). The mixture was refluxed for 3 h and 100 ml distilled to remove diethylamine. Water (50 ml) was added and reflux continued for 16 h. The mixture was concentrated to 75 ml and water (80 ml) was added. The precipitate of nitrile + amide was filtered off. From the filtrate crude 4-chloro-3-indolylacetic acid (4.4 g) was isolated after acidification (hood!) with conc. HCl.

A mixture of nitrile + amide in ethanol (50 ml) and NaOH (20 g) in water (70 ml) was refluxed for 6 h. After concentration to about 60 ml, addition of water (80 ml) and filtration, more crude acid (10.6 g) was isolated after acidification with conc. HCl.

Crude 4-chloro-3-indolylacetic acid (15 g) was reprecipitated with conc. HCl from 40 ml of 10 % NaOH, recrystallized from water (1500 ml, a red insoluble fraction discarded) and from ethyl acetate:hexane 1:3. Yield 8.4 g (40 %), m.p. 184–187 °C.

Fischer indolization. To a fresh solution (60 °C) of 3-formylpropionic acid prepared from glutamic acid ¹⁷ (0.1 mol) was added the appropriate phenylhydrazine.HCl (0.05 mol, Aldrich) dissolved in 30 % acetic acid. The pH was adjusted to 4 with NaOH (5 M). After cooling the precipitate was collected and dissolved in pyridine (75 ml). Conc. HCl (100 ml) and 85 % H₃PO₄ (25 ml) were added and the mixture refluxed for 16 h protected from light under N₂.

The reaction mixture was diluted with water (600 ml), the tars filtered off, and the filtrate extracted repeatedly with ether. The combined ether fractions (600 ml) were washed with water and the indolylacetic acid extracted back into 0.5 M NaOH (200 ml).

Table 1. Yields, corrected melting points and ^1H NMR spectral data,¹³ δ measured in CD_3COCD_3 on a Jeol JNM-PMX 60 instrument at 60 MHz. All compounds had broad peaks between δ 8 and 11 ($-\text{COOH}$ and $>\text{NH}$).

3-Indolylacetic acid derivative	Starting material phenylhydrazine.HCl	Yield %	M.p. °C (dec.)	δ s ($-\text{CH}_3-$)	m (arom.)
4-Chloro-	(4-Chloroindole)	40	184–187 ^a	4.00	7.0–7.4 (4 H)
6-Chloro-	(6-Chloroindole)	38	182–184 ^b	3.76	6.9–7.7 (4 H)
5-Chloro-	4-Chloro-	28	156–159 ^c	3.76	7.0–7.7 (4 H)
7-Chloro-	2-Chloro-	23	163–165 ^d	3.77	6.9–7.7 (4 H)
4,6-Dichloro-	3,5-Dichloro-	7	210–214	3.97	7.0 (1 H) 7.4 (2 H)
4,7-Dichloro-	2,6-Dichloro-	9	214–217	4.00	7.1 (2 H) 7.4 (1 H)
5,7-Dichloro-	2,4-Dichloro-	22	202–204 ^e	3.76	7.2 (1 H) 7.4 (1 H) 7.6 (1 H)
6,7-Dichloro-	2,3-Dichloro-	11	170–175	3.76	7.1–7.6 (3 H)
5-Chloro-7-methyl-	4-Chloro-2-methyl-	4	178–180	3.73 ^f	6.9 (1 H) 7.3 (1 H) 7.5 (1 H)
7-Bromo-	2-Bromo-	7	180–182	3.77	6.8–7.7 (4 H)

Literature⁸ m.p.'s: ^a 185–187 °C, ^b 187–188 °C, ^c 158–160 °C, ^d 164–165 °C, ^e 194–197 °C, ^f 5-Chloro-7-methyl-3-indolylacetic acid also had a peak at δ 2.46 (s, $-\text{CH}_3$).

After boiling the indolylacetic acid was precipitated with conc. HCl (pH 1). If possible, the soapy tars separating first were filtered or decanted off, before crystals appeared. Recrystallization twice from water, water/ethanol, toluene, or ethyl acetate/hexane.

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