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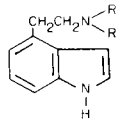
Received March 22, 1982

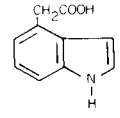
N-Substituted 4-(2'-aminoethyl)indoles are attainable in good yields from indole-4-acetic acid (**2**). Several methods of preparation for **2** were tried or considered. A new sequence involving Arndt-Eistert homologation of indole-4-carboxylic acid has been devised, which is no more laborious than a literature homologation sequence involving indole-4-acetonitrile, and which provides somewhat better overall yields than the literature method.

J. Heterocyclic Chem., **19**, 1195 (1982).

Prior communications (1,2) have described biological effects of a series of *N*-dialkylated 4-(2'-aminoethyl)indoles **1a-c**. Herein is described the synthesis of these compounds.



1a R = CH_3
1b R = C_2H_5
1c R = n-C_3H_7



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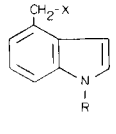
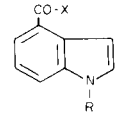
The literature reveals that the preparation and synthetic manipulation of 4-substituted indoles has received only limited attention. In the present study, it was speculated that indole-4-acetic acid (**2**), which had been prepared from 1-naphthylamine by a long and cumbersome procedure (3), would be a useful intermediate leading to **1**. Plieninger, *et al.*, (3) stated that more classical approaches to **2** by means of one-carbon homologation of the alcohol **3** or the acid **5** were not applicable, due to the inaccessibility of the alkyl chloride **4** or the acyl chloride **6**. Ponticello and Baldwin (4) homologated ethyl indole-4-carboxylate to indole-4-acetic acid **2** by lithium aluminum hydride reduction of the *N*-tosyl derivative, to form the *N*-tosyl-4-hydroxylmethylindole (**3a**); conversion of this (with triphenylphosphine/carbon tetrachloride) to the 4-chloromethyl system **4a**; and displacement of the chlorine with cyanide anion. Base hydrolysis of the resulting *N*-tosylindole-4-acetonitrile gave **2** in fairly good overall yield.



3 X = OH, R = H
3a X = OH, R = Ts
4 X = Cl, R = H
4a X = Cl, R = Ts

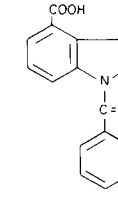


5 X = OH
6 X = Cl

In the present work, it was found that the *N*-unprotected 4-hydroxymethyl system **3** could not be converted into the chloromethyl derivative **4** by any variation of the triphenylphosphine- or phosphorustriamide/carbon tetrachloride method (5). No identifiable product(s) could be isolated. However, **3** was converted into its trimethylsilyl ether **7**, and this could be converted into the nitrile **8** with potassium cyanide, albeit in poor overall yield (25% from **3**).

7 **8**

While this route obviates masking the ring nitrogen, the low yields attainable suggested the desirability of an alternate route. Arndt-Eistert homologation of *N*-protected indole-4-carboxylic acid was investigated, as shown in Scheme I. The overall yield in the homologation (**5** → **2**, Scheme I) was 56%, which is somewhat higher than was reported for the Ponticello-Baldwin route (4). The phase transfer catalysis procedure for *N*-benzoylation (**9** → **10**) has been introduced (6) for selective acylation of indoles at the N-1 position. Hydrogenolysis of the benzyl ester **10** proceded in almost quantitative yield in ethyl acetate solution. When ethanol was used as the solvent, an approximately 20% yield of the indoline **14** resulted, contaminating the desired reduction product.



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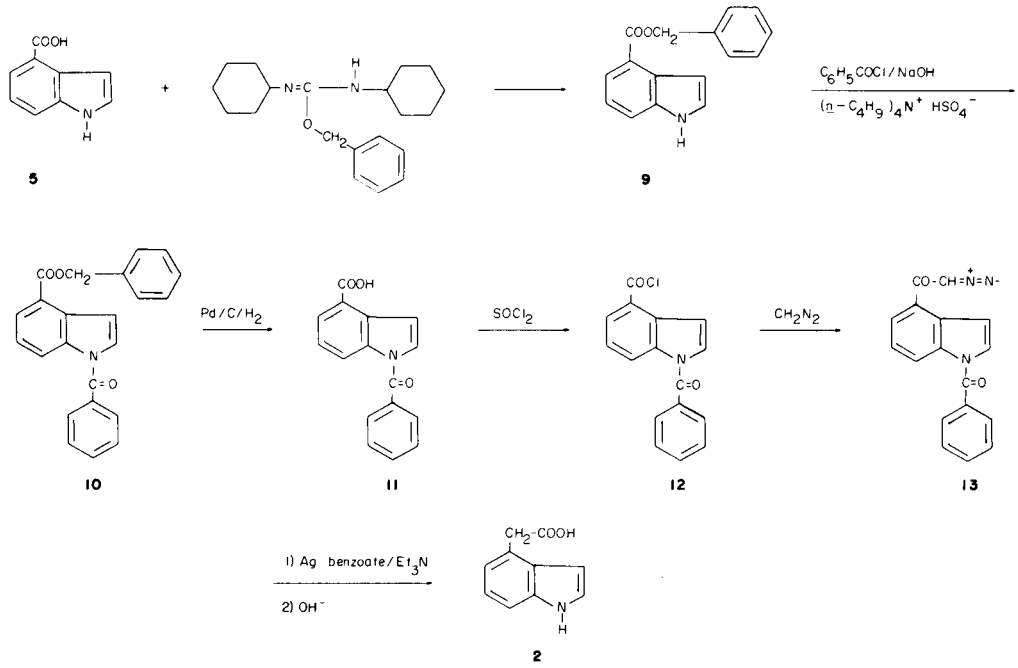
Indole-4-acetic acid **2** was converted directly into *N*-substituted amides by treatment with the appropriate amine in the presence of hexamethylphosphorus tri-

Scheme I

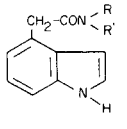
Arndt-Eistert Homologation of Indole-4-carboxylic Acid



amide/carbon tetrachloride (7,8). Two primary amines were used in this amide-forming procedure, to evaluate its utility. Yields with the primary amines were decidedly lower than with the secondary amines (See Table I). The amide products were reduced to the corresponding tertiary amines with lithium aluminum hydride, and the amines were characterized as their salts with fumaric acid (See Table II). Halide salts of these products were extremely hygroscopic, and they rapidly decomposed in air.

Table I

Indole-4-acetamides

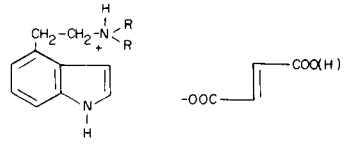


Compound No.	R	R'	Yield, %	Mp, °C	Formula	Analysis Calcd.	Found
15	H	C_2H_5	41	121-122 (a)	$C_{12}H_{14}N_2O$	C 71.26	C 71.12
						H 6.98	H 7.02
						N 13.85	N 13.77
16	H	*n*-C_3H_7	56	89-90 (a)	$C_{13}H_{16}N_2O$	C 72.19	C 71.93
						H 7.46	H 7.54
						N 12.95	N 12.81
17	CH_3	CH_3	79	139-141 (a) (b)	$C_{12}H_{14}N_2O$	C 71.26	C 71.01
						H 6.98	H 6.90
						N 13.85	N 13.74
18	C_2H_5	C_2H_5	91	123-125 (a)	$C_{14}H_{18}N_2O$	C 73.01	C 72.93
						H 7.88	H 7.73
						N 12.17	N 12.19
19	*n*-C_3H_7	*n*-C_3H_7	85	112-113 (a)	$C_{16}H_{22}N_2O$	C 74.38	C 74.39
						H 8.58	H 8.67
						N 10.84	N 10.97

(a) From chloroform-petroleum ether. (b) Lit (12) mp 139-142°.

Table II

4-(2'-Dialkylaminoethyl)indoles, Fumarate or Bifumarate Salts



Compound No.	R	Yield, %	Mp °C	Formula	Analysis Calcd.	Found
1a	CH_3	83	184-185 dec (a)	$C_{28}H_{36}N_4O_4$ (c)	C 68.27	C 68.38
					H 7.36	H 7.48
					N 11.38	N 11.38
1b	C_2H_5	70	159-160 (a)	$C_{32}H_{44}N_4O_4$ (c)	C 70.04	C 69.84
					H 8.08	H 8.23
					N 10.21	N 10.13
1c	nC_3H_7	61	154-155 (b)	$C_{20}H_{28}N_2O_4$ (d)	C 66.64	C 66.40
					H 7.83	H 8.01
					N 7.77	N 7.67

(a) From ethanol-ether. (b) From ethanol-ether-petroleum ether (bp 37.1-57.5°). (c) Fumarate salt. (d) Bifumarate salt.

EXPERIMENTAL

Melting points are uncorrected and were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus. Infrared spectra were recorded with a Beckman IR 4240 instrument, and nuclear magnetic resonance spectra were recorded with a Varian Associates EM-360A spectrometer with internal tetramethylsilane reference. Mass spectra were recorded on a Finnigan 1015 mass spectrometer. Elemental analyses were preformed by Galbraith Laboratories, Knoxville, Tennessee.

N,N-Dimethylformamide, hexamethylphosphoric triamide, and methylene chloride were dried by storage over 4 Å molecular sieves; benzene and diethyl ether were dried with metallic sodium; and tetrahydrofuran was dried by distilling from lithium alumiun hydride.

Indole-4-methanol (**3**).

A solution of 11.7 g (0.0795 mole) of methyl indole-4-carboxylate (4) in 300 ml of anhydrous ether was added dropwise to 59 ml (0.2065 mole) of sodium bis(2-methoxyethoxy) aluminum hydride (3.5 *M* in benzene) in 300 ml of anhydrous ether. The resulting mixture was stirred at room temperature under nitrogen for 12 hours. A saturated solution of sodium sulfate was then added dropwise until a white suspension resulted. This mixture was filtered through *celite* and the filtrate was washed successively with water, 10% sodium carbonate solution, and saturated sodium chloride solution, and then it was dried over magnesium sulfate. Evaporation of the volatiles afforded a liquid residue which crystallized on standing and was recrystallized from chloroform-petroleum ether (bp 37-57°) to give 8.3 g (85%) of product, mp 67-68°, lit (9) mp 56-57°; nmr (deuteriochloroform): δ 2.3 (s, 1H, O*H*), 4.94 (s, 2H, CH_2), 6.62 (m, 1H, C-3 *H*), 7.0-7.35 (m, 4H, Ar*H*), 8.45 (br s, 1H, N-1 *H*); ir (potassium bromide): 3520 (N-1 H), 3270 cm^{-1} (OH); ms: m/e 147 (M^+).

Anal. Calcd. for C_9H_9NO: C, 73.44; H, 6.16; N, 9.52. Found: C, 73.25; H, 6.04; N, 9.57.

4-Cyanomethylindole (**8**).

Chlorotrimethylsilane (1.95 ml, 0.01536 mole) was added dropwise at room temperature to a stirred solution of 1.5 g (0.012 mole) of **3** and 2.1 g (0.02075 mole) of triethylamine in 45 ml of dry tetrahydrofuran under nitrogen. The reaction mixture was stirred at room temperature for 2 hours, then it was filtered and the filtrate was evaporated under reduced pressure. The residue was taken up in 50 ml of anhydrous ether and this suspension was filtered. Evaporation of the filtrate afforded the trimethylsilyl ether **7** as a clear oil which was used in the next step without purification; nmr (deuteriochloroform): δ 0.14 (s, 9H, SiCH_3), 5.04 (s, 2H, ArCH_2), 6.61 (m, 1H, C-3 *H*), 7.0-7.34 (m, 4H, Ar*H*), 8.1 (br s, 1H, N-1 *H*); ir (film) 3420 cm^{-1} (N-1 H).

A mixture of the crude silyl ether **7** and 2 g (0.0482 mole) of sodium cyanide in 45 ml of oxygen-free hexamethylphosphoric triamide was heated at 180-185° (bath temperature) under nitrogen for 24 hours. The resulting mixture was poured into 300 ml of ice-cold water and the aqueous phase was extracted with three 50 ml portions of ether. The organic phase was washed successively with water, cold dilute hydrochloric acid (twice), and saturated sodium chloride solution, and was then dried over magnesium sulfate. The volatiles were removed under reduced pressure and the residue was chromatographed twice on silica gel and was eluted first with chloroform and then with chloroform-benzene-ether (8:2:2) to afford 0.4 g (25% from **3**) of solid material. Recrystallization from benzene-petroleum ether (bp 37-57°) gave an analytically pure sample, mp 110-111°, lit (3) mp 115°; ir (potassium bromide): 3345 (N-1 H), 2230 cm^{-1} (CN); ms: m/e 156 (M^+).

Anal. Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.79; H, 5.26; N, 17.79.

Benzyl Indole-4-carboxylate (**9**).

A solution of 5 g (0.031 mole) of indole-4-carboxylic acid **5** (4) and 10.7 g (0.034 mole) of *N,N'*-dicyclohexyl-*O*-benzylisourea (10) in 20 ml of dry *N,N*-dimethylformamide was heated at 65-70° (bath temperature) under nitrogen for 3 hours. Methylene chloride (50 ml) was added to the reaction mixture and the resulting mixture was filtered through celite. The filtrate was evaporated under reduced pressure; the residue was taken up in 100 ml of benzene and this solution was washed successively with two portions of 10% sodium carbonate solution, water, and saturated sodium chloride solution, and then it was dried over magnesium sulfate. Evaporation of the benzene afforded the crude product as a yellowish oil, which solidified on standing and was recrystallized from benzene-hexane to yield 6.4 g (82%) of pure material, mp 72-73°. Dry column chromatography of the mother liquors on silica gel (benzene-chloroform 7:3) afforded an additional 0.55 g of product for a total yield of 89%; nmr (deuteriochloroform): δ 5.43 (s, 2H, OCH_2), 7.08-7.56 (m, 9H, Ar*H*), 7.96 (d of d, 1H, C-5 *H*), 8.5 (br s, 1H, N-1 *H*); ir (potassium bromide): 3330 (N-1 H), 1680 cm^{-1} (C=O); ms: m/e 251 (M^+).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.61; H, 5.30; N, 5.56.

Benzyl 1-Benzoylindole-4-carboxylate (**10**).

A solution of 12.6 g (0.09 mole) of benzoyl chloride in 60 ml of methylene chloride was added dropwise over 30 minutes to a well-stirred suspension of 15 g (0.0422 mole) of **9**, 6 g (0.15 mole) of powdered sodium hydroxide, and 0.21 g (0.00062 mole) of tetra-*n*-butylammonium hydrogen sulfate in 180 ml of methylene chloride under nitrogen, while the temperature of the reaction mixture was maintained below 15°. Stirring was continued for an additional 30 minutes. The resulting suspension was filtered and the filtrate was evaporated under reduced pressure. The residue was taken up in 200 ml of benzene. This solution was washed with water and then with saturated sodium chloride solution, and was dried over magnesium sulfate. Evporation of the benzene afforded a solid which was recrystallized from benzene-hexane to give 20.5 g (97%) of product, mp 99-100.5°; nmr (deuteriochloroform): δ 5.42 (s, 2H, CH_2), 7.12-7.74 (m, 13H, Ar*H*), 8.08 (d, 1H, C-5 *H*), 8.63 (d, 1H, C-7 *H*); ir (potassium bromide): 1700, 1670 cm^{-1} (C=O); ms: m/e 355 (M$^+$).

Anal. Calcd. for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.55; H, 4.99; N, 4.06.

1-Benzoylindole-4-carboxylic Acid (**11**).

Compound **10** (6.5 g, 0.0245 mole) in 130 ml of ethyl acetate was hydrogenated over 0.325 g of 10% palladium on charcoal at room temperature and an initial pressure of 30 psig. Uptake of hydrogen was completed in 12 hours. The reduction mixture was filtered and the catalyst was washed with several portions of tetrahydrofuran. Evaporation of the combined filtrate and washings afforded the crude product which was crystallized from tetrahydrofuran-benzene to yield 4.5 g (93%) of product, mp 265-267°; nmr (deuteriodimethyl sulfoxide): δ 7.27-7.83 (m, 8H, Ar*H*), 8.0 (d, 1H, C-5 *H*), 8.55 (d, 1H, C-7, *H*), 12.95 (br s, 1H, O*H*); ir (potassium bromide): 2200-3200 (OH), 1670 cm^{-1} (C=O); ms: m/e 265 (M$^+$).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.40; H, 4.33; N, 5.17.

1-Benzoyl-4-diazoacetylindole (**13**).

A solution of 6.15 ml (0.084 mole) of thionyl chloride in 60 ml of methylene chloride was added dropwise to a suspension of 5.5 g (0.0205 mole) of **11** in 172 ml of methylene chloride, and the mixture was heated under reflux under nitrogen for 12 hours. Evaporation of the volatiles afforded the crude acid chloride **12** which was used without purification. A solution of crude **12** in 110 ml of dry tetrahydrofuran was added dropwise over 15 minutes at 0° to a stirred solution of 3.45 ml (0.0248 mole) of triethylamine and diazomethane (prepared from 7.6 g (0.0355 mole) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) in 110 ml of anhydrous ether. Stirring was continued at 0° for an additional 3 hours under nitrogen. The resulting suspension was filtered and the precipitate was washed on the filter with several portions of tetrahydrofuran. The combined filtrate and washings were evaporated under reduced pressure and the residue was chromatographed (dry column) on silica gel and eluted with 1:1 benzene-chloroform to afford 4.7 g (78%) of the diazoketone **13**, mp 145° dec; nmr (deuteriochloroform): δ 6.00 (s, 1H, C*H*=N$^+$), 7.2-7.95 (m, 9H, Ar*H*), 8.67 (d of d, 1H, C-7, *H*); ir (potassium bromide): 2095 (CH=$^+$N=N-), 1665 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.37; H, 3.97; N, 14.36.

Indole-4-acetic Acid (**2**).

A 10% solution of silver benzoate (0.5 ml) in triethylamine was added to a refluxing suspension of 10 g (0.0346 mole) of **13** in 110 ml of 99% ethanol, under nitrogen. A second 0.5 ml portion of the silver salt solution was added when the evolution of nitrogen slowed. This procedure was continued until further addition of silver benzoate solution caused no further evolution of nitrogen (5 additions over 15 minutes). The reaction mixture was heated under reflux for an additional 1 hour, cooled, and filtered through celite. The filtrate was evaporated under reduced pressure, the residue was taken up in 100 ml of ether, and this solution was washed twice with 10% sodium carbonate solution, then with saturated sodium chloride solution, and was dried over magnesium sulfate. Evaporation of the volatiles afforded 1.1 g of a crude mixture of ethyl 1-benzoylindole-4-acetate and ethyl indole-4-acetate. (The separation and characterization of these two products is described below). A solution of 10.5 g of the crude mixture of products and 15.75 g (0.394 mole) of sodium hydroxide in 105 ml of methanol and 210 ml of water was heated at 60-65° (bath temperature) under nitrogen for 4 hours. Most of the methanol was evaporated under reduced pressure and the aqueous phase remaining was washed with ether. Acidification of the aqueous phase at 0° with cold, dilute hydrochloric acid afforded a solid which was recrystallized from ethanol-benzene to yield 5.1 g (89%) of material, mp 207-208°; lit (3) mp 205°; nmr (deuteriodimethylsulfoxide): δ 3.78 (s, 2H, CH_2), 6.49 (m, 1H, C-3 *H*), 6.8-7.5 (m, 4H, A4*H*), 11.2 (br s, 1H, N-1 *H*), 12.2 (br s, 1H, O*H*); ir (potassium bromide): 3400 (N-1 H), 3200-2200 (OH), 1675 cm^{-1} (C=O); ms: m/e 175 (M$^+$).

Ethyl 1-Benzoylindole-4-acetate and Ethyl Indole-4-acetate.

A crude mixture of esters (0.595 g) from preparation of **2** was chromatographed on silica gel and eluted with chloroform to afford two compounds.

a) Ethyl 1-Benzoylindole-4-acetate.

This compound was obtained as a yellowish oil that solidified on standing to yield 0.385 g of material, mp 55-56°; nmr (deuteriochloroform): δ 1.23 (t, 3H, CH_3), 3.87 (s, 2H, ArCH_2), 4.13 (q, 2H, OCH_2), 6.69 (d, 1H, C-3 *H*), 7.1-7.87 (m, 8H, Ar*H*), 8.33 (d of d, 1H, C-7 *H*); ir (potassium bromide): 1715 (C=O ester), 1665 cm^{-1} (C=O, N-1 amide); ms: m/e 307 (M$^+$).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.07; H, 5.71; N, 4.56.

b) Ethyl Indole-4-acetate.

This compound was obtained as a reddish oil, yield, 0.084 g; nmr: δ 1.23 (t, 3H, CH_3), 3.9 (s, 2H, ArCH_2), 4.13 (q, 2H, OCH_2), 6.57 (m, 1H, C-3 *H*),6.87-7.38 (m, 4H, ArH), 8.3 (br s, 1H, N-1 *H*); ir (potassium bromide): 3400 (N-1 H), 1720 (C=O, ester); ms: m/e 203 (M$^+$).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 70.91; H, 6.48; N, 6.89. Found: C, 70.79; H, 6.48; N, 6.68.

Indole-4-acetamides.

A solution of 1.1 ml (0.0114 mole) of carbon tetrachloride in 10 ml of dry tetrahydrofuran was added dropwise over 30 minutes to a well-stirred suspension (under nitrogen at -20°) of indole-4-acetic acid **2** and 1.15 g (6.0 mmole) of hexamethylphosphorus triamide (technical, 85%) in 30 ml of dry tetrahydrofuran which was saturated with the appropriate primary or secondary amine. The resulting solution was stirred at room temperature for 12 hours. The reaction mixture was then filtered and the filtrate was evaporated under reduced pressure. The residue was taken up in 50 ml of benzene, washed with water then with saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of the benzene gave a semi-solid residue which solidified upon trituration with petroleum ether (bp 37-57°) and was recrystallized, see Table I.

4-(2′-Dialkylaminoethyl)indoles.

A suspension of 3.96 mmoles of the appropriate indole-4-acetamide and 1.5 g (39.5 mmoles) of lithium aluminum hydride in 50 ml of dry tetrahydrofuran was heated under reflux under nitrogen for 12 hours. After cooling to room temperature, saturated sodium sulfate solution was added dropwise until a white suspension formed. This mixture was filtered through celite and the filtrate was evaporated under reduced pressure. The residue was taken up in 100 ml of dry ether, the solution was cooled in an ice bath, and was treated with a saturated ethereal solution of fumaric acid. The solid which separated was recrystallized, see Table II.

Acknowledgement.

This investigation was supported in part by grant GM-22365, National Institute of General Medical Sciences.

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