

Biologically Active Compounds. III.

The Synthesis of α -Alkylamino- α -arylacetamides*

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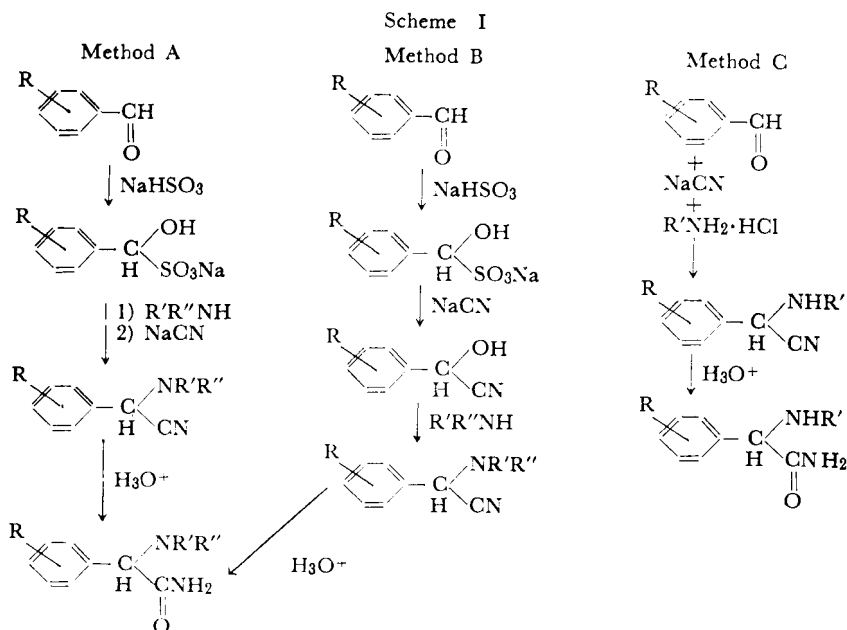
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A series of α -monoalkylamino- α -arylacetamides and α -dialkylamino- α -arylacetamides have been synthesized *via* the corresponding nitriles. Some of these compounds have been found to exhibit moderate activity as herbicides.

This work has been done as an extension of our early study on the synthesis of N-arylglycynitriles and N-arylglycinamides^{1,2)} to investigate the plant growth regulating activities of α -alkylamino- α -arylacetamides, and whether the amino linkage might be substituted for the ether linkage of α -methoxyphenylacetic acid without destroying its well-known, characteristic mode of action³⁾ as is the case with phenoxyacetic acid derivatives.

α -Dialkylamino- α -arylacetamides were syn-

thesized by the hydrolysis of the corresponding nitriles which were prepared from aldehyde-bisulfite adduct, dialkylamine, and sodium cyanide (see Method A or B in Scheme I). α -Monoalkylamino- α -arylacetamides were not obtained in good yields by the above procedures, while the yields were improved when the nitriles were prepared by the use of aldehydes, hydrochloride of amines, and sodium cyanide (see Method C in Scheme I).



The physical properties, yields, and analytical data of α -dialkylamino- α -arylacetoni-

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triles, α -dialkylamino- α -arylacetamides, and α -monoalkylamino- α -arylacetamides are summarized in Table I, II, and III, respectively. Examples of infrared spectra are given in Figure I.

It has been found that some of the title compounds such as α -ethylamino- α -(4-bromophenyl)acetamide (**22**), α -methylamino- α -(2,4-dichlorophenyl)acetamide (**29**), α -ethylamino- α -(2,4-dichlorophenyl)acetamide (**30**), α -ethylamino- α -(4-tolyl)acetamide (**34**), α -methylamino- α -(4-methoxyphenyl)acetamide (**35**) had moderate activity as herbicides.

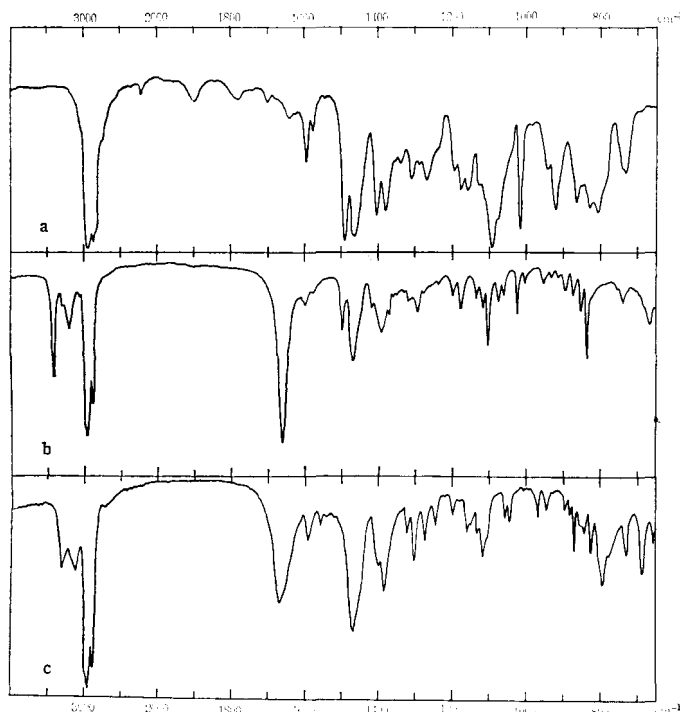
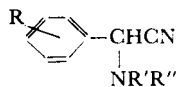


Fig. 1. Infrared spectra of: (a) **7**, liquid film; (b) **15**, nujol; (c) **30**, nujol.

Table I. α -Dialkylamino- α -arylacetonitriles

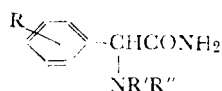


Compd.	R	R'	R''	Method	Bp/mm or (mp), °C	Yield, %	Formula	% calcd			% found		
								C	H	N	C	H	N
1	2-Br	CH ₃	CH ₃	A	117-118/4	77.1	C ₁₀ H ₁₁ BrN ₂	50.22	4.64	11.72	50.11	4.79	10.95
2	4-Br	CH ₃	CH ₃	A	(46-48)	88.5	C ₁₀ H ₁₁ BrN ₂	50.22	4.64	11.72	50.39	4.74	11.61
3	2-Cl	CH ₃	CH ₃	A	(36-39)	90.4	C ₁₀ H ₁₁ ClN ₂	61.70	5.70	14.39	61.60	5.63	13.97
4	2-Cl	C ₂ H ₅	C ₂ H ₅	A	142-144/10	57.2	C ₁₂ H ₁₅ ClN ₂	64.71	6.79	12.58	64.89	6.71	12.10
5	3-Cl	CH ₃	CH ₃	A	108-109/3	85.5	C ₁₀ H ₁₁ ClN ₂	61.70	5.70	14.39	61.82	5.90	13.48
6	4-Cl	C ₂ H ₅	C ₂ H ₅	B	118-119/3	69.0	C ₁₂ H ₁₅ ClN ₂	64.71	6.79	12.58	64.57	6.87	13.03
7	4-Cl	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	A	164-166/3	59.0	C ₁₆ H ₂₃ ClN ₂	68.92	8.31	10.05	69.09	8.43	9.49
8	2,4-Cl ₂	CH ₃	CH ₃	B	130-133/4	74.7	C ₁₀ H ₁₀ Cl ₂ N ₂	52.42	4.40	12.23	52.63	4.66	12.51

Experimental Section

Melting points and boiling points are uncorrected and the compounds listed in Table I, II, and III are new.

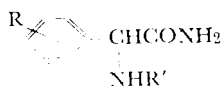
α -Monoalkylamino- α -arylacetonitriles and α -dialkylamino- α -arylacetonitriles were prepared by one of the following procedures adapted from reported method.⁴⁻¹³ Three different methods (A,¹³ B,⁴) and C¹¹) are illustrated by

Table II. α -Dialkylamino- α -arylacetamides

Compd.	R	R'	R''	Method	Mp, °C	Yield, % ^a	Solvent of recrystn ^b	Formula	% calcd			% found		
									C	H	N	C	H	N
9	2-Br	CH ₃	CH ₃	A	134-136	38.8	B	C ₁₀ H ₁₃ BrN ₂ O	46.71	5.09	10.90	46.47	5.07	11.04
10	4-Br	CH ₃	CH ₃	A	138-139	91.1	B	C ₁₀ H ₁₃ BrN ₂ O	46.71	5.09	10.90	47.04	5.13	11.35
11	2-Cl	CH ₃	CH ₃	A	112-114	60.7	B	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.50	5.90	13.37
12	2-Cl	C ₂ H ₅	C ₂ H ₅	A	93-94	65.2	W	C ₁₂ H ₁₇ ClN ₂ O	59.87	7.12	11.64	59.73	7.21	11.50
13	3-Cl	CH ₃	CH ₃	A	155-156	80.8	B	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.62	6.26	13.21
14	4-Cl	C ₂ H ₅	C ₂ H ₅	B	123-124	91.4	B	C ₁₂ H ₁₇ ClN ₂ O	59.87	7.12	11.64	60.04	7.10	11.85
15	4-Cl	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	A	127-129	66.3	B	C ₁₆ H ₂₅ ClN ₂ O	64.74	8.49	9.44	64.70	8.51	9.18
16	2,4-Cl ₂	CH ₃	CH ₃	B	116-118	64.5	W	C ₁₀ H ₁₂ Cl ₂ N ₂ O	48.60	4.90	11.34	48.76	4.98	11.93

^a Yields calculated after one recrystallization are given.

^b B = benzene, W = water.

Table III. α -Monoalkylamino- α -arylacetamides

Compd.	R	R'	Method	Mp, °C	Yield, % ^a	Solvent of recrystn ^b	Formula	% calcd			% found		
								C	H	N	C	H	N
17	H	<i>i</i> -C ₃ H ₇	C	78-79	76.2	B	C ₁₁ H ₁₆ N ₂ O	68.71	8.39	14.57	68.91	8.18	14.45
18	H	<i>n</i> -C ₄ H ₉	C	85-86	37.5	W	C ₁₂ H ₁₈ N ₂ O	69.87	8.79	13.58	69.79	8.92	13.78
19	2-Br	CH ₃	C	129-131	56.9	W	C ₉ H ₁₁ BrN ₂ O	44.46	4.56	11.53	44.72	4.83	11.23
20	2-Br	C ₂ H ₅	C	114-115	52.9	W	C ₁₀ H ₁₃ BrN ₂ O	46.71	5.09	10.90	47.00	5.25	10.59
21	4-Br	CH ₃	C	162-163	54.7	B	C ₉ H ₁₁ BrN ₂ O	44.46	4.56	11.53	44.47	4.67	11.23
22	4-Br	C ₂ H ₅	C	130-131	57.0	B	C ₁₀ H ₁₃ BrN ₂ O	46.71	5.09	10.90	46.72	5.24	10.66
23	2-Cl	CH ₃	C	120-121	49.3	W	C ₉ H ₁₁ ClN ₂ O	54.41	5.58	14.10	54.46	5.59	13.42
24	2-Cl	C ₂ H ₅	C	101-102	43.7	W	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.59	6.35	13.14
25	3-Cl	CH ₃	C	121-122	42.3	W	C ₉ H ₁₁ ClN ₂ O	54.41	5.58	14.10	54.70	5.78	13.76
26	3-Cl	C ₂ H ₅	C	128-130	36.7	W	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.49	6.35	13.27
27	4-Cl	CH ₃	C	151-152	61.2	W	C ₉ H ₁₁ ClN ₂ O	54.41	5.58	14.10	54.36	5.59	14.12
28	4-Cl	C ₂ H ₅	C	129-130	58.7	W	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.66	6.31	13.01
29	2,4-Cl ₂	CH ₃	C	107-108	69.1	B	C ₉ H ₁₀ Cl ₂ N ₂ O	46.37	4.32	12.02	46.54	4.53	11.69
30	2,4-Cl ₂	C ₂ H ₅	C	69-71	46.7	W	C ₁₀ H ₁₂ Cl ₂ N ₂ O	48.60	4.90	11.34	48.88	5.13	11.08
31	3,4-Cl ₂	CH ₃	C	158-159	48.4	W	C ₉ H ₁₀ Cl ₂ N ₂ O	46.37	4.32	12.02	46.62	4.58	11.64
32	3,4-Cl ₂	C ₂ H ₅	C	138-139	54.5	B	C ₁₀ H ₁₂ Cl ₂ N ₂ O	48.60	4.90	11.34	48.84	5.14	11.02
33	4-CH ₃	CH ₃	C	164-165	36.0	W	C ₁₀ H ₁₄ N ₂ O	67.38	7.92	15.72	67.60	8.07	15.74
34	4-CH ₃	C ₂ H ₅	C	144-145	41.6	W	C ₁₁ H ₁₆ N ₂ O	68.71	8.39	14.57	68.78	8.51	14.55
35	4-CH ₃ O	CH ₃	C	166-167	36.3	B	C ₁₀ H ₁₄ N ₂ O ₂	61.83	7.26	14.43	61.78	7.34	14.23
36	4-CH ₃ O	C ₂ H ₅	C	132-133	70.1	B	C ₁₁ H ₁₆ N ₂ O ₂	63.44	7.75	13.45	63.67	7.86	13.38

^a Since these aminonitriles were not isolated, yields are based on the amount of aldehyde used. Yields calculated after one recrystallization are given.

^b B = benzene, W = water.

the following experiments.

Method A. α -(N,N-Dimethylamino)- α -(2-chlorophenyl)acetonitrile (3). — With stirring, 20 g (0.14 mole) of 2-chlorobenzaldehyde was added to a slurry of 15 g (0.14 mole) of sodium bisulfite in 30 ml of water. After heating for 15 min on a water bath, 24 g (0.21 mole) of 40% aqueous dimethylamine was added and then stirred for 30 min. The resulting mixture was cooled in an ice-water bath and a solution of 7.6 g (0.15 mole) of sodium cyanide in 20 ml of water was added dropwise at 10°. The mixture was stirred at room temperature for an additional 3 hr. The oil was separated and it was combined with ethereal extract of the aqueous layer. The ethereal extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The residue was recrystallized from ethanol to give 23.7 g (90.4%) of **3**, mp 36–37°. IR: 2200 cm⁻¹ (nitrile ν C \equiv N).

α -(N,N-Dimethylamino)- α -(2-chlorophenyl)acetamide (11). — To a 25 ml of concentrated sulfuric acid was added dropwise 21.5 g (0.11 mole) of aminonitrile **3** with stirring. The stirred mixture was heated for 30 min at 50–60° and the stirring continued for 3 hr at room temperature. The reaction mixture was poured slowly onto 100 g of crushed ice. When the solution was neutralized with concentrated ammonium hydroxide there precipitated a solid, which was collected on a filter and washed with cooled water, and dried. The crude product, on recrystallization from water, gave 16.9 g (64.5%) of **11**, mp 111–113°. Further recrystallizations from water gave a pure sample of mp 112–114°. IR: 3330, 3130 (amide ν NH) and 1680 cm⁻¹ (amide ν C=O).

Method B. α -(N,N-Dimethylamino)- α -(2,4-dichlorophenyl)acetonitrile (8). — To a stirred solution of 25 g (0.24 mole) of sodium bisulfite in 70 ml of water was added 25 g (0.14 mole) of 2,4-dichlorobenzaldehyde in 70 ml of ethanol and heated on a water bath for 40 min. Upon cooling the solid was collected on a filter. To a stirred slurry of 2,4-dichlorobenzaldehyde-bisulfite addition product in 150 ml of water was added dropwise a solution of 13.8 g (0.21 mole) of sodium cyanide in 40 ml of water with cooling and stirred for an additional 3 hr. 2,4-Dichloro-mandelonitrile, which separated from cooled

solution, was dissolved in 400 ml of ethanol followed by the addition of 64 g (0.56 mole) of 40% aqueous dimethylamine. The mixture was allowed to stand for overnight. After the removal of solvent and excess dimethylamine, the residue was taken up in ether, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The residue was distilled to give 24.3 g (74.1%) of **8**, bp 130–133°/4 mm. IR: 2220 cm⁻¹ (nitrile ν C \equiv N).

α -(N,N-Dimethylamino)- α -(2,4-dichlorophenyl)acetamide (16). — This amide was prepared from aminonitrile **8** in the same manner as described in method A for aminoamide **11**. A total of 16.9 g (64.5%) of **16**, recrystallized from water, was obtained, mp 116–118°. IR: 3340, 3130 (amide ν NH) and 1680 cm⁻¹ (amide ν C=O).

Method C. α -(N-Methylamino)- α -(2-bromophenyl)acetamide (19). — To a stirred solution of 10.1 g (0.15 mole) of methylamine hydrochloride in 75 ml of water was added a solution of 11.0 g (0.23 mole) of sodium cyanide in 20 ml of water and treated portionwise with a solution of 27.8 g (0.15 mole) of 2-bromobenzaldehyde in 40 ml of methanol. After stirring for 3 hr, the oil was separated and washed with water. The oily aminonitrile was converted with concentrated sulfuric acid to amide as described in the method A. Recrystallization from water yielded 20.8 g (56.9%) of **19**, mp 127–129° and 129–131° after further recrystallizations from water. IR: 3200 (amine ν NH) and 1695 cm⁻¹ (amide ν C=O).

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