Chemical Constitution and Insecticidal Action

2. SUBSTITUTED α -AMINONITRILES

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The high contact insecticidal activity of certain thiocyanic esters of alcohols of appropriate molecular weight and stereochemical composition prompted the investigation of other compounds containing the cyano group. So far as is known, the insecticidal activity of nitriles is markedly less than that of the corresponding thiocyanates. From our own observations, for example, lauronitrile has only a fraction of the aphicidal activity of dodecyl thiocyanate. If, as has been suggested by Hoggarth & Sexton (1947), the insecticidal activity of the thiocyanates is in part due to the special chemical reactivity of the carbon atom in the SCN group, then it follows that the introduction of other groups which modify the reactivity of the C atom of the CN group in a similar way may be expected to give compounds having insecticidal properties.

The cyanamides were considered since they, like the thiocyanates, have the CN group separated from the rest of the molecule by a heteroatom, but an investigation with Dr W. H. Davies showed that their high chemical reactivity (notably their tendency to polymerization) rendered them unattractive for the purpose in view. The separation of the nitrogen atom from the CN group gives the α -aminonitriles, a class of compound which is readily prepared with a variety of structural permutations. Although these have additional reactive features (see Discussion, p. 472) the CN group can be hydrolyzed under appropriate experimental conditions, as can the CN group in the thiocyanates. It was, therefore, decided to conduct a systematic investigation into their insecticidal activity. Some very powerful insecticides were thereby discovered from amongst the many dozens of compounds examined (see Collie, Hill & Sexton, 1939; Sexton, 1939).

Our work was interrupted by the war, and since then the appearance of the newer chlorinated hydrocarbon contact insecticides has not encouraged us to reopen the investigation. Nevertheless, points of considerable theoretical interest emerged, and this communication records such of the results as have a bearing on the problem of correlating constitution with activity. Since our work was carried out, certain compounds of this broad chemical class have been found by Siegler & Gertler (1946) to be toxic

to codling moth larvae (*Cydia pomonella* L.), but so far as we are aware they have not been mentioned in any other scientific publication.

METHODS

Preparation of compounds

The general preparative methods are based upon the principle of condensing an aldehyde or ketone cyanohydrin with NH_3 or a primary or secondary amine, and four variations of experimental technique were employed (Jay & Curtius, 1894; Knoevenagel, 1904; Kötze & Merkel, 1926; Walther & Hübner, 1916). Trimeric methyleneaminoacetone nitrile (' α -hydroformamine cyanide') was obtained by the 'literature' method (*Organic Syntheses*, Coll. Vol. I, 348; Johnson & Rinehart, 1924). Many of the other compounds had already been described in the literature, but some were new, and where these had marked biological activity, their identity was checked by elementary analysis. Details of the preparation of three of the most important of the new compounds are appended, and Table 1 gives the properties of all the new compounds.

α -Phenylmethylaminooctonic nitrile,

Purified heptaldehyde (405 ml.) was added during 30 min. with stirring to 40% NaHSO_3 solution (615 ml.). The hot solution was then treated with methylaniline (360 ml.) during 20 min., during which time the reaction mixture assumed a jelly-like consistency. After 2.5 hr. at 70–75° the mass became transparent and fluid. A solution of 90% NaCN (180 g.) in water (360 ml.) was then added during 20 min., the temperature being kept below 70°. Stirring was continued for a further 20 min., and after addition of 1 l. of water, the supernatant oil was separated, washed and dried. Yield, 567 g. (82% of theory on heptaldehyde). The material had b.p. 156–157°/2 mm., and when freshly distilled was a white fluorescent oil. On storage it gradually turns yellow. (Found: C, 78.85; H, 10.0; N, 11.7. $\text{C}_{15}\text{H}_{22}\text{N}_2$ requires C, 78.3; H, 9.6; N, 12.1%.)

$\alpha\beta$ -Bis(α -cyanoheptylamino)ethane,

Purified heptaldehyde (134 ml.) was added to 40% NaHSO_3 solution (310 ml.). The solution was maintained at 60° for 30 min., when 90% ethylenediamine (37 ml.) was added. After 2 hr. stirring at 60°, a solution of 90% NaCN (56 g.) in water (172 ml.) was run in (30 min.), and after a further 30 min. the oil was separated and washed first with brine, then twice with water. It was dried over MgSO_4 and slowly solidified, giving white plates (from light petroleum), m.p. 45°. (Found: C, 70.3; H, 10.6; N, 18.1. $\text{C}_{18}\text{H}_{34}\text{N}_4$

requires C, 70.6; H, 11.1; N, 18.3%.) Treatment in glacial acetic acid with NaNO_2 gave the *dinitroso* derivative, m.p. 84–87°. (Found: N, 22.6. $\text{C}_{18}\text{H}_{28}\text{O}_2\text{N}_4$ requires N, 23.1%.)

As originally prepared, this substance was an oil, and it was only when further preparations were made that it was eventually obtained in the solid state. Solidification of the oil is sometimes extremely slow, and the earlier tests

were performed with liquid preparations. Biological tests showed, however, that there was practically no difference in aphicidal activity between the original liquid preparations and the pure solid, and the original preparations are considered to consist substantially of the desired material. Heptaldehyde cyanohydrin, a possible contaminant in the liquid material, was not aphicidal.

Table 1. *Preparation and properties of new aminonitriles*

No.	Formula	Physical constants
23	$\text{C}_6\text{H}_5\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_5)\text{CN}$	M.p. 90–91°
27	$\text{HOC}_2\text{H}_4\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN}^*$	B.p. 126–128°/20 mm.
24	$\text{C}_6\text{H}_5(\text{CH}_3)\text{N} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN}$	B.p. 162–164°/15 mm.
20	$\text{C}_6\text{H}_5(\text{C}_6\text{H}_5)\text{N} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN}$	B.p. 155–156°/15 mm.
29	$\text{HOC}_2\text{H}_4\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_5)\text{CN}$	B.p. 160°/16 mm.
11	$(\text{CH}_3)_2\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 120°/16 mm.
12	$(\text{C}_4\text{H}_9)_2\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 171°/17 mm.
16	$(\text{C}_5\text{H}_{11})_2\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 185–190°/18 mm.
30	$\text{C}_6\text{H}_{11}\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 170°/18 mm.
31	<i>cyclo</i> $\text{C}_6\text{H}_{11}\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 150°/16 mm.
15	$\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 156°/16 mm.
15a	$\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	Low m.p., b.p. 166°/16 mm.
28	$\text{HOC}_2\text{H}_4\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	M.p. 78–80°
26	$\text{C}_6\text{H}_5\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 170°/17 mm.
17	$\text{C}_6\text{H}_5(\text{CH}_3)\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 156–157°/2 mm.
19	$\text{C}_6\text{H}_5(\text{C}_6\text{H}_5)\text{N} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	B.p. 192–194°/18 mm.
36	<i>cyclo</i> $\text{C}_6\text{H}_{11}\text{NH} \cdot \text{C}(\text{CH}_3)_2\text{CN}$	M.p. 52–53°
37	$\text{HOC}_2\text{H}_4\text{NH} \cdot \text{C}(\text{CH}_3)_2\text{CN}$	B.p. 101–103°/27 mm.
42	$\text{C}_6\text{H}_5\text{NH} \cdot \text{C}(\text{CH}_3)[\text{CH}_2 \cdot \text{CH}(\text{CH}_3)_2] \cdot \text{CN}$	M.p. 52–53°
45	$\text{NH} \cdot \text{C}_2\text{H}_4\text{OH}$	M.p. 72–73°
47a	$\text{N}(\text{C}_2\text{H}_5)_2$	Liquid
10	$(\text{C}_2\text{H}_5)_2\text{N} \cdot \text{CH}(\text{C}_{17}\text{H}_{35})\text{CN}$	Waxy solid
63	$[-\text{CH}_2\text{NH} \cdot \text{C}(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CN}]_2$	M.p. 46–47°
53	$[-\text{CH}_2\text{N}(\text{CH}_3) \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}]_2$	M.p. 48–51°
57	$\left[\begin{array}{c} -\text{CH}_2 \\ -\text{CH}_2 \end{array} \right] \text{N} \cdot \text{CH}(\text{CH}_3) \cdot \text{CN}]_2$	M.p. 165°
58	$\left[\begin{array}{c} -\text{CH}_2 \\ -\text{CH}_2 \end{array} \right] \text{N} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN}]_2$	M.p. 149–151°
59	$(p)\text{C}_6\text{H}_4[\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN}]_2$	M.p. 116–118°
60	$(p)\text{C}_6\text{H}_4[\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}]_2$	M.p. 145°
51	$[-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN}]_2$	Undistillable liquid
52	$[-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}]_2$	Undistillable liquid
61	$\left[\text{—} \langle \text{C}_6\text{H}_4 \rangle \text{—} \text{NH} \cdot \text{CH}(\text{C}_6\text{H}_7)\text{CN} \right]_2$	M.p. 182–184°
54	$[-\text{CH}_2\text{NH} \cdot \text{C}(\text{CH}_3)(\text{C}_{11}\text{H}_{23})\text{CN}]_2$	Undistillable liquid

The new compounds listed in this table were not subjected to elementary analysis since (a) they were all of the same chemical type, prepared by standardized methods, and (b) their physical properties were in accord with expectations from the properties of near homologues, which have been fully characterized and described in the literature. For some of the more important new compounds, analyses are appended to the detailed preparative descriptions given on pp. 468–470.

* C_3H_7 , C_4H_9 , C_6H_{11} , etc. indicate normal primary straight-chain alkyl radicals unless otherwise stated.

$\alpha\beta$ -Bis(*N*-methyl- α' -cyanoheptylamino)ethane,

Redistilled heptaldehyde (22.8 g.) was slowly run into 40% NaHSO₃ (57.2 ml.) at 60–70°. After 30 min. a solution of *NN'*-dimethylethylenediamine dihydrochloride (16.1 g.) in 2*N*-NaOH (100 ml.) was added. After further stirring (1 hr.) at the same temperature, a solution of NaCN (12 g.) in water (18 ml.) was added. The oil which separated was washed with brine, and dried with MgSO₄; yield, 32.8 g. (94% of theory). It could not be distilled without decomposition, but it solidified slowly and had m.p. 48–51° (from methanol). (Found: C, 71.95; H, 10.8; N, 17.3. C₂₀H₃₈N₄ requires C, 71.8; H, 11.4; N, 16.8%.)

Biological testing

Sorting tests were carried out using aphids (usually the chrysanthemum aphid, *Macrosiphoniella sanborni* G., but the bean aphid, *Doralis rumicis* L. (= *Aphis rumicis* L., (*fabae* Scop.)), when the former were not available) and adult blowflies (*Calliphora erythrocephala* Meig.) with contact spraying in the Tattersfield apparatus, and for stomach poisoning effects using the grain weevil, *Sitophilus granarius* L., which was allowed to feed on 'biscuits' prepared from flour and water containing the substance under test. These methods, including the methods used for the preparation of the sprays, are described by Davies & Sexton (1948); in brief, the dispersions for spraying were made by adding ethanolic solutions of the substances under test to a dilute solution of a dispersing agent, so that the final sprays contained 50% ethanol. The possible interfering effect of the ethanol was appreciated, and the activity of promising substances was confirmed by the examination of specially prepared dispersions. The ethanol dispersion technique served to provide a standard method of presentation, applicable to most of the compounds examined, and so to permit comparisons of activity in groups of closely related compounds. Cases where this dispersion technique was not applicable are noted in the tables. In the stomach poison tests, lead arsenate was used as a standard of comparison, and the figures in brackets in Table 2 are the toxicities of lead arsenate in the individual experiments. Toxicities are expressed as 'absolute mortality', a figure derived after adjustment for mortalities caused by sprays or 'biscuits' from which the poison was omitted (Davies & Sexton, 1948).

RESULTS

The earliest tests were stomach poison tests, and, using the 'biscuit' method, α -hydroformamine cyanide was found to be highly toxic not only to the grain weevil, but also to the flour moth, *Ephestia kühniella* Zell., and moderately toxic to leather-jackets. It was without effect on rice moth larvae (*Corcyra cephalonica* Staint.). Iminodiacetonitrile, NH(CH₂CN)₂, was also toxic to the grain weevil, but the methylene derivative of this, CH₂[N(CH₂CN)]₂, was non-toxic. It was these results which led to the decision to conduct a systematic investigation into the α -aminonitriles. The results of the sorting tests are summarized in Table 2.

The results of the above preliminary evaluation showed that high aphicidal activity could be

obtained with compounds of the aminonitrile class. The next stage of the investigation was, therefore, a further examination of the more promising compounds at greater dilutions, and also an extension of the investigation to compounds derived from diamines. In selecting compounds for further study some account was taken of their potential availability. The results of the further sorting tests, using the standard ethanol dispersion method on chrysanthemum aphid in the Tattersfield apparatus, are given in Table 3.

Since most of the figures for mortality in Table 3 had been obtained by using the 50% ethanol sprays, it was necessary to make compositions which could be diluted with water to provide sprays which were essentially aqueous in nature, though the presence of a surface-active agent as emulsifier was of course necessary. For this purpose concentrated emulsions of the following composition by weight were prepared and were diluted either with water or with 0.1% 'Agral 2' (wetting agent) and sprayed on chrysanthemum aphid using the Tattersfield apparatus.

1. C₆H₅(CH₂)₃N.CH(C₆H₁₃)CN (Compound 17) 54%; ethanolamine oleate 36%; ethoxyethanol 10%.
2. [—CH₂NH.CH(C₆H₁₃)CN]₂ (Compound 49) 15.6%; sulphonated cod oil 38.3%; ethoxyethanol 46.1%.
3. Compound 49, 20%; 'Agral' Liquid Wetter 43%; ethoxyethanol 37%.
4. Compound 49, 8.3%; castor oil 16.7%; trichloroethylene 47%; casein 4.5%; borax 2.1%; water 64.5%.
5. Compound 49, 9.1%; triethanolamine oleate 89.1%; ethoxyethanol 1%.
6. [—CH₂NH.CH(C₆H₁₃)CN]₂ (Compound 50) 20%; 'Agral' Liquid Wetter 43%; ethoxyethanol 37%.
7. Compound 50, 15.6%; sulphonated cod oil 38.3%; ethoxyethanol 46.1%.
8. Compound 50, 10%; castor oil 10%; trichloroethylene 45%; casein 4.3%; borax 2.1%; water 64.5%.

The results of spraying tests with the above emulsions at 0.05% active ingredient are given in Table 4. Clearly, although the degree of activity was considerably affected by the nature of the emulsion, the high aphicidal activity revealed by the sorting test was genuine. This was further confirmed by trials of dry dust preparations (3% on talc) against bean and hop aphid, *Phorodon pruni* Scop., on infested plants, with nicotine and 2-thio-3-methylbenzthiazolone (Davies & Sexton, 1948) included for comparison. The results are given in Table 5. Possibly the superiority of nicotine in this experiment was due to its fumigant action. It may be mentioned at this point that, in experiments on infested plants, marked variations in phytocidal activity between the different emulsions were also noted, and that the most effective emulsions from the aphicidal point of view were not necessarily the most phytocidal.

Table 2. *Insecticidal sorting tests with (mono) α -aminonitriles*

No.	Compound	Conc. (%)	...	Percentage absolute mortality				Grain weevils (‘biscuit’ method)
				Aphids		Blowflies		
				0.35	0.2	0.55	0.35	
1	N(CH ₂ CN) ₃			28	—	—	17	—
2	(CH ₃) ₂ N · CH ₂ CN			—	3 (b)	50	—	22 (58)*
3	(C ₂ H ₅) ₂ N · CH ₂ CN			—	6 (b)	69	—	8 (58)
4	(C ₄ H ₉) ₂ NCH ₂ CN			—	3 (b)	97	—	57 (58)
5	N · CH ₂ CN			—	3 (b)	85	—	10 (58)
6	C ₆ H ₅ (CH ₃)N · CH ₂ CN			—	3 (b)	27	—	83 (47)
7	(C ₂ H ₅) ₂ N · CH(CH ₃)CN			—	28 (b)	17	—	8 (92)
8	(C ₂ H ₅) ₂ N · CH(C ₆ H ₁₃)CN			—	88 (b)	99	—	88 (44)
9	(C ₂ H ₅) ₂ N · CH(C ₆ H ₅)CN			—	34 (b)	100	—	99 (44)
10	(C ₂ H ₅) ₂ N · CH(C ₁₇ H ₃₅)CN			97	18†	—	4	—
11	(CH ₃) ₂ N · CH(C ₆ H ₁₃)CN			77	—	92	—	78 (50)
12	(C ₄ H ₉) ₂ N · CH(C ₆ H ₁₃)CN			100	—	100	—	16 (50)
13	(C ₄ H ₉) ₂ N · CH(CH · CH · CH ₃)CN			100	—	—	18	—
14	(HOC ₂ H ₄) ₂ N · CH(C ₆ H ₁₃)CN			41, 25†	—	—	3, 6†	—
15	N · CH(C ₆ H ₁₃)CN			100	—	100	—	54 (50)
15a	N · CH(C ₆ H ₁₃)CN			90†	—	58†	—	—
16	(C ₆ H ₁₁) ₂ N · CH(C ₆ H ₁₃)CN			100†	—	—	19†	—
17	C ₆ H ₅ (CH ₃)N · CH(C ₆ H ₁₃)CN			100	—	—	19	3 (50)
18	<i>cyclo</i> C ₆ H ₁₁ (C ₂ H ₅)N · CH(C ₆ H ₁₃)CN			100	—	—	—	20 (95)
19	C ₆ H ₅ (C ₂ H ₅)N · CH(C ₆ H ₁₃)CN			28†	—	—	58†	—
20	C ₆ H ₅ (C ₂ H ₅)N · CH(C ₅ H ₇)CN			53, 4†	—	—	96, 81†	56 (95)
22	H(C ₆ H ₅)N · CH ₂ CN			—	17 (b)	31	—	90 (45)
23	H(C ₆ H ₅)N · CH(CH ₃)CN			37	—	—	4	21 (42)
24	C ₆ H ₅ (CH ₃)N · CH(C ₃ H ₇)CN			64†	—	—	54†	12 (41)
25	H(C ₆ H ₅)N · CH(C ₃ H ₇)CN			27	—	—	37	10 (41)
26	H(C ₆ H ₅)N · CH(C ₆ H ₁₃)CN			54	—	59	—	8 (50)
27	HOC ₂ H ₄ NH · CH(C ₃ H ₇)CN			56	—	—	9	9 (95)
28	HOC ₂ H ₄ NH · CH(C ₆ H ₁₃)CN			100	100	22	—	2 (59)
29	HOC ₂ H ₄ NH · CH(C ₆ H ₅)CN			39	—	16	—	11 (59)
31	<i>cyclo</i> C ₆ H ₁₁ NH · CH(C ₆ H ₁₃)CN			100	—	99	—	20 (56)
35	H(C ₆ H ₅)N · C(CH ₃) ₂ CN			54	—	—	48	8 (41)
40	H(C ₆ H ₅)N · C(CH ₃)(C ₂ H ₅)CN			86	71†	—	65	5 (41)
42	H(C ₆ H ₅)N · C(CH ₃)(C ₄ H ₉ ^β)CN			97	39†	—	28	6 (41)
44	NH(C ₆ H ₅) CN			100	60†	—	10	5 (51)
45	NH · C ₂ H ₄ OH CN			0	—	—	26	0 (95)
46	NH · C ₆ H ₁₁ (<i>cyclo</i>) CN			82	20†	—	11	0 (42)

* The figures in brackets in this column give the mortality with a lead arsenate bait.

† Emulsified by means of a sulphonated oil.

The chrysanthemum aphid was used except where (b) indicates the bean aphid.

In addition to the compounds listed above, the following gave absolute mortalities of not more than 15% to all three insects:

No.	Compound	No.	Compound
21	$\text{CH}_2\text{NH} \cdot \text{CH}_2\text{CN}$	37	$\text{HOC}_2\text{H}_4\text{NH} \cdot \text{C}(\text{CH}_3)_2\text{CN}$
30	$\text{C}_6\text{H}_{11}\text{NH} \cdot \text{CH}(\text{C}_6\text{H}_{13})\text{CN}$	38	$\text{NH}_2\text{C}(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CN}$
32	Benzoyl derivative of 31	39	Oxalate and tartrate of 38
33	$\text{NH}_2\text{C}(\text{CH}_3)_2\text{CN}$	43	$\text{HOC}_2\text{H}_4\text{NH} \cdot \text{C}(\text{CH}_3)(\text{C}_4\text{H}_9\beta)\text{CN}$
34	Four acyl derivatives of 33	47	CN NH_2
36	<i>cyclo</i> $\text{C}_6\text{H}_{11}\text{NH} \cdot \text{C}(\text{CH}_3)_2\text{CN}$	41	$\text{NH}_2\text{C}(\text{CH}_3)(\text{C}_4\text{H}_9\beta)\text{CN}$

Table 3. *Further aphicidal sorting tests with aminonitriles*

No.	Compound	Conc. (%)	Percentage absolute mortality of chrysanthemum aphis			
			0.35	0.2	0.05	0.025
48	$[-CH_2NH \cdot CH(CH_3)CN]_2$	100	100	98	40	—
49	$[-CH_2NH \cdot CH(C_6H_7)CN]_2$	100	100	100	96	23
50	$[-CH_2NH \cdot CH(C_6H_{13})CN]_2$	100	100	100	100	98
17	$C_6H_5(CH_3)N \cdot CH(C_6H_{13})CN$	100	100	80	35	—
51	$[-CH_2CH_2CH_2NH \cdot CH(C_2H_7)CN]_2$	100	100	100	34	—
52	$[-CH_2CH_2CH_2NH \cdot CH(C_6H_{13})CN]_2$	100	100	100	89	—
53	$[-CH_2N(CH_3) \cdot CH(C_6H_{13})CN]_2$	100	100	100	98	90
54	$[-CH_2NH \cdot CH(CH_3)(C_{11}H_{23})CN]_2$	90	90	26	16	—
55		21	21	—	—	—
56		0	0	—	—	—
57		100	100	—	—	—
58		0	0	—	—	—
59	$(p)C_6H_4[NH \cdot CH(C_6H_7)CN]_2$	8	8	—	—	—
60	$(p)C_6H_4[NH \cdot CH(C_6H_{13})CN]_2$	11	11	—	—	—
61	$[-(1:4-cyclo)C_6H_9NH \cdot CH(C_6H_7)CN]_2$	18	18	—	—	—
62	$[-CH_2NH \cdot C(CH_3)_2CN]_2$	26	26	—	—	—
63	$[-CH_2NH \cdot C(CH_3)(C_2H_5)CN]_2$	48	48	—	—	—
64	$[-CH_2NH \cdot CH(C_6H_5)CN]_2$	8	8	—	—	—
12	$(C_4H_9)_2N \cdot CH(C_6H_{13})CN$	100	100	95	58	—
15		—	—	100	77	43
31	$cycloC_6H_{11}NH \cdot CH(C_6H_{13})CN$	—	—	100	84	13
28	$HOC_2H_4NH \cdot CH(C_6H_{13})CN$	—	—	100	58	—
13	$(C_4H_9)_2N \cdot CH(CH_2CH_2CH_3)CN$	—	—	100	25	—
18	$cycloC_6H_{11}(C_2H_5)NCH(C_6H_{13})CN$	—	—	100	72	—
—	$C_{12}H_{25}SCN$	100	100	100	100	63

Table 4. *Toxicity of aminonitrile emulsions to chrysanthemum aphis with a concentration of 0.05% insecticide*

Emulsion	Percentage absolute mortality	
	Diluted with water	Diluted with 0.1% 'Agradal 2'
1	100	—
Spray of active ingredient in 50% ethanol	49	—
2	37.5	—
3	25	—
4	69	44
5	58	47
Spray of active ingredient in 50% ethanol	62	—
6	96	98
7	98	60
8	100	100
Spray of active ingredient in 50% ethanol	100	—

Table 5. *Toxicity of 3% dusts to aphis*

Insecticide	Percentage kill	
	Bean aphid	Hop aphid
$[-CH_2NH \cdot CH(C_6H_{13})CN]_2$	39	22
$C_6H_5(CH_3)N \cdot CH(C_6H_{13})CN$	63	47
48	2
Nicotine	98	97.5

DISCUSSION

The first point which emerges from a study of the above results is the variation in toxicity to different insect species, an effect which was observed in

studies of organic sulphur compounds and which, indeed, is probably a general feature of organic insecticides (Davies & Sexton, 1948). Certain of the more potent insecticides (Table 2) showed high toxicity to all three test insects, but the toxicity was specific where evaluation at lower dosages was carried out. For example, the two compounds

and

when tested at 0.2 %, gave 100 % absolute mortality of aphids but were non-toxic to blowflies. Again, extended evaluation of compounds having marked stomach-poison activity against the grain weevil showed that they were much inferior to lead arsenate against various leaf-eating larvae. This was true, for example, with $(\text{C}_2\text{H}_5)_2\text{N} \cdot \text{CH}(\text{C}_6\text{H}_5)\text{CN}$ (Table 2) which, though more toxic than lead arsenate to the grain weevil, was practically without action against a wide range of leaf-eating larvae. The specificity of α -hydroformamine cyanide as a stomach poison has already been referred to. We found phenylglycine nitrile to be more toxic than lead arsenate to the grain weevil. Siegler & Gertler (1946) found it to be less toxic than lead arsenate to the codling moth, but they found the *p*-tolyl analogue to be more toxic than lead arsenate to the codling moth.

Considering the contact insecticidal action and particularly the effects against aphids, it is clear that the physical properties of the molecule play an important part in influencing its toxicity. Consideration of Tables 2 and 3 shows numerous instances of this, including the effects of ascending an homologous series (cf. the results of Bousquet, Salzberg & Dietz, 1935, with thiocyanates). A further illustration of the importance of physical properties is provided by the effect of introducing an aliphatic hydroxyl group. This will tend to decrease the lipid/water partition, a property which is of profound importance in certain narcotics, and which may be equally relevant in contact insecticides. If this is so, it is to be expected that the introduction of a hydroxyl group may produce changes as great as the move of several steps in an homologous series. A good instance of this is seen in the comparison of compounds 8 and 14 (Table 2). Of the compounds containing aliphatic OH, only one (no. 28, Tables 2 and 3) showed marked aphicidal activity. Clearly, therefore, the inclusion of such groups is not necessarily deleterious, but until more is known of the precise relationships of water and lipid solubility with insecticidal activity, no predictions are possible. Another physicochemical factor of apparent significance is that of molecular shape. This is illustrated by the comparison of two pairs of compounds, 30 with 46 and 51 with 55. The molecular shape may be

expected to have a profound effect on physical properties, and thus to influence such factors as lipid/water partition and membrane permeability.

As regards the chemical reactivity of the aminonitriles, their behaviour on hydrolysis is of possible significance. This can take two pathways:

and liberation of cyanide in the biophase must be considered as having a possible bearing on their mode of action. We do not believe, however, that this is the ultimate mechanism of the insecticidal activity for the following reasons. Phenylmethylaminooctonic nitrile (no. 17) causes 80 % absolute mortality of chrysanthemum aphids at 0.2 %. This is equivalent to a concentration of approximately 0.02 % HCN. With compound no. 50, producing 98 % absolute mortality at 0.025 %, the equivalent HCN concentration would be only 0.004 %. Actual experiment showed that sodium cyanide was practically non-toxic to chrysanthemum aphids at 0.04 %. This evidence is reinforced by the lack of aphicidal activity in heptaldehyde cyanohydrin, a fat-soluble compound which can also give rise to cyanide on decomposition.

It is our view that the insecticidal activity of the α -aminonitriles discussed in this paper is to be attributed partly to their chemical reactivity which enables them to become attached to cell constituents. This may be through the unsaturated nature of the cyano group, as in thiocyanates. Alternatively, it may be due to a displacement reaction whereby some group such as NH_2 in the cell displaces the group $R_2\text{N}$ from the aminonitrile. We have, indeed, observed that heating $(\text{C}_2\text{H}_5)_2\text{N} \cdot \text{CH}(\text{C}_6\text{H}_5)\text{CN}$ with aniline causes evolution of diethylamine. Superimposed on this reactivity and indeed dominating the entire situation, is the effect of the physicochemical properties of the molecule as a whole, the correct adjustment of such factors as lipid/water partition, molecular shape, surface activity, etc., determining the absorption of the insecticide and its distribution within the organism. This parallels the case of the thiocyanates, and conforms to the general views regarding contact insecticidal action put forward by Lauser, Martin & Muller (1944) and further illustrated by Davies & Sexton (1948).

SUMMARY

1. The insecticidal properties of a series of substituted α -aminonitriles have been examined, and marked activity found in certain compounds.

2. There is marked specificity in the resistance of different insects to individual compounds.

3. α -Phenylmethylaninooctioic nitrile, and $\alpha\beta$ -bis(α' -cyano- α -heptylamino)ethane,

have aphicidal activity only slightly less than that of dodecyl thiocyanate or nicotine.

4. The mode of action of these insecticides is discussed in relation to their chemical reactivity and their physicochemical properties.

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The Occurrence of Phenolic Substances in Arthropods

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Pryor (1940) showed that the hardening of the protein component of insect cuticle is due to the tanning action of an agent produced by oxidation of a phenolic substance. In the analogous hardening of the cockroach ootheca, Pryor, Russell & Todd (1946) showed that the phenolic substance concerned is 3:4-dihydroxybenzoic acid (I) and suggested a possible mechanism for the hardening process. It was clearly desirable to examine a number of insect species in order to establish the range of phenolic substances which might be concerned.

Polyhydric phenols appear to be widely distributed in arthropods, although very few have actually been isolated, most investigators having simply demonstrated their presence in ethanolic extracts by means of colour reactions. In this way, Pryor (1940) has shown that *o*-dihydric phenols occur in representatives of six orders of insects (Orthoptera, Odonata, Coleoptera, Hemiptera, Lepidoptera, Hymenoptera), and Lafon (1943) has found them in insects and in Arachnida (Scorpionidea, Araneida). In insects, phenols are associated with some of the layers of the epicuticle (Wigglesworth, 1947; Webb, 1947) and with the brown proteins (sclerotins) which are responsible for the hardness of the exocuticle. They also occur in the epicuticle of

arthropods, whose exocuticle is hardened with calcium carbonate; by a less specific test (the reduction of ammoniacal silver oxide, performed on paraffin sections) we have shown that they are probably present in the epicuticle of a typical diplopod (*Tachypodoiulus niger* Leach), and Dennell (1947*b*) has found them in the epicuticle of several species of Crustacea Malacostraca. Using the same test, Beament (1947) has found that some of the layers of the chorion of the eggs of *Rhodnius prolixus* Stål (Hemiptera; Reduviidae) are rich in dihydric phenols.

The earliest recorded isolation of a phenolic substance from insects is that of Villon, who is reported by Slater (1887) as having obtained 15 g. of an 'alcohol soluble tannin' from 500 g. of *Sitophilus granarius* L. Schmalfuss & Müller (1927) isolated 3:4-dihydroxyphenylalanine from the elytra of two species of *Melolontha*. Schmalfuss, Heider & Winkelmann (1933) isolated 3:4-dihydroxyphenylacetic acid (II) from the elytra of *Tenebrio molitor* L., and the same acid was obtained by Schmalfuss (1937) from the cuticles of *Cetonia aurata* L., *Potosia cuprea* F. and *Melolontha hippocastani* F. (Coleoptera; Scarabaeidae). More recently, Pryor *et al.* (1946) isolated 3:4-dihydroxybenzoic acid (protocatechuic