214. *Reactions of Nitriles. Part I. Condensation of Methyleneaminoacetonitrile with Aldehydes.*

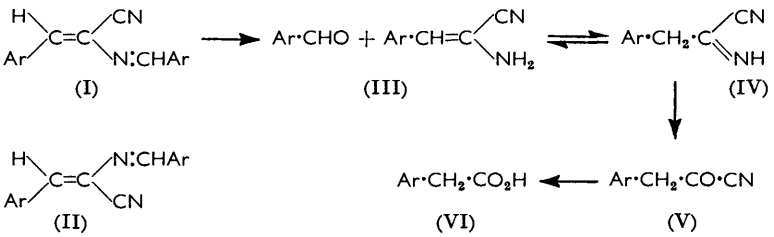
By (Miss) D. D. Vaghani and J. R. Merchant.

The preparation of a number of 2-cyanostyrene derivatives by the condensation of methyleneaminoacetonitrile with aromatic aldehydes is described. In alkali or acids the styrenes yield phenylacetic acids or imidazole derivatives.

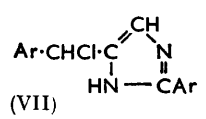
Mahajani and Ray [1] report that methyleneaminoacetonitrile reacts with aldehydes to form unsaturated nitriles which on reduction give amino-acids, *e.g.*, with formaldehyde and acetaldehyde it yields DL-serine and DL-threonine respectively.[1,2]

With the object of preparing substituted phenylalanines we caused various aromatic aldehydes to react with methyleneaminoacetonitrile in presence of sodium ethoxide. Numerous other basic catalysts failed to cause condensation, as did dry hydrogen chloride (except that for veratraldehyde piperidine could be used); and of the aldehydes tried many gave only the derived acids or indefinite products.

p-Anisaldehyde gave *p*-anisic acid and two crystalline isomers that are assigned structures (I) and (II) on the basis of analyses and the following infrared bands, common to both of them: 4·56 (C≡N); 6·19, 6·27 (C=C–Ar); 6·42 μ (C=N). Of the two, the higher-melting is assigned the *trans*-structure (H and CN at the C=C linkage) (II) because of its ultraviolet absorption (in ethanol) at 242, 283, 360, and 375 mμ (log ε 4·15, 4·43, 4·49, 4·5), the isomer having maxima at 240, 285, and 360 mμ (log ε 2·11, 1·99, 2·7), and because the low-melting gave the high-melting form when its hydrochloride was heated in nitrobenzene. Six other aldehydes gave similar products, but only three of these were obtained in both forms. The same products were obtained by condensation with aminoacetonitrile in place of methyleneaminoacetonitrile, and the original reaction doubtless involved hydrolysis of the latter reagent to the former and condensation of the aminoacetonitrile with two mols. of aldehyde.



Heating the product (II; Ar = *p*-MeO·C_6H_4) with aqueous acid or alkali gave *p*-methoxyphenylacetic acid, presumably by the steps (III)—(VI). Hydrolysis with alcoholic alkali gave the same acid (VI) with a very small amount of the acid Ar·CH=C(CO_2H)·N:CHAr. Hydrolysis with alcoholic hydrochloric acid gave the acid (VI) and a compound, $C_{18}H_{17}ClN_2O_2$, that gave a picrate and was recovered unchanged on treatment with boiling acid or alkali. From this stability and from infrared bands at 3 (NH), 6·53 (C=N), 8·07, 8·55, and 9·76 (OMe), and 6·34, 6·64, and 12 μ (arene), and absence of a C≡N band, this product is assigned the imidazole structure (VII). Most of the other products of types (I) and (II) gave similar products on treatment with aqueous or alcoholic acid. Formation of imidazoles from anilinoacetonitrile and aldehydes has been reported by Minovici.[3]



(VII)

[1] Mahajani and Ray, *J. Indian Chem. Soc.*, 1956, **33**, 455.
[2] Guha and Ray, *J. Indian Chem. Soc.*, 1958, **35**, 695.
[3] Minovici, *Ber.*, 1896, **29**, 2097.

Experimental

Condensation of Aldehydes with Methyleneaminoacetonitrile.—A boiling suspension of the nitrile (0·05 mole) in absolute ethanol (60 c.c.) was mixed with a boiling solution of the aldehyde (0·05 mole) in ethanol (30 c.c.). The mixture was allowed to cool to 44° and sodium ethoxide (0·05 mole) in ethanol (57·5 c.c.) was added in portions with shaking. The mixture was kept at 48° for 24 hr. A small amount of unchanged nitrile was removed and the solution acidified with acetic acid. The colourless precipitate of arenecarboxylic acid was collected. The alcoholic filtrate, on concentration to less than half its volume and cooling, deposited the yellow cis(H/CN)-α-*arylideneaminocinnamonitrile* (I) that was collected, washed with alcohol and water, and recrystallised from alcohol or benzene (yield 0·6—0·8 g.). In some cases small amounts of the trans-*isomer* was deposited when the mother-liquor was kept for 4—5 days. The *products* are recorded in Table 1.

Table 1. *Substituted α-arylideneaminocinnamonitriles* (I, II).

			Found (%)				Required (%)		
Subst.	Form *	M. p.	C	H	N	Formula	C	H	N
p-MeO	*cis*	130°	73·9	5·2	9·4	$C_{18}H_{16}N_2O_2$	74·0	5·4	9·6
	trans	142	74·0	5·6	9·3				
p-EtO	*cis*	108	—	—	8·8	$C_{20}H_{20}N_2O_2$	75·0	6·3	8·7
	trans	140	74·9	6·3	8·6				
p-Ph·CH_2·O	*cis*	148	81·3	5·3	6·6	$C_{30}H_{24}N_2O_2$	81·1	5·4	6·3
p-NMe_2	*cis*	223	75·5	6·8	17·9	$C_{20}H_{22}N_4$	75·5	6·9	17·6
3,4-CH_2O_2	*cis*	218	67·4	3·4	8·9	$C_{18}H_{12}N_2O_4$	67·5	3·7	8·8
3,4-$(MeO)_2$	*cis*	172	68·0	6·0	7·7	$C_{20}H_{20}N_2O_4$	68·2	5·7	8·0
	trans	178	68·3	6·0	8·3				
2,4-$(MeO)_2$	*cis*	159	67·9	5·4	8·3	$C_{20}H_{20}N_2O_4$	68·2	5·7	8·0
	trans	170	68·0	5·4	8·1				

Reagents found unsuccessful were piperidine (except for veratraldehyde), diethylamine, sodium methoxide and butoxide, potassium carbonate, sodium acetate and hydroxide, and hydrogen chloride.

When sodium ethoxide was used, benzaldehyde, *p*-tolualdehyde, *p*-chloro- and *p*-methoxy-benzaldehyde, and 2-formylthiophen gave only the corresponding acids; *p*-nitro- and *p*-hydroxy-benzaldehyde and protocatechualdehyde gave indefinite products.

Condensation of Aldehydes with Aminoacetonitrile.—A boiling suspension of aminoaceto-nitrile hydrogen sulphate (0·025 mole) in absolute alcohol (30 c.c.) and a solution of an aldehyde (0·025 mole) in boiling alcohol (15 c.c.) were mixed. Sodium ethoxide (0·05 mole) in alcohol (57·5 c.c.) was added to the mixture at 44°, and the whole was kept at room temperature for 24 hr. This gave the *cis*-isomer of the arylideneaminocinnamonitrile. In the case of 2,4-di-methoxybenzaldehyde, the *trans*-isomer was also obtained in very small amount, after concentration of the mother-liquor at reduced pressure.

Treatment of the Cinnamonitriles with Aqueous Hydrochloric Acid.—The nitrile was heated

Table 2. *Substituted phenylacetic acids.*

		Found (%)			Calc. (%)	
Subst.	M. p.	C	H	Formula	C	H
p-MeO	84°	65·1	5·9	$C_9H_{10}O_3$	65·1	6·0
p-EtO	83	66·8	6·8	$C_{10}H_{12}O_3$	66·6	6·6
p-Ph·CH_2·O	120	74·3	5·4	$C_{15}H_{14}O_3$	74·4	5·7
3,4-CH_2O_2	123	60·3	4·7	$C_9H_8O_4$	60·0	4·4
3,4-$(MeO)_2$	96	61·1	6·2	$C_{10}H_{12}O_4$	61·2	6·1
2,4-$(MeO)_2$	107	61·4	6·4	$C_{10}H_{12}O_4$	61·2	6·1

on a steam-bath with 15% hydrochloric acid (40 c.c. per g.) with shaking; the nitrile dissolved and an oil separated. The cooled mixture was extracted repeatedly with ether. The combined extracts were extracted with sodium hydrogen carbonate solution. This carbonate extract was acidified with hydrochloric acid, yielding the arylacetic acid which was recovered

by means of ether, sublimed or recrystallised and identified by a mixed m. p. determination. The acids thus obtained are recorded in Table 2.

On evaporation the original ether layer afforded a brown oil that gave the 2,4-dinitrophenylhydrazone of the corresponding aldehyde.

Hydrolysis with concentrated hydrochloric acid and dilute sulphuric acid gave the same result.

Hydrolysis of the Cinnamonitriles with Alcoholic Hydrochloric Acid.—The nitrile (I; Ar = *p*-MeO·C_6H_4) (2 g.) was refluxed for 2 hr. with alcohol (125 c.c.) which had been saturated with dry hydrogen chloride at 0°. The solution was then distilled at reduced pressure. The residual brown syrup, on cooling, gave the crystalline 3-(α-*chloro*-4-*methoxybenzyl*)-2-p-*methoxyphenylimidazole* (0·55 g.). When washed with a little acetone and repeatedly crystallised from dilute alcohol it formed needles, m. p. 184° (Found: C, 65·9; H, 5·4; N, 8·8; Cl, 10–6; OMe, 18·9. $C_{18}H_{17}ClN_2O_2$ requires C, 65·8; H, 5·1; N, 8·5; Cl, 10·8; 2OMe, 18·9%).

The acetone solution, on evaporation under reduced pressure, left a residue which was taken up in ether (insoluble part was rejected). The ether layer was washed successively with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The carbonate extract, on acidification with dilute hydrochloric acid, afforded *p*-methoxyphenylacetic acid, m. p. and mixed m. p. 83° (from water), that was isolated by means of ether.

The ethoxy-analogue (I; Ar = *p*-EtO·C_6H_4) gave the analogous *imidazole*, m. p. 187° (Found: C, 67·3; H, 6·2; N, 8·3. $C_{20}H_{21}ClN_2O_2$ requires C, 67·4; H, 5·9; N, 7·9%).

The nitrile (I; R = 3,4-CH_2O_2:C_6H_3) (2 g.) from piperonaldehyde was refluxed with alcoholic hydrochloric acid (150 c.c., prepared as above) for 3 hr. The precipitated ammonium chloride was filtered off and the alcohol removed under reduced pressure, giving a mixture of brown oil and ammonium chloride. This was treated with ether and dilute hydrochloric acid, a brown mass remaining insoluble. This mass was washed with acetone and the residue was crystallised repeatedly from dilute alcohol to give the *imidazole*, m. p. 183° (0·070 g.) (Found: N, 7·8; Cl, 9·5. $C_{18}H_{13}ClN_2O_4$ requires N, 7·8; Cl, 9·8%). Homopiperonylic acid was obtained from the ether-soluble part, by working up as above.

The nitrile [I; Ar = 3,4-$(MeO)_2C_6H_3$] (4 g.) was refluxed with alcoholic hydrochloric acid (300 c.c.) for 2 hr. An orange insoluble *hydrochloride* of the nitrile was then filtered off, washed with alcohol, and crystallised from dioxan in needles, m. p. 200° (2·4 g.) (Found: N, 7·7; Cl, 8·7. $C_{20}H_{21}ClN_2O_4$ requires N, 7·5; Cl, 9·1%). When crystallised from boiling nitrobenzene this hydrochloride yielded the basic trans-*nitrile*, which was isolated from the solution by precipitation with light petroleum and crystallised from benzene in needles, m. p. 178° (Found: C, 68·3; H, 6·0; N, 8·2. $C_{20}H_{20}N_2O_4$ requires C, 68·2; H, 5·7; N, 7·9%). The original alcoholic filtrate was evaporated under reduced pressure, giving a residue which was treated with a little acetone; ammonium chloride separated and was filtered off. Removal of acetone from the filtrate yielded a brown mass which on treatment with ether and dilute hydrochloric acid gave the *hydrochloride* of an imidazole (124 mg.). Crystallised from alcohol, this had m. p. 235° (decomp.) (Found: C, 57·0; H, 5·5; N, 6·5; Cl, 16·1. $C_{20}H_{22}Cl_2N_2O_4$ requires C, 56·6; H, 5·2; N, 6·6; Cl, 16·5%). On working up the ether-soluble part, as described above, it gave a brown mass whence sublimation afforded homoveratric acid.

Hydrolysis of the Cinnamonitriles with Alcoholic Alkali.—The nitrile (I; Ar = *p*-MeO·C_6H_4) (1 g.) was boiled under reflux with alcoholic sodium hydroxide (1 g. in 94 c.c. of 70% alcohol) for 16 hr. The solvent was distilled off at reduced pressure and the residue treated with water and extracted with ether. The ether layer was washed, dried (Na_2SO_4), and distilled to give a brown oil (0·22 g.) which gave anisaldehyde 2,4 dinitrophenylhydrazone. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ether layer was washed, dried, and evaporated. The residue, on treatment with benzene, afforded 4-*methoxy*-α-(p-*methoxybenzylideneamino*)*cinnamic acid* (0·050 g.). This crystallised from alcohol in prisms, m. p. 258° (Found: N, 4·1. $C_{18}H_{17}O_4N$ requires N, 4·5%). The benzene-soluble part gave homoanisic acid, m. p. 84°.

The nitrile [I; Ar = 3,4-$(MeO)_2C_6H_3$] was hydrolysed as above to α-(3,4-*dimethoxybenzylideneamino*)-3,4-*dimethoxycinnamic acid*, m. p. 260°. This was purified by dissolving it in sodium hydroxide and reprecipitating it with dilute hydrochloric acid as it was highly insoluble in all solvents (Found: N, 3·7. $C_{18}H_{13}NO_6$ requires N, 4·1%).

INSTITUTE OF SCIENCE, MAYO ROAD,
BOMBAY-1.

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