102. *Some Reactions of Amidines with Derivatives of Malonic Acid.*

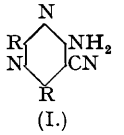
By G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham.

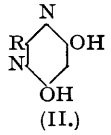
Following an observation that formamidine and malononitrile condense to give 4-amino-5-cyanopyrimidine, the reactions of amidines with several derivatives of malonic acid have been investigated, formamidine, acetamidine, benzamidine, and α-furylamidine being used as representative amidines. With malononitrile, derivatives of 4-amino-5-cyanopyrimidine are invariably produced, the aminomethylene- or substituted aminomethylene-malononitrile presumably acting as an intermediate in the reaction. Production of aminomethylene- or substituted aminomethylene-derivatives also takes place with ethyl cyanoacetate, although here normal condensation to give derivatives of 4-amino-6-hydroxypyrimidine is also possible. Condensation of formamidine and ethyl cyanoacetate in presence of sodium ethoxide gives, according to conditions, ethyl methenylbiscyanoacetate and a compound, $C_9H_9O_3N_3$, provisionally regarded as a pyridine derivative. A possible mechanism for the formation of these compounds is suggested. With ethyl malonate, amidines condense normally in each case to give derivatives of 4 : 6-dihydroxypyrimidine; production of aminomethylene compounds does not occur.

Baddiley, Lythgoe, and Todd (preceding paper) have reported that condensation of formamidine with malononitrile yielded 4-amino-5-cyanopyrimidine (I; R = H) instead of 4 : 6-diaminopyrimidine, which would have been expected by analogy with the condensation of guanidine with malononitrile (Traube, *Annalen*, 1904, **331**, 64). No other cases of the condensation of amidines with malononitrile have hitherto been recorded, and the unexpected course of the formamidine condensation led us to investigate the behaviour of this and other amidines with various derivatives of malonic acid.

With ethyl malonate all the amidines investigated condensed normally, giving derivatives of 4 : 6-*dihydroxypyrimidine* (II; R = H). Formamidine gave (II; R = H), and α-furylamidine 4 : 6-*dihydroxy*-2-α-*furylpyrimidine* (II; R = C_4H_3O). Acetamidine and benzamidine are already known to yield respectively (II; R = Me) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) and (II; R = Ph) (Pinner, *Ber.*, 1908, **41**, 3517).

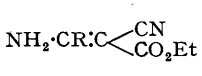
In common with formamidine other amidines reacted abnormally with malononitrile, giving derivatives of (I; R = H); acetamidine gave 4-amino-5-cyano-2 : 6-dimethylpyrimidine (I; R = Me) and benzamidine 4-*amino*-5-*cyano*-2 : 6-*diphenylpyrimidine* (I; R = Ph). α-Furylamidine, however, gave β-(α-*furyl*)-β-*aminomethylenemalononitrile* (III; R = C_4H_3O). In the production of compounds of type (I) those of type (III) are almost certainly intermediates; similar compounds are formed by the interaction of *NN'*-disubstituted formamidines with compounds containing a reactive methylene group (Dains, *Ber.*, 1902, **35**, 2496). For example, *NN'*-diphenylformamidine reacts with ethyl malonate to give ethyl anilinomethylenemalonate and aniline, which react further to produce a monoanilide (IV); secondary condensation to a pyrimidine derivative is impossible in this case. Except in the case of a α-furylamidine we were unable to isolate the hypothetical intermediates (III), presumably because they react too rapidly with a second molecule of amidine. We have shown that formamidine and aminomethylenemalononitrile (III; R = H) condense rapidly, producing (I; R = H). Again, on refluxing in alcoholic solution, α-furylamidine condenses with β-(α-furyl)-β-aminomethylenemalononitrile (III; R = C_4H_3O), giving 4-*amino*-5-*cyano*-2 : 6-*di*-α-*furylpyrimidine* (I; R = C_4H_3O). It may be noted in passing that acetiminoether reacts with aminomethylene derivatives of type (III) to give pyrimidines (Hromatka, D.R.-P. 667,990). Where formation of a compound of type (III) is prevented by substitution in the methylene group of malononitrile, condensation with an amidine proceeds normally; *e.g.*, benzeneazomalononitrile and formamidine yield 4 : 6-diamino-5-benzeneazopyrimidine (Baddiley, Lythgoe, and Todd, *loc. cit.*).


(I.)


(II.)

$NH_2{\cdot}CR{:}C(CN)_2$ (III.)


(IV.)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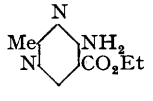
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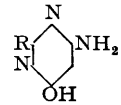
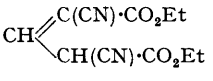
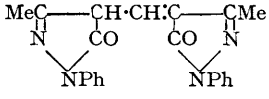

(VII.)

Further support for the hypothesis that compounds of type (III) act as intermediates in the abnormal condensations with malononitrile is found in the reactions of ethyl cyanoacetate with amidines. Contrary to Traube (*loc. cit.*), who records a failure to isolate any product from the reaction of formamidine with ethyl cyanoacetate, we obtained ethyl aminomethylenecyanoacetate (V; R = H) in good yield; (V; R = H) did not undergo further condensation with formamidine, but it reacted readily with thioacetamide in presence of sodium ethoxide, giving ethyl 4-amino-2-methylpyrimidine-5-carboxylate (VI), identified by comparison with an authentic specimen. Traube (*Centr.*, 1902, II, 1229) obtained 4-amino-6-hydroxy-2-methylpyrimidine (VII; R = Me) from ethyl potassiocyanoacetate and acetamidine. In the course of some other work Mr. L. C. Payman in this laboratory has shown that use of the free ester instead of the alkali metal derivative gives the *aminomethylene* derivative (V; R = Me). It may be observed that the substance isolated by Földi, von Fodor,

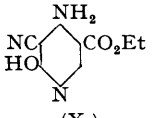
Demjén, Szekeres, and Halmos (*Ber.*, 1942, **75**, 755) as a by-product in the reaction between acetamidine and carbethoxyacetiminoether is almost certainly impure (V; R = Me). When benzamidine is condensed with ethyl cyanoacetate in alcoholic solution, 4-amino-6-hydroxy-2-phenylpyrimidine (VII; R = Ph) and ethyl β-amino-α-cyano-β-phenylacrylate (V; R = Ph) are produced simultaneously in approximately equal amounts; in presence of sodium ethoxide (VII; R = Ph) is the main product (Traube and Herrmann, *Ber.*, 1904, **37**, 2267). As with malononitrile, substitution of the methylene group in ethyl cyanoacetate prevents the occurrence of abnormal reaction; thus ethyl cyanosuccinate and acetamidine yield ethyl 4-amino-6-hydroxy-2-methylpyrimidine-5-acetate (Andersag and Westphal, D.R.-P., 671,787). The results obtained in the above reactions with ethyl cyanoacetate indicate that use of a more stable amidine (*e.g.*, benzamidine) or presence of an alkali-metal·ethoxide favours normal condensation to a pyrimidine of type (VII), whereas absence of a condensing agent or a highly reactive amidine (*e.g.*, formamidine) favours production of an aminomethylene derivative (V). As might be expected on general grounds, acetamidine occupies a position intermediate between formamidine and benzamidine in such reactions.

The reaction of formamidine with ethyl cyanoacetate in presence of sodium ethoxide gave rise to two further compounds. One of these, obtained with 0·5 mol. of sodium ethoxide, was identified as ethyl methenylbiscyanoacetate (VIII); its formation is analogous to that of the methenylbispyrazolone derivative (IX) recorded by Dains and Brown (*J. Amer. Chem. Soc.*, 1909, **31**, 1148). The second, obtained when the reaction was carried out in presence of 1·5 mols. of sodium ethoxide, was a *substance*, $C_9H_9O_3N_3$, which we regard provisionally as a pyridine derivative, possibly (X), although a final decision has not been reached. The formation of ethyl 2 : 6-dihydroxypyridine-3 : 5-dicarboxylate on warming (VIII) with alcohol has been recorded by Dimroth (*Ber.*, 1902, **35**, 2882). A compound (X) could arise by a condensation involving two molecules of ethyl cyanoacetate to produce the amide (XI), followed by cyclisation of the latter after the manner of a Thorpe reaction. Our view that the substance $C_9H_9O_3N_3$ is a pyridine derivative of the type indicated finds additional support in the similarity of its absorption spectrum to that of ethyl 2 : 6-dihydroxypyridine-3 : 5-dicarboxylate. In this connection it may be mentioned that interaction of formamidine and ethyl acetoacetate in presence of sodium ethoxide gives rise to a *compound*, m. p. 79—80°, which we regard provisionally as (XII) and which is analogous to the hypothetical amide (XI). From this reaction Pinner (*Ber.*, 1886, **18**, 2846) obtained a substance, m. p. 73°, which he described on very scanty evidence as ethyl β-cyanocrotonate; we were unable to obtain any compound having this composition and we are of the opinion that Pinner's product was simply a rather impure specimen of the product we believe to be (XII). The compound, m. p. 79—80°, has the composition required by structure (XII) and on catalytic hydrogenation absorbs 3 mols. of hydrogen, but rigid proof of constitution has not yet been obtained.

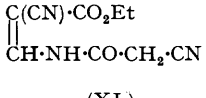
(VIII.) 



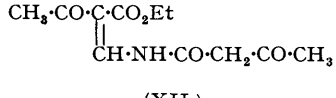
(IX.)



(X.)



(XI.)



(XII.)

Arising from the investigations above reported, a few of the condensations described were carried out, formiminoether being substituted for formamidine. As expected, similar products were obtained, although the yields were usually lower. With ethyl cyanoacetate, formiminoether condensed to give the aminomethylene derivative (V; R = H); when carried out in presence of sodium ethoxide, the main product was ethyl methenylbiscyanoacetate, although small amounts of (V; R = H) were also formed. With malononitrile, a small amount of 4-amino-5-cyanopyrimidine was formed, and with ethyl acetoacetate ethyl aminomethyleneacetoacetate was produced in low yield together with traces of a compound, m. p. 201°, which was not further investigated.

Experimental.

1. *Condensations with Ethyl Malonate.*—4 : 6-*Dihydroxypyrimidine* (II; R = H). Formamidine hydrochloride (80·5 g.) was added to ice-cold alcoholic sodium ethoxide (69 g. ≡ 3 atoms of sodium in 1 l. of alcohol), followed, after filtration from sodium chloride, by ethyl malonate (160 g.), and the mixture was kept overnight. The solid which separated was collected, dissolved in water, and the solution acidified with hydrochloric acid. The precipitated 4 : 6-*dihydroxypyrimidine* was recrystallised from hot water (yield, 80%). It was practically insoluble in organic solvents and on heating decomposed above 230° (Found : C, 42·2; H, 3·6; N, 25·6. $C_4H_4O_2N_2$ requires C, 42·8; H, 3·6; N, 25·0%).

4 : 6-*Dihydroxy*-2-*α-furylpyrimidine* (II; R = C_4H_3O). α-Furylamidine hydrochloride (1·46 g.) (Pinner, *Ber.*, 1892, **25**, 1416), alcoholic sodium ethoxide (0·69 g. ≡ 3 atoms of sodium in 10 c.c. of alcohol), and ethyl malonate (1·6 g.) were refluxed for 2 hours, and the product left overnight and then worked up as above. The *pyrimidine* (yield, 42%) separated from water in colourless needles which decomposed above 290° (Found : C, 53·8; H, 3·5; N, 15·1. $C_8H_6O_3N_2$ requires C, 53·9; H, 3·4; N, 15·7%).

2. *Condensations with Malononitrile.*—4-*Amino*-5-*cyano*-2 : 6-*dimethylpyrimidine* (I; R = Me). Acetamidine hydrochloride (9·45 g.), alcoholic sodium ethoxide (2·3 g. ≡ 1 atom of sodium in 50 c.c. of alcohol), and malononitrile (6·6 g.) were refluxed together for 3 hours. After cooling, the precipitate was collected, washed free from salt with cold water, and recrystallised from alcohol. 4-Amino-5-cyano-2 : 6-dimethylpyrimidine was obtained in colourless plates,

m. p. 218° (yield, 50%) (Found : C, 56·2; H, 4·8; N, 38·2. Calc. for $C_7H_8N_4$: C, 56·9; H, 5·4; N, 37·8%). Huber and Hölscher, (*Ber.*, 1938, **71**, 87), who prepared this compound by a different route, give m. p. 220·5°.

4-Amino-5-cyano-2 : 6-diphenylpyrimidine (I; R = Ph), prepared in similar fashion from benzamidine and malononitrile, crystallised from ethyl acetate in colourless needles, m. p. 211° (yield, 45%) (Found : C, 75·1; H, 4·4; N, 20·1. $C_{17}H_{12}N_4$ requires C, 75·0; H, 4·4; N, 20·6%).

β-(α-Furyl)-β-aminomethylenemalononitrile (IV; R = C_4H_3O). When an alcoholic solution of α-furylamidine (from 3·3 g. of the hydrochloride) and malononitrile (1·32 g.) was kept overnight, colourless needles separated; recrystallised from water, the *compound* had m. p. 182° (yield, 30%) (Found : C, 60·3; H, 3·4; N, 26·7. $C_8H_5ON_3$ requires C, 60·4; H, 3·1; N, 26·4%). The same compound was obtained (yield, 17%) when α-furyliminoether was substituted for α-furylamidine in the condensation.

4-Amino-5-cyano-2 : 6-di-α-furylpyrimidine (I; R = C_4H_3O). The above compound (IV; R = C_4H_3O) (0·8 g.), α-furylamidine hydrochloride (0·65 g.), and alcoholic sodium ethoxide (from 0·115 g. ≡ 1 atom of sodium in 25 c.c. of alcohol) were refluxed for 8 hrs. The solid which separated was freed from salt by washing with water and recrystallised from ethyl acetate, forming colourless needles, m. p. 245—246° (Found : C, 61·6; H, 3·2; N, 22·0. $C_{13}H_8O_2N_4$ requires C, 61·9; H, 3·2; N, 22·2%).

Condensation of formamidine with aminomethylenemalononitrile. Aminomethylenemalononitrile (1·85 g.) (Passalacqua, *Gazzetta*, 1913, **43**, II, 566) was added to an alcoholic solution of formamidine (from 1·6 g. of the hydrochloride) at room temperature. After 30 mins. the precipitated solid was collected and recrystallised from alcohol. The product (yield, 42%) had m. p. 249°, undepressed by 4-amino-5-cyanopyrimidine (m. p. 250°; Baddiley, Lythgoe, and Todd, *loc. cit.*).

3. *Condensations of Formamidine with Ethyl Cyanoacetate.*—(a) *Ethyl aminomethylenecyanoacetate* (V; R = H). Formamidine hydrochloride (4 g.), alcoholic sodium ethoxide (1·15 g. ≡ 1 atom of sodium in 35 c.c. of alcohol), and ethyl cyanoacetate (2·5 g.) were refluxed together for 5 hrs., and the solution filtered from sodium chloride, evaporated to small bulk, and diluted with water. The ethyl aminomethylenecyanoacetate which separated crystallised from ethyl acetate in needles, m. p. 140° (yield, 80%) (Found : C, 51·2; H, 6·0; N, 19·7. Calc. for $C_6H_8O_2N_2$: C, 51·5; H, 5·8; N, 20·0%). De Bollemont (*Bull. Soc. chim.*, 1901, **25**, 41) gives m. p. 130°.

The above aminomethylene derivative (1·2 g.) was refluxed for 30 mins. with thioacetamide (0·63 g.) and alcoholic sodium ethoxide (0·19 g. ≡ 1 atom of sodium in 10 c.c. of alcohol), and the solution evaporated to small bulk. Ethyl acetate was added, sodium hydrogen sulphide removed, and the filtrate evaporated. The viscous residue on trituration with water yielded a quantity of white solid. Recrystallised from alcohol, this formed needles, m. p. 119—120°, undepressed by authentic ethyl 4-amino-2-methylpyrimidine-5-carboxylate (m. p. 120°; Todd and Bergel, J., 1937, 364).

(b) *Ethyl methenylbiscyanoacetate* (VIII). Formamidine hydrochloride (12 g.), ethyl cyanoacetate (16·8 g.), and alcoholic sodium ethoxide (5·1 g. ≡ 1·5 atoms of sodium in 75 c.c. of alcohol) were refluxed for 5 hours, the mixture evaporated to dryness, and the residue (sodium salt) dissolved in water. On acidification ethyl methenylbiscyanoacetate separated; recrystallised from dioxan (yield, 60%), it had m. p. 187° (decomp.), undepressed by an authentic specimen prepared according to Ruhemann and Browning (J., 1898, **73**, 282) (Found : N, 12·0. Calc. for $C_{11}H_{12}O_4N_2$: N, 11·9%). Light absorption in alcohol : Maxima at 2255 A. (ε, 10,700), 2735 A. (ε, 9,400), and 3560 A. (ε, 35,000).

(c) *Compound* $C_9H_9O_3N_3$. Formamidine hydrochloride (4 g.) was added to cold alcoholic sodium ethoxide (2·87 g. ≡ 2·5 atoms of sodium in 60 c.c. of alcohol), and the solution filtered from sodium chloride. After addition of ethyl cyanoacetate (5·6 g.) and keeping for 4 hours the precipitate was collected, dissolved in water, and the solution acidified. The *product* which separated crystallised from hot water in colourless needles (1·2 g.), m. p. 280—281° (decomp.) (Found : C, 51·9; H, 4·3; N, 19·8. $C_9H_9O_3N_3$ requires C, 52·2; H, 4·3; N, 20·3%). Light absorption in alcohol : Maxima at 2730 A. (ε, 23,000) and 3370 A. (ε, 28,000). Ethyl 2 : 6-dihydroxypyridine-3 : 5-dicarboxylate (Dimroth, *loc. cit.*) showed maxima at 2690 A. (ε, 19,700) and 3260 A. (ε, 18,500) in alcoholic solution.

4. *Condensation of Benzamidine with Ethyl Cyanoacetate.*—An alcoholic solution of benzamidine (from 3·12 g. of the hydrochloride) was refluxed with ethyl cyanoacetate (2·26 g.) for 8 hours. After the solvent had been evaporated and water (20 c.c.) added, the crystalline solid was collected and extracted with hot water. Crystallisation of the residue from alcohol gave ethyl β-amino-α-cyano-β-phenylacrylate (V; R = Ph), m. p. 123—124°, undepressed by a specimen (m. p. 125°) prepared by the method of Atkinson, Ingham, and Thorpe (J., 1907, **91**, 590) (yield, 28%). The hot aqueous extract on cooling deposited 4-amino-6-hydroxy-2-phenylpyrimidine (yield, 21%), m. p. 252° (Traube and Herrmann, *loc. cit.*, give m. p. 252°). When, in the above condensation, benzamidine was replaced by benziminoether, the only product identified was ethyl β-amino-α-cyano-β-phenylacrylate (yield, 8%).

5. *Condensation of Formamidine with Ethyl Acetoacetate.*—Formamidine hydrochloride (8 g.) and cold alcoholic sodium ethoxide (4·6 g. ≡ 2 atoms of sodium in 100 c.c. of alcohol) were mixed and filtered from sodium chloride; ethyl acetoacetate (26 g.) was added, and the mixture left for 2 hours. The precipitate was collected, dissolved in water, and the solution acidified. The *compound* which separated crystallised from light petroleum (b. p. 40—60°) in colourless needles (14·5 g.), m. p. 78—79° (Found : C, 54·8; H, 6·4; N, 5·8. $C_{11}H_{15}O_5N$ requires C, 54·8; H, 6·4; N, 5·6%). Microhydrogenation (PtO_2) : 30·6 mg. absorbed 9·94 c.c. of hydrogen at 14° and 733 mm., corresponding to 3·2 mols. of hydrogen. Attempts to obtain this substance by condensation of ethyl acetoacetate with ethyl aminomethylenecyanoacetate were unsuccessful.

6. *Condensations using Formiminoether in Place of Formamidine.*—(a) *With malononitrile.* Formiminoether (from 5·5 g. of the hydrochloride) and malononitrile (1·65 g.), kept in alcoholic solution (50 c.c.) for 12 hours and worked up in the usual way, gave a small amount (0·15 g.) of 4-amino-5-cyanopyrimidine, m. p. 250°.

(b) *With ethyl cyanoacetate.* In absence of sodium ethoxide formiminoether and ethyl cyanoacetate, refluxed in alcoholic solution for 4—5 hours, gave ethyl aminomethylenecyanoacetate (yield, 63%). In presence of sodium ethoxide ethyl methenylbiscyanoacetate was produced (yield, *ca.* 50%) together with a small amount of ethyl aminomethylenecyanoacetate; no evidence of the formation of the compound $C_9H_9O_3N_3$ was obtained.

(c) *With ethyl acetoacetate.* Formiminoether (from 5·5 g. of the hydrochloride) and ethyl acetoacetate (6·5 g.) in absolute alcohol (20 c.c.) were left at room temperature for 2 days, and the solution evaporated. The residue was extracted first with light petroleum (b. p. 40—60°) and then with ether. After concentration of the ethereal extract a very small amount of solid, m. p. 201°, separated. Further concentration yielded ethyl aminomethyleneacetoacetate, m. p. 43—45°, undepressed by an authentic specimen.

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