Pyrimidine Derivatives and Related Compounds. A Novel Synthesis of Pyrimidines, Pyrazolo[4,3-*d*]pyrimidines and Isoxazolo[4,3-*d*]pyrimidine.

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Benzoylacetonitrile (II) reacted with trichloroacetonitrile (III) to yield the β-amino-β-trichloromethylacrylonitrile IV. Compound IV reacted with hydrazine hydrate to yield 5-amino-4-cyano-3-phenylpyrazole (V) and with 2-aminopyridine to yield the aminopyridine derivative VIII (*cf.*, Chart I). Compound IV reacted with III to yield 2,4-bis(trichloromethyl)-5-cyano-6-phenylpyrimidine (I) which could be converted into a variety of pyrazolo[4,3-*d*]pyrimidine derivatives by treatment with hydrazine hydrate under a variety of different experimental conditions (*cf.*, Chart II).

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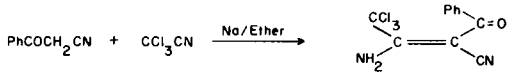
The isolation and characterisation of the nucleoside antibiotics formaycin and formaycin B as 3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidines (1-4) has generated renewed interest in the synthesis of pyrazolo[4,3-*d*]-pyrimidines (5,6). In continuation of our program directed toward the development of new procedures for the synthesis of fused pyrimidines (7-10), we report here a novel synthesis of 5-cyano-2,4-bis(trichloromethyl)-6-phenyl-pyrimidine (I) and its conversion into pyrazolo[4,3-*d*]-pyrimidines and isoxazolo[4,3-*d*]pyrimidines. Thus, benzoylacetonitrile (II) reacted with trichloroacetonitrile (III) in the presence of sodium metal to yield the β-amino-β-trichloromethylacrylonitrile derivative IV. The structure of IV was established based on its elemental and spectral data. Moreover, compound IV could be converted into the known (13) 5-amino-4-cyano-3-phenylpyrazole (V) by the action of hydrazine hydrate. The formation of V in this reaction may be assumed to proceed *via* formation of the intermediate amidazone VII in a manner similar to that previously reported for the reaction of other β-amino-β-trichloromethylacrylonitriles (11) with the same reagent. However, possible formation of the hydrazone VII as an intermediate in this reaction cannot be ruled out based on the available data (*cf.*, Chart I).

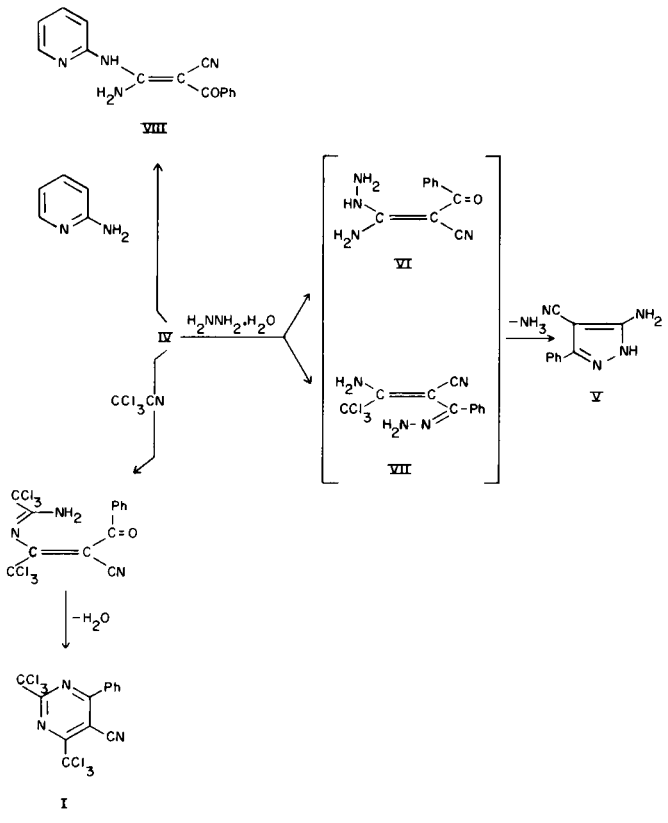


Similar to the behaviour of similar compounds of similar structure, compound IV also reacted with 2-aminopyridine to yield the aminopyridine derivative VIII.

Compound IV reacted with III to yield the 2,4-bis-(trichloromethyl)-5-cyano-6-phenylpyrimidine derivative I. The formation of this product might be assumed to proceed *via* the sequence illustrated in Chart I. This constitutes a new route for synthesis of 2,4-disubstituted pyrimidines. The scope and limitations for this new synthesis will be the subject of a separate communication.

The potential utility of I for building up fused pyrimidine derivatives has been investigated. It has been found that I condenses with hydrazine hydrate in the absence of a solvent *via* elimination of chloroform to yield a product for which structure IX or possibly the isomeric X seemed possible. Structure IX was considered

Chart I



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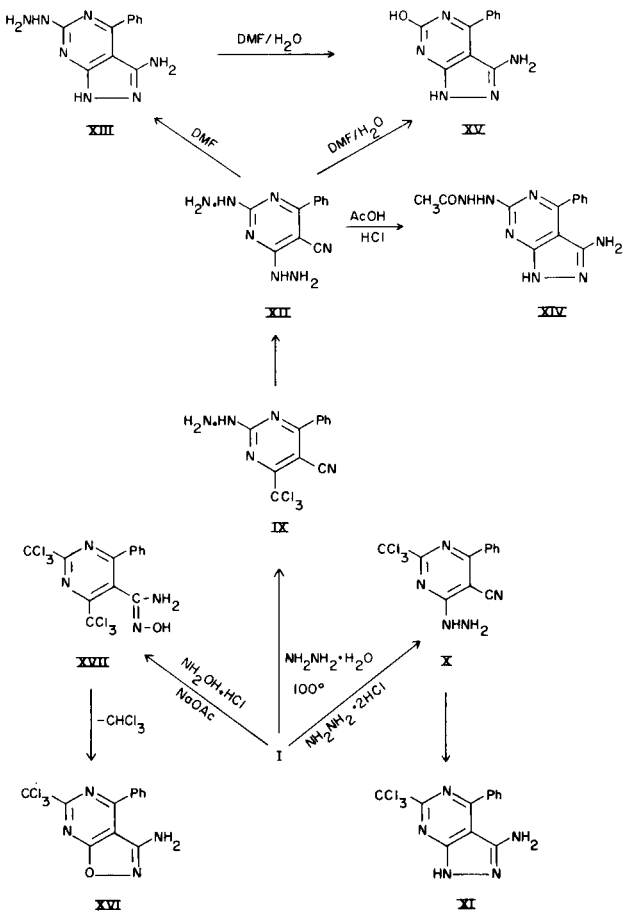
most likely for this product based on its stability under the conditions reported (14,15) to effect cyclization of 3-hydrazinonitriles. On the other hand, when I was treated with hydrazine dihydrochloride, the pyrazolo-[4,3-*d*]pyrimidine derivative XI was formed. The formation of XI from I and hydrazine dihydrochloride might be assumed to proceed *via* addition of the hydrazine to the protonated nitrile to form the intermediate amidazone, which then cyclises into XI with elimination of chloroform.

The hydrazino pyrimidine derivative IX reacted with an excess of hydrazine hydrate to yield the dihydrazino derivative XII. Compound XII was converted into the 6-hydrazino-3-aminopyrazolo[4,3-*d*]pyrimidine derivative XIII on refluxing in DMF. On the other hand, the acetylhydrazino derivative XIV could be obtained upon treatment of XII with acetic acid and hydrochloric acid. Further, the hydroxy derivative XV could be prepared *via* treatment of XII with a DMF-water mixture.

Similar to its behaviour toward the action of hydrazine dihydrochloride, compound I reacted with hydroxylamine hydrochloride and sodium acetate to yield the 3-amino-isoxazolo[4,3-*d*]pyrimidine derivative XVI, probably *via* the intermediate amidoxime XVII.



EXPERIMENTAL

All melting points are uncorrected. If spectra were obtained (potassium bromide) on a Pyunicam SP 1000 Spectrophotometer. Analytical data were performed in the analytical data nit at Cairo University.

β-Amino-β-trichloromethyl-α-benzoylacrylonitrile (IV).

To a suspension of benzoylacetonitrile (14.5 g.) in a 2:1 ether-benzene mixture (150 ml.), 5.0 g. of ifnely divided sodium metal were added. The mixture was stirred overnight at room temperature and then treated with 10.4 ml. (0.1 mole) of trichloroacetonitrile. The reaction mixture was left overnight at room temperature, then refluxed for four hours and evaporated *in vacuo*. The remaining oil was triturated with an ethanol-water mixture and the, so formed, solid product was collected by filtration and crystallised from ethanol.

Compound IV formed colourless crystals, m.p. 170°, yield 11.0 g.; ir: 1620 (δ NH_2), 1660 (benzoyl CO), 2220 (conjugated CN) and 3300 cm^{-1} (γ NH).

Anal. Calcd. for $C_{11}H_7Cl_3N_2O$: C, 45.6; H, 2.4; Cl, 36.8. Found: C, 45.6; H, 2.8; Cl, 36.6.

5-Amino-4-cyano-3-phenylpyrazole (V).

A solution of IV (8.4 g.) in pyridine (100 ml.) was treated with hydrazine hydrate (1.5 ml.) and the mixture was refluxed for five hours. The solid product obtained on standing was collected by filtration and crystallised from methanol-water.

Compound V formed colourless crystals, m.p. 195°, yield 5 g.; ir: 2180 (conjugated CN) and a broad band at 3100, 3400 cm^{-1} (NH vibrations).

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.2; H, 4.4; N, 30.4. Found: C, 65.4; H, 4.7; N, 30.3.

Compound V was found identical (m.p. and mixed m.p.) with the product previously described by Elnagdi, *et al.* (13).

β-Amino-β-(2-aminopyridinyl)-α-benzoylacrylonitrile (VIII).

A mixture of IV (2.8 g.) and 2-aminopyridine (1.0 g.) was heated at 100° (bath-temperature), until no more chloroform could be detected (*ca.* 3 hours). The reaction mixture was allowed to cool and was then triturated with ethanol. The solid product, so formed, was collected by filtration and crystallised from ethanol.

Compound VIII formed colourless crystals, m.p. 192°, yield 1.5 g.; ir: 1640 (benzoyl CO), 2190 (conjugated CN), 3050, 3240 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.1; H, 4.5. Found: C, 67.9; H, 4.3.

5-Cyano-2,4-ditrichloromethyl-6-phenylpyrimidine (I).

To a solution of IV (2.8 g.) in an ether/benzene mixture (50 ml., 2:1), 0.5 g. of finely divided sodium were added. The mixture was stirred for three hours at room temperature and then treated with 1.0 ml. of trichloroacetonitrile (0.1 mole). The reaction mixture was left overnight at room temperature, then refluxed for four hours and evaporated *in vacuo*. The remaining product was then dissolved in ethanol and gradually treated with water. The solid product obtained on standing was collected by filtration and crystallised from ethanol.

Compound I formed colourless crystals, m.p. 150°, yield 2.2 g.; ir: 2250 cm^{-1} (CN).

Anal. Calcd. for $C_{13}H_5Cl_6N_3$: C, 37.5; H, 1.2; Cl, 51.6. Found: C, 37.5; H, 1.5; Cl, 51.5.

5-Cyano-4-trichloromethyl-2-hydrazino-6-phenylpyrimidine (IX).

A mixture of I (2 g.) and hydrazine hydrate (0.8 ml. 99%) was heated at 100° (bath temperature until no more chloroform odour could be detected (*ca.* 3 hours). The reaction was then cooled, triturated with ethanol and the resulted solid product was collected by filtration.

Compound IX formed colourless crystals, m.p. 260° from ethanol, yield 70%; ir: 2215 (conjugated CN), 3360 cm^{-1} (NH)

Anal. Calcd. for $C_{12}H_8Cl_3N_5$: C, 43.8; H, 2.4; Cl, 32.3. Found: C, 44.0; H, 2.6; Cl, 32.0.

3-Amino-6-trichloromethyl-4-phenylpyrazolo[4,3-*d*]pyrimidine (XI).

A solution of I (4.0 g.) in ethanol (100 ml.) was treated with hydrazine dihydrochloride (1.0 g.) and then with 4.4 g. of sodium acetate. The reaction mixture was refluxed for five hours and then evaporated *in vacuo*. The remaining product was then triturated with ethanol and the resulting solid product was collected by filtration and crystallised from ethanol.

Compound XII formed pale yellow crystals, m.p. 265°, yield 3.0 g.; ir: 1660 (δ NH_2), 3250, 3310, 3500 cm^{-1} (ν NH_2).

Anal. Calcd. for $C_{12}H_8Cl_3N_5$: C, 43.8; H, 2.4; Cl, 32.4. Found: C, 44.0; H, 2.6; Cl, 32.1.

5-Cyano-2,4-dihydrazino-6-phenylpyrimidine (XII).

A suspension of IX (2.0 g.) in hydrazine hydrate (3.0 ml.) was refluxed for three hours. The reaction mixture was then triturated with ethanol and the resulting solid product was collected by filtration and crystallized from DMF.

Compound XII formed buff crystals, m.p. 180°, yield 50%; ir: 2220 (conjugated CN) and a broad band at 3200, 3350 cm^{-1} (NH).

Anal. Calcd. for $C_{11}H_{11}N_7$: C, 54.8; H, 4.6. Found: C, 55.1; H, 4.8.

3-Amino-6-hydrazino-4-phenylpyrazolo[4,3-*d*]pyrimidine (XIII).

A solution of XII (2.0 g.) in DMF (15 ml.) was refluxed for three hours. The solvent was then removed *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from DMF.

Compound XIII formed yellow crystals, m.p. 350°, yield 50%; ir: 1650 (δ NH_2) 3270 and 3350 cm^{-1} (ν NH_2).

Anal. Calcd. for $C_{11}H_{11}N_7$: C, 54.7; H, 4.6; N, 40.7. Found: C, 54.4; H, 4.4; N, 40.8.

3-Amino-6-β-acetylhydrazino-4-phenylpyrazolo[4,3-*d*]pyrimidine (XIV).

A solution of XII (2.0 g.) in acetic acid (30 ml.) and hydrochloric acid (3 ml., 37.5%) was refluxed for three hours. The solvent was then removed *in vacuo*; the remaining product was triturated with water and neutralised with ammonium hydroxide. The resulting solid product was collected by filtration and crystallised from DMF.

Compound XIV formed yellow crystals, m.p. 245°, yield 1.0 g.; ir: 1630 (δ NH_2); 1705 (acetyl CO), 3250, 3300, 3400, 3450 cm^{-1} (ν NH).

Anal. Calcd. for $C_{13}H_{12}N_7O$: C, 55.3; H, 4.3. Found: C, 55.5; H, 4.3.

3-Amino-6-hydroxy-4-phenylpyrazolo[4,3-*d*]pyrimidine (XV).

A solution of XII (2.0 g.) in DMF (30 ml.) and water (5.0 ml.) was refluxed for ten hours. The solvent was then evaporated *in vacuo*. The remaining product was treated with water and evaporated again till most of remaining DMF was removed. The remaining product was then triturated with water and the resulting solid was collected by filtration and crystallised from DMF.

Compound XV formed yellow crystals, m.p. > 350°, yield 1.5 g.

Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.1; H, 4.0. Found: C, 57.9; H, 4.3.

Compound XV could also be obtained *via* treatment of XIII with a DMF water mixture.

3-Amino-6-trichloromethyl-4-phenylisoxazolo[4,3-*d*]pyrimidine (XVI).

A solution of I (2.0 g.) in ethanol (50 ml.) was treated with hydroxylamine hydrochloride (1.0 g.) and sodium acetate (2.2 g.). The reaction mixture was then refluxed for five hours and then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from benzene-petroleum ether 60-80.

Compound XVI formed buff crystals, m.p. 225°, yield 0.8 g.

Anal. Calcd. for $C_{11}H_7Cl_3N_4O$: C, 43.7; H, 2.1; Cl, 32.1. Found: C, 44.0; H, 2.4; Cl, 32.3.

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