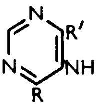
99. *The Synthesis of Some 9-Furfurylpurines and Some Related Heterocyclic Compounds.*

By R. Hull.

The synthesis is described of some 9-furfurylpurines and related triazolopyrimidines from the appropriate 5-amino-4-furfurylaminopyrimidines.

A previous paper[1] described the preparation of 6-amino-9-furfurylpurine as a possible antiviral agent which might antagonise the formation of nucleic acid. This work has now been extended to other derivatives of 9-furfurylpurine. Corresponding 8-azapurines (*v*-triazolo[*d*]pyrimidines) were also synthesised because of the many features of biological interest found in " aza "-analogues of naturally occurring metabolites.[2] During the completion of this work Timmis, Cooke, and Spickett[3] have independently described the synthesis of some related 9-substituted purines.


(I)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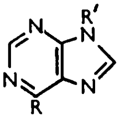
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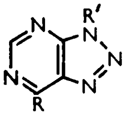
(IV)

Synthesis of 6-dimethylamino-9-furfurylpurine (III; $R = NMe_2$, $R' = C_5H_5O$) and its analogue (IV; $R = NMe_2$, $R' = C_5H_5O$) involved the intermediates (I and II; $R = NMe_2$, $R' = NH{\cdot}C_5H_5O$). Analogous intermediates were used for the furfuryl- (III; $R = R' = C_5H_5O$) and morpholino-purine (III; R = morpholino, $R' = C_5H_5O$) and their analogues (IV; $R = R' = C_5H_5O$; and R = morpholino, $R' = C_5H_5O$).

4 : 6-Dichloro-5-nitropyrimidine (I; $R = R' = Cl$), the key intermediate, was obtained by the action of phosphoryl chloride and dimethylaniline on 4 : 6-dihydroxy-5-nitropyrimidine.[4] During the preparation of large quantities, 4-chloro-6-methylanilino-5-nitropyrimidine (I; $R = Cl$, $R' = NMePh$) was isolated as a by-product: a similar side reaction has been noticed in other chlorinations.[5] Replacement of one of the halogens can be accomplished by ammonia[4] or by mono-[6] or di-methylamine acetate.[7] However, yields may be so low as to limit this procedure.[8] In our experiments, 2 mols. of morpholine reacted with one of 4 : 6-dichloro-5-nitropyrimidine and gave the monosubstituted pyrimidine (I; $R = Cl$, R′ = morpholino) in reasonable yield. Under similar conditions, however, 2 mols. of furfurylamine and triethylamine gave the disubstituted pyrimidine (I; $R = R' = NH{\cdot}C_5H_5O$). 4-Chloro-6-furfurylamino-5-nitropyrimidine (I; $R = Cl$, $R' = NH{\cdot}C_5H_5O$) was obtained upon treating the dichloro-compound (I; $R = R' = Cl$) with stoicheiometric proportions of triethylamine and furfurylamine acetate.

Replacement of the second chlorine atom in compounds (I; $R = Cl$, $R' = NMe_2$ and morpholino) by furfurylamine and subsequent reduction with Raney nickel at laboratory temperature gave the aminopyrimidines (II; $R = NMe_2$ and morpholino, $R' = NH{\cdot}C_5H_5O$). Cyclisation of the 5-aminopyrimidines, including (II; $R = R' = NH{\cdot}C_5H_5O$), then led,

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[1] Hull, *J.*, 1958, 2746.

[2] Barlow and Welch, *J. Amer. Chem. Soc.*, 1956, **78**, 1258.

[3] Timmis, Cooke, and Spickett, " Ciba Foundation Symposium on the Chemistry and Biology of Purines," Churchill Ltd., London 1957, p. 134.

[4] Boon, Jones, and Ramage, *J.*, 1951, 96.

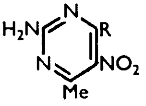
[5] King, King, and Spensley, *J.*, 1947, 1247; Ross, *J.*, 1948, 1129.

[6] Brown, *J. Appl. Chem.*, 1957, **7**, 109; Robins and Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 492.

[7] Rose, *J.*, 1954, 4116.

[8] Boon, *J.*, 1957 2146.

either to the purines (III; R = NMe_2 and morpholino, R′ = C_5H_5O) and (III; R = $NH{\cdot}C_5H_5O$, R′ = C_5H_5O) with acetic anhydride and ethyl orthoformate, or to the triazolopyrimidines (IV; R = NMe_2, and morpholino, R′ = C_5H_5O) and (IV; R = $NH{\cdot}C_5H_5O$, R′ = C_5H_5O) by treatment with nitrous acid.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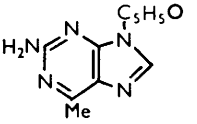
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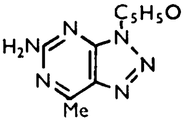
(VII)

A similar series of reactions was carried out with the chloropyrimidine (V; R = Cl), obtained from the readily accessible hydroxypyrimidine (V; R = OH), which yielded the purine (VI) and the triazolopyrimidine (VII), the last compound having been reported by Timmis *et al.*[3]

EXPERIMENTAL

4-*Chloro*-6-*methylanilino*-5-*nitropyrimidine*.—4 : 6-Dichloro-5-nitropyrimidine was prepared from 4 : 6-dihydroxy-5-nitropyrimidine according to the method of Boon, Jones, and Ramage,[4] and recrystallised from light petroleum (b. p. 80—100°). After storage the mother-liquors deposited yellow plates which crystallised from light petroleum, to give 4-chloro-6-methylanilino-5-nitropyrimidine, m. p. 128—130° (Found: C, 50·4; H, 3·4; N, 21·6; Cl, 13·5. $C_{11}H_9O_2N_4Cl$ requires C, 49·9; H, 3·4; N, 21·2; Cl, 13·4%).

4-*Dimethylamino*-6-*furfurylamino*-5-*nitropyrimidine*.—4-Chloro-6-dimethylamino-5-nitropyrimidine[7] (6 g.) in dioxan (50 ml.) was added to a stirred solution of furfurylamine (5·5 g.) in dioxan (15 ml.) at 15—20°. After 1½ hr., water (250 ml.) was added and the *product* (6 g.; m. p. 80°) collected. It crystallised from alcohol in yellow needles, m. p. 85—86° (Found: C, 50·2; H, 4·8; N, 27·0. $C_{11}H_{13}O_3N_5$ requires C, 50·2; H, 4·9; N, 26·6%).

5-*Amino*-4-*dimethylamino*-6-*furfurylaminopyrimidine*.—4-Dimethylamino-6-furfurylamino-5-nitropyrimidine (3·3 g.) in methanol (35 ml.), hydrogenated over Raney nickel at room temperature and pressure and worked up in the usual manner, gave the *aminopyrimidine* which crystallised from aqueous alcohol as plates (2·7 g.; m. p. 145°) (Found: C, 56·7; H, 6·3; N, 30·7. $C_{11}H_{15}ON_5$ requires C, 56·65; H, 6·4; N, 30·05%).

6-*Dimethylamino*-9-*furfurylpurine*.—5-Amino-4-dimethylamino-6-furfurylaminopyrimidine (1·17 g.) in ethyl orthoformate (7 ml.) and acetic anhydride (7 ml.) was heated under reflux during 1½ hr. Excess of reagent was removed under diminished pressure, and water was added to the residue. The *product* (0·85 g.) crystallised from aqueous alcohol in needles, m. p. 117—118° (Found: C, 59·3; H, 5·4; N, 29·0. $C_{12}H_{13}ON_5$ requires C, 59·3; H, 5·35; N, 28·8%).

6-*Dimethylamino*-1′-*furfuryl*-1′ : 2′ : 3′-*triazolo*(5′ : 4′-4 : 5)*pyrimidine*.—Sodium nitrite (0·25 g.) in water (3 ml.) was added to a solution of 5-amino-4-dimethylamino-6-furfurylaminopyrimidine (0·8 g.) in acetic acid (10 ml.) at 10°. After ½ hr. the solution was added to water (70 ml.) and the *triazolopyrimidine* (0·85 g.) was collected and washed with water. It crystallised from aqueous alcohol in pale yellow needles, m. p. 116° (Found: C, 53·6; H, 5·3; N, 33·7. $C_{11}H_{12}ON_6$ requires C, 54·1; H, 4·9; N, 34·3%).

4-*Chloro*-6-*morpholino*-5-*nitropyrimidine*.—Morpholine (5·3 g.) in methanol (20 ml.) was added slowly to a stirred solution of 4 : 6-dichloro-5-nitropyrimidine (5·8 g.) in methanol (100 ml.) at 4° ± 2°. After 2 hr. the solid (5·6 g.) was collected and washed with water. Recrystallisation from light petroleum (b. p. 80—100°) gave the *morpholinopyrimidine* as yellow needles, m. p. 101—102° (Found: C, 39·9; H, 4·0; N, 23·3. $C_8H_9O_3N_4Cl$ requires C, 39·25; H, 3·7; N, 22·9%).

4-*Furfurylamino*-6-*morpholino*-5-*nitropyrimidine*.—Furfurylamine (0·5 g.) and triethylamine (0·5 g.) in dioxan (5 ml.) were added slowly to a stirred solution of 4-chloro-6-morpholino-5-nitropyrimidine (1·2 g.) in dioxan (10 ml.) at 15—20°. After a further ½ hr. excess of water was added and the *product* (1·5 g.; m. p. 134—135°) collected. It crystallised from alcohol in pale yellow needles, m. p. 140—141° (Found: C, 51·4; H, 5·1; N, 23·6. $C_{13}H_{15}O_4N_5$ requires C, 51·2; H, 4·9; N, 23·0%).

5-Amino-4-furfurylamino-6-morpholinopyrimidine.—4-Furfurylamino-6-morpholino-5-nitropyrimidine (3·05 g.) in methanol (100 ml.), hydrogenated over Raney nickel at room temperature and pressure and worked up in the usual manner, gave the *aminopyrimidine* (2·8 g.). It crystallised from water in needles, m. p. 145° (Found: C, 56·5; H, 6·3; N, 25·1. $C_{13}H_{17}O_2N_5$ requires C, 56·7; H, 6·2; N, 25·45%).

9-Furfuryl-6-morpholinopurine.—5-Amino-4-furfurylamino-6-morpholinopyrimidine (2·75 g.) in ethyl orthoformate (12 ml.) and acetic anhydride (12 ml.) was heated under reflux during 1 hr. Excess of reagent was removed under diminished pressure and the residue was treated with 2·5N-sodium hydroxide (15 ml.) and alcohol (20 ml.) at 30—40° during 15 min. Excess of alcohol was removed under diminished pressure. The *product* (2·4 g.; m. p. 85°) crystallised from light petroleum (b. p. 100—120°) in prismatic needles, m. p. 88—89° (Found: C, 58·8; H, 5·5; N, 24·5. $C_{14}H_{15}O_2N_5$ requires C, 58·95; H, 5·2; N, 24·55%).

1′-Furfuryl-6-morpholino-1′ : 2′ : 3′-triazolo(5′ : 4′-4 : 5)pyrimidine.—Sodium nitrite (0·14 g.) in water (1·5 ml.) was added to a solution of 5-amino-4-furfurylamino-6-morpholinopyrimidine (0·5 g.) in acetic acid (4 ml.) at 10°. After 1½ hr. the solution was diluted with water and the *triazolopyrimidine* (0·5 g.) collected. It crystallised from alcohol in needles, m. p. 130—131° (Found: C, 55·0; H, 5·0; N, 29·0. $C_{13}H_{14}O_2N_6$ requires C, 54·55; H, 4·9; N, 29·35%).

4 : 6-Bisfurfurylamino-5-nitropyrimidine.—4 : 6-Dichloro-5-nitropyrimidine (55 g.) in methanol (500 ml.) was added in ½ hr. to a stirred solution of furfurylamine (55 g.) and triethylamine (57·5 g.) in methanol (200 ml.) at 15—20°. After a further 1 hr. the *product* (77 g.) was collected and washed with water. It crystallised from aqueous alcohol as pale brown needles, m. p. 131° (Found: C, 53·3; H, 4·5; N, 21·8. $C_{14}H_{13}O_4N_5$ requires C, 53·3; H, 4·1; N, 22·2%).

5-Amino-4 : 6-bisfurfurylaminopyrimidine.—4 : 6-Bisfurfurylamino-5-nitropyrimidine (16·5 g.) in methanol was hydrogenated over Raney nickel at room temperature and pressure and worked up in the usual manner. It gave the *aminopyrimidine* (14·8 g.) as plates, m. p. 114—116°, from light petroleum (b. p. 100—120°) (Found: C, 59·4; H, 5·9; N, 25·4. $C_{14}H_{15}O_2N_5$ requires C, 59·0; H, 5·3; N, 24·6%).

9-Furfuryl-6-furfurylaminopurine.—5-Amino-4 : 6-bisfurfurylaminopyrimidine (1·0 g.) in ethyl orthoformate (5 ml.) and acetic anhydride (5 ml.) was heated under reflux during 1 hr. Excess of reagent was removed under diminished pressure and the residue was then treated with 2·5N-sodium hydroxide (10 ml.) and alcohol (5 ml.) at 40° during 15 min. After cooling, the solid (1·05 g.) was collected and washed with water. Recrystallisation from water gave the *purine* as needles, m. p. 140° (Found: C, 60·4; H, 4·6; N, 23·0. $C_{15}H_{13}O_2N_5,\frac{1}{3}H_2O$ requires C, 59·8; H, 4·55; N, 23·25%).

1′-Furfuryl-6-furfurylamino-1′ : 2′ : 3′-triazolo(5′ : 4′-4 : 5)pyrimidine.—Sodium nitrite (0·73 g.) in water (3·5 ml.) was added slowly to a solution of 5-amino-4 : 6-bisfurfurylaminopyrimidine (2·85 g.) in acetic acid (40 ml.) at 15—20°. After ½ hr., the solution was added to water (250 ml.), and the *triazolopyrimidine* (2·4 g.) collected and washed with water. It crystallised from aqueous alcohol in needles, m. p. 124—126° (Found: C, 57·3; H, 4·0; N, 29·0. $C_{14}H_{12}O_2N_6$ requires C, 56·8; H, 4·05; N, 28·4%).

2-Amino-4-furfurylamino-6-methyl-5-nitropyrimidine.—Furfurylamine (4·0 g.) was added to a hot filtered solution of 2-amino-4-chloro-6-methyl-5-nitropyrimidine[4] (3·5 g.) in alcohol (80 ml.), and the whole was heated under reflux during 1 hr. On the following morning the *furfurylaminopyrimidine* (2·3 g.; m. p. 167—168°) was collected. Recrystallisation from alcohol gave yellow plates, m. p. 168—169° (Found: C, 48·0; H, 4·2; N, 28·6. $C_{10}H_{11}O_3N_5$ requires C, 48·2; H, 4·4; N, 28·1%).

2 : 5-Diamino-4-furfurylamino-6-methylpyrimidine.—2-Amino-4-furfurylamino-6-methyl-5-nitropyrimidine (1·6 g.) in methanol (100 ml.) was hydrogenated over Raney nickel at room temperature and pressure. After filtration from the catalyst, the solvent was removed and the residue (1·1 g.) was dried on a porous tile. Recrystallisation from toluene (carbon) gave the *diaminopyrimidine* as rhombs, m. p. 123—124° (Found: C, 55·0; H, 6·0; N, 31·7. $C_{10}H_{13}ON_5$ requires C, 54·8; H, 5·9; N, 32·0%).

2-Amino-9-furfuryl-6-methylpurine.—2 : 5-Diamino-4-furfurylamino-6-methylpyrimidine (15 g.), acetic anhydride (100 ml.), and ethyl orthoformate (100 ml.) were heated under reflux during 1 hr. Excess of reagent was removed under diminished pressure and the residue was then treated with 2·5N-sodium hydroxide (100 ml.) and ethanol (50 ml.) at 40° during 15 min. After cooling, the solid was collected and washed with water. Recrystallisation from aqueous alcohol gave the *purine* (6·2 g.) as needles, m. p. 113—114° (Found: C, 56·7; H, 5·5; N, 29·6. $C_{11}H_{11}ON_5,0{\cdot}25H_2O$ requires C, 56·6; H, 5·0; N, 29·95%).

2-*Amino*-1′-*furfuryl*-6-*methyl*-1′ : 2′ : 3′-*triazolo*(5′ : 4′-4 : 5)*pyrimidine*.—Sodium nitrite (1·24 g.) in water (10 ml.) was added to a solution of 2 : 5-diamino-4-furfurylamino-6-methylpyrimidine (3·73 g.) in acetic acid (100 ml.) at 10°. After 10 min. the solution was added to water (500 ml.), and the *triazolopyrimidine* (3·7 g., m. p. 150—152°) was collected and washed with water. It crystallised from water in needles, m. p. 153° (Found: C, 52·1; H, 4·5; N, 36·3. $C_{10}H_{10}ON_6$ requires C, 52·2; H, 4·35; N, 36·5%).

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