Purine Studies. Part XIV.[1] Trifluoroacetyl and Formyl Derivatives of 4,5-Diamino-6-methyl-2-methylthiopyrimidine, their Ethylation Products, and Derived Purines

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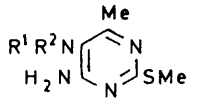
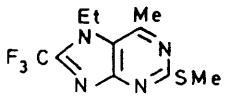
The acylation products from 4,5-diamino- and 5-amino-4-ethylamino-derivatives of 6-methyl-2-methylthiopyrimidine obtained by using trifluoroacetylating agents have been compared with those obtained by using acetylating and formylating agents. The site of *N*-ethylation of the trifluoroacetyl derivatives is in some cases different from that in the corresponding acetyl and formyl analogues. The disparity in reactivity is related to the higher lability of the trifluoroacetyl group than of the acetyl and formyl groups. Conversion of the acyl derivatives into the respective purines is described.

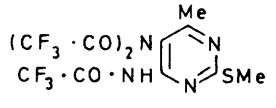
THE reported facility with which 5-(*N*-alkyltrifluoroacetamido)-4,6-dichloropyrimidines[2] undergo deacylation to the corresponding 5-alkylamino-4,6-dichloropyrimidines, when treated with aqueous alkali, prompted a study of the reactions of 4,5-diamino-6-methyl-2-methylthiopyrimidine (1). It was hoped that a successful conversion into the 4-amino-5-ethylamino-analogue (2), required as an intermediate for the preparation of 7-ethylpurines, could be effected. Heating (1) with trifluoroacetic acid gave the 5-trifluoroacetamidopyrimidine (3). An alternative route, in which trifluoroacetic anhydride was added in the cold to an ethanolic solution of the diaminopyrimidine, was limited to small-scale preparations owing to the vigour of the reaction. Ethylation, with iodoethane, of compound (3) in dimethylformamide did not give the 5-(*N*-ethyltrifluoroacetamido)-derivative (4); the product isolated was the 7-ethylpurine (5). One example of spontaneous cyclisation to a purine under similar alkylating conditions has been noted.[3]



(1) $R^1 = R^2 = H$
(2) $R^1 = Et$, $R^2 = H$
(3) $R^1 = CO \cdot CF_3$, $R^2 = H$
(4) $R^1 = CO \cdot CF_3$, $R^2 = Et$



(5)



(6)

When the diaminopyrimidine (1) was treated with an excess of cold trifluoroacetic anhydride in the absence of solvent, a triacylated pyrimidine resulted. The structure followed from comparisons of the n.m.r. spectrum with those of the triacetylated analogue, reported previously[4] (Table 1), which show the compound to be 5-bistrifluoroacetylamino-6-methyl-2-methylthio-4-trifluoroacetamidopyrimidine (6). The same triacylated pyrimidine was formed when the monoacylated derivative (3) was similarly treated with cold anhydride. Ethylation, under the same conditions as for the monoacylated pyrimidine (3) gave an oil which, when treated with cold aqueous triethylamine in an effort to remove the trifluoroacetyl groups, was converted into the 7-ethyl-8-trifluoromethylpurine (5). This result was unexpected, as ethylation of the corresponding triacetyl analogue had been found[4] to give alkylated pyrimidines which on cyclisation afforded 9-ethyl-8-methylpurines. This anomalous alkylation behaviour can be rationalised as being a reflection of the difference in lability between the acetyl and trifluoroacetyl groups towards alkali. With the former class of derivative any removal of acetyl groups is found to follow alkylation of the 4-amino-group, whereas in the case of the tristrifluoroacetylpyrimidine displacement of two acyl groups occurs prior to alkylation, owing to the presence of alkali, and thus the monoacylated derivative (3) is the one actually alkylated. Evidence to support this rationalisation is the fact that passage of a solution of the tristrifluoroacetyl derivative in ethyl acetate down a column of alumina results in only the 5-trifluoroacetamido-derivative (3) being recovered. Complete deacylation occurs when the tristrifluoroacetylpyrimidine (6) is dissolved in dilute sodium hydroxide. Under thermal conditions (*e.g.* sublimation) a similar lability is seen in the conversion into 6-methyl-2-methylthio-8-trifluoromethylpurine (7).

Similar acylation studies were performed on 5-amino-4-ethylamino-6-methyl-2-methylthiopyrimidine. The 5-trifluoroacetamido-derivative (8) was obtained with trifluoroacetic acid, whereas with an excess of trifluoroacetic anhydride a diacylated derivative, shown by its n.m.r. spectrum to be the 4,5-diacylaminopyrimidine (9), was formed. Conversion of the latter into the 9-ethylpurine (10) resulted either under fusion conditions or on heating in dimethylformamide containing

[1] Part XIII, D. J. Brown and L. G. Stephanson, *Austral. J. Chem.*, 1974, **27**, 1371.
[2] C. Temple, R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, 1963, **28**, 923.
[3] J. A. Montgomery and K. Hewson, *J. Org. Chem.*, 1961, **26**, 4469.
[4] M. D. Fenn and J. H. Lister, *J.C.S. Perkin I*, 1974, 1300.

TABLE 1

^{1}H N.m.r. spectra of acylaminopyrimidines (δ values) [a]

6-Methyl-2-methylthiopyrimidine	R	2-SMe	6-Me	4-NH_2	5-NH_2	CH_2·CH_3	CH_2·CH_3	CHO	Ac
4,5-$(NH_2)_2$		2·37	2·15	6·29	4·23				
4-NHEt-5-NH_2		2·33	2·08	6·40	4·20	1·19	3·40		
4-NH_2-5-NH·COR	H	2·42	2·10	6·83	9·17			8·25	
	Me [b]	2·40	2·07	6·70	9·00				2·03
	CF_3	2·42	2·05	7·13	10·67				
4-NHEt-5-NH·COR	H	2·40	2·04	6·90	9·15	1·10	3·47	8·23	
	Me [b]	2·40	2·50	6·90	8·95	1·10	3·50		2·00
	CF_3	2·60	2·27	6·90	8·30	1·22	3·70		
4,5-$(NH·COR)_2$	H	2·50	2·27	10·10	10·00			8·26, 9·54	
	Me [b]	2·45	2·20	10·10	9·10				2·05, 2·25
4-NEt·COR-5-NH·COR	Me [b]	2·35	2·50		9·50	1·05	3·60		2·05, 1·95
	CF_3	2·53	2·12		8·20	1·14	3·47		
4-NH·COR-5-$N(COR)_2$	Me [b]	2·29	2·55	10·20					2·18, 2·25, 2·25
	CF_3	2·50	2·13	10·40					
4-NH_2-5-NEt·COR	H	2·42	2·15	7·15		1·02	3·68	7·95	
	Me [b]	2·38	2·08	7·00		0·95	3·53		1·67

[a] Spectra recorded in $(CD_3)_2SO$ dried over molecular sieves (type 4A). [b] Ref. 4.

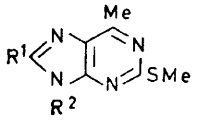
TABLE 2

Ionisation constants and u.v. spectra

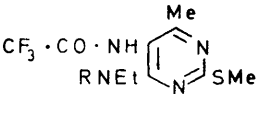
Purine	pK (λ) [a]	$\lambda_{max.}$/nm (log ε) [b] [pH; ionic species]
7-Et-6-Me-2-SMe	2·33 ± 0·04 (270)	305 (3·72), *255* (*4·00*), 238 (4·34), [7·0; 0]
		311 (3·67), 247 (4·19), 231 (4·15), [0·5; +]
7-Et-6,8-Me_2-2-SMe	3·28 ± 0·5 (260)	304 (3·83), *255* (*4·00*), 238 (4·34), [7·0; 0]
		311 (3·67), 247 (4·19), 231 (4·15), [0·5; +]
7-Et-6-Me-2-SMe-8-CF_3	0·45 ± 0·04 (260)	317 (3·56), *220* (*3·90*), 239 (4·17), [7·0; 0]
		335 (3·41), *267* (*4·00*), 248 (4·33), [−1·6; +]
9-Et-6,8-Me_2-2-SMe [c]	3·51 ± 0·05 (325)	298 (3·95), 261 (3·94), 233 (4·28), [7·0; 0]
		307 (3·75), *274* (*3·94*), *260* (*4·05*), 243 (4·21), 233 (4·18), [0; +]
9-Et-6-Me-2-SMe-8-CF_3	1·36 ± 0·05 (305)	304 (3·97), 259 (3·86), 236 (4·27), [7·0; 0]
		311 (3·59), 276 (4·07), 246 (4·33), [−0·84; +]
6,8-Me_2-2-SMe [d]	9·70 ± 0·06 (240)	299 (3·92), *265* (*3·70*), 239 (4·26), [12·0; −]
	3·04 ± 0·04 (300)	299 (3·89), 254 (3·96), 227 (4·23) [7·0; 0]
		305 (3·79), 254 (4·06), 225 (4·14) [1·2; +]
6-Me-2-SMe-8-CF_3	5·67 ± 0·04 (260)	303 (3·92), *260* (*3·72*), 239 (4·31) [8·0; −]
	1·25 ± 0·03 (270)	304 (3·89), 249 (4·00), 230 (4·24) [3·5; 0]
		312 (3·51), 270 (4·13), 237 (4·29) [−0·8; +]

[a] Analytical wavelength (nm). [b] Inflections in italics. [c] Ref. 5. [d] D. J. Brown, R. L. Jones, A. A. Angyal, and G. W. Grigg *J.C.S. Perkin I*, 1972, 1819.

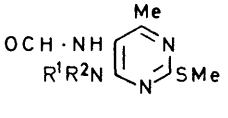
potassium carbonate. No triacylated 4-*N*-ethyl analogue of (6) could be obtained.



(7) $R^1 = CF_3$, $R^2 = H$
(10) $R^1 = CF_3$, $R^2 = Et$
(14) $R^1 = H$, $R^2 = Et$



(8) R = H
(9) R = CO·CF_3



(11) $R^1 = CHO$, $R^2 = H$
(12) $R^1 = Et$, $R^2 = H$
(13) $R^1 = Et$, $R^2 = CHO$

The formylation reactions of the diamine (1), noted previously,[4] were extended by using formic acetic anhydride in place of formic acid, and the diformyl derivative (11) was obtained. Ethylation, under the above conditions, gave the 4-ethylamino-5-formamidopyrimidine (12). An attempt to convert this into the diformyl derivative (13) under mild conditions gave instead the known [5] 9-ethylpurine (14). Alkylation of the diformylaminopyrimidine thus follows the same mode as in alkylation of the di- and tri-acetylated analogues.

A comparison of n.m.r. data (Table 1) reveals little difference in the respective chemical shifts of the trifluoroacetyl, acetyl, and formyl derivatives. The downfield displacement of either a 4- or 5-amino-proton signal following trifluoroacetylation parallels that seen after acetylation or formylation. This result is perhaps unexpected in view of the strong inductive effect of the trifluoromethyl group, an illustration of which is ob-

[5] R. J. Badger, D. J. Brown, and J. H. Lister, *J.C.S. Perkin I*, 1974, 152.

tained when the pK_a values of the 8-methylpurines and the corresponding 8-trifluoromethyl analogues (Table 2) are compared. The effect of this group is also reflected in the shifts in u.v. absorptions, generally to higher wavelengths. Owing to the insolubility of many of the acyl derivatives in $CDCl_3$ no determinations of the extent of hydrogen bonding in these derivatives were carried out.

EXPERIMENTAL

^1H N.m.r. spectra were recorded at 33° on a Perkin-Elmer R10 (60 MHz) instrument, with tetramethylsilane as standard. Ionisation constants were measured spectrophotometrically at 20° in buffers of ionic strength 10^{-2}M by the methods [6] outlined in ref. 7. U.v. spectra were recorded on a Unicam SP 800 spectrophotometer; peak positions were checked manually with an SP 500 instrument.

5-Bistrifluoroacetylamino-6-methyl-2-methylthio-4-trifluoroacetamidopyrimidine (6).—A solution of 4,5-diamino-6-methyl-2-methylthiopyrimidine (1 g) in trifluoroacetic anhydride (15 ml) was stirred for 3 h. The precipitate was then filtered off (2·8 g) and washed with petroleum (b.p. 40—60°). Crystallisation from water gave the *tristrifluoroacetylated pyrimidine* as the trihydrate, m.p. 98—99° (Found: C, 28·3; H, 2·8; N, 10·8. $C_{12}H_7F_9N_4O_3S,3H_2O$ requires C, 28·2; H, 2·6; N, 10·9%). The same trihydrate (m.p., i.r. spectrum) results when 4-amino-6-methyl-2-methylthio-5-trifluoroacetamidopyrimidine in trifluoroacetic anhydride is left for 4 h, then evaporated, and the residual oil is allowed to crystallise. Intensive drying, carried out in an attempt to prepare the anhydrous form, gave only an oil, the i.r. spectrum of which suggested that some dehydration had occurred.

Deacylation of the Triacylated Pyrimidine (6).—(a) *By alumina*. The acylated derivative in ethyl acetate gave a major band at R_F 0·5 on an alumina (Merck type E) preparative t.l.c. plate. Extraction of the band with cold ethyl acetate gave a solid having the same R_F value. The i.r. spectrum, m.p., and R_F value of this product were identical with those of 4-amino-6-methyl-2-methylthio-5-trifluoroacetamidopyrimidine (see later), showing that two trifluoroacetyl groups had been removed by this treatment.

(b) *By 0·2N-sodium hydroxide*. When the triacylated derivative was kept in 0·2N-sodium hydroxide for 1·5 h a crystalline precipitate was obtained, identical (i.r. spectrum, m.p.) with authentic 4,5-diamino-6-methyl-2-methylthiopyrimidine.

6-Methyl-2-methylthio-8-trifluoromethylpurine (7).—On heating a sample of 5-bistrifluoroacetylamino-6-methyl-2-methylthio-4-trifluoroacetamidopyrimidine at 200° for 1 h a sublimate of *6-methyl-2-methylthio-8-trifluoromethylpurine*, m.p. 152—153° [from petroleum (b.p. 80—100°)] was obtained (Found: C, 38·7; H, 3·0; N, 22·6. $C_8H_7F_3N_4S$ requires C, 38·7; H, 2·8; N, 22·6%).

4-Amino-6-methyl-2-methylthio-5-trifluoroacetamidopyrimidine (3).—A solution of 4,5-diamino-6-methyl-2-methylthiopyrimidine (0·8 g) in trifluoroacetic acid (5 ml) was heated on a steam-bath for 2 h. The oil remaining after evaporation was taken up in ethyl acetate and passed down an alumina (1 × 10 in) column and the column was then eluted with ethyl acetate until the band showing a pale yellow fluorescence in u.v. light had been washed through. The microcrystalline product gave the *5-trifluoroacetamidopyrimidine* (0·43 g), m.p. 180—181° [from water (carbon)] (Found: C, 35·7; H, 3·6; N, 20·6. $C_8H_9F_3N_4OS$ requires C, 36·1; H, 3·4; N, 21·0%). The same derivative (i.r. spectrum, t.l.c.) results when a solution of the triacylated derivative in ethyl acetate is passed through a column of alumina.

7-Ethyl-6-methyl-2-methylthio-8-trifluoromethylpurine (5).—(a) *From the tristrifluoroacetylated pyrimidine*. To a solution of 5-bistrifluoroacetylamino-6-methyl-2-methylthio-4-trifluoroacetamidopyrimidine (1·5 g) in dimethylformamide (12 ml) containing potassium carbonate (1 g), iodoethane (0·55 g) was added. After stirring for 20 h, water (25 ml) was added and the solution extracted with ether (3 × 25 ml). Evaporation of the dried (Na_2SO_4) extract gave an oil, the i.r. spectrum of which showed the presence of both carbonyl and amino-groups. Treatment of the oil with triethylamine (1·5 ml) in water (10 ml), in an attempt to remove the acyl groups, gave a solid. Crystallisation from aqueous methanol gave *7-ethyl-6-methyl-2-methylthio-8-trifluoromethylpurine* (0·2 g), m.p. 165—166° (Found: C, 43·3; H, 4·2; N, 20·0. $C_{10}H_{11}F_3N_4S$ requires C, 43·5; H, 4·0; N, 20·3%).

(b) *From the monoacylated pyrimidine*. Iodoethane (0·17 g) was added to a stirred solution of 4-amino-6-methyl-2-methylthio-5-trifluoroacetamidopyrimidine (0·25 g) in dimethylformamide (5 ml) containing potassium carbonate (0·25 g). After 18 h the solution was filtered from inorganic solids, then water (10 ml) was added and the solution was extracted with ether. The extract afforded the purine (5) (m.p., i.r. spectrum, t.l.c.) on crystallisation from aqueous ethanol.

4-Ethylamino-6-methyl-2-methylthio-5-trifluoroacetamidopyrimidine (8).—5-Amino-4-ethylamino-6-methyl-2-methylthiopyrimidine (0·2 g) in ethanol (5 ml) was treated slowly with trifluoroacetic anhydride (0·75 ml) (vigorous reaction!) After 2 h the solution was taken to dryness and the residue (0·22 g) washed with ether. Crystallisation from ethyl acetate gave the *5-trifluoroacetamidopyrimidine* as the dihydrate, m.p. 185—186° (Found: C, 36·6; H, 4·9; N, 16·6. $C_{10}H_{13}F_3N_4OS,2H_2O$ requires C, 36·4; H, 5·2; N, 17·0%).

4-(N-Ethyltrifluoroacetamido)-6-methyl-2-methylthio-5-trifluoroacetamidopyrimidine (9).—5-Amino-4-ethylamino-6-methyl-2-methylthiopyrimidine (0·2 g) and trifluoroacetic anhydride (3 ml) were left at room temperature for 15 h. The product was filtered off and washed with ether to give the *4,5-bistrifluoroacetamidopyrimidine* (0·2 g) as a monohydrate, m.p. 169—170° (Found: C, 35·5; H, 3·4; N, 13·6. $C_{12}H_{12}F_6N_4O_2S,H_2O$ requires C, 35·1; H, 3·5; N, 13·7%). Intensive drying (124°; 12 h *in vacuo*) gave the *hemihydrate* (Found: C, 36·1; H, 3·5; N, 14·0. $C_{12}H_{12}F_6N_4O_2S,0{\cdot}5H_2O$ requires C, 36·1; H, 3·3; N, 14·0%). This derivative (0·3 g) also results from heating under reflux (1·5 h) the same diaminopyrimidine (0·2 g) in the anhydride (5 ml) then triturating the oil obtained on evaporation with ether.

9-Ethyl-6-methyl-2-methylthio-8-trifluoromethylpurine (10).—The above 5-amino-4-ethylaminopyrimidine (0·2 g) was heated under reflux in trifluoroacetic anhydride (3 ml) for 3 h. As the i.r. spectrum of the oil remaining after

[6] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.
[7] A. Albert and E. P. Serjeant, ' Determination of Ionisation Constants,' Chapman and Hall, London, 2nd edn., 1971.

evaporation showed that the uncyclised diacylated pyrimidine was the main constituent, the crude product was taken up in dimethylformamide (3 ml) containing potassium carbonate (0·05 g) and heated under reflux (0·75 h). After removal of the inorganic solids the solution was diluted with water (10 ml) and then evaporated to dryness. The residue was crystallised from aqueous methanol to give the *purine* (0·1 g), m.p. 98—99° (Found: C, 43·5; H, 4·2; N, 20·0. $C_{10}H_{11}F_3N_4S$ requires C, 43·5; H, 4·0; N, 20·3%). In an alternative cyclisation the gum obtained after acylation of the diamine (0·4 g) was heated in a metal-bath at 250° for 0·5 h. The melt was extracted with chloroform and the extracts were taken to dryness. Crystallisation of the residue from aqueous methanol gave the purine (0·25 g).

4,5-Diformamido-6-methyl-2-methylthiopyrimidine (11).—Formic acetic anhydride (8 ml) and 4,5-diamino-6-methyl-2-methylthiopyrimidine (0·9 g) were heated at 50° for 1 h. Evaporation to dryness and crystallisation of the residue from n-propanol gave *4,5-diformamido-6-methyl-2-methylthiopyrimidine* (0·6 g), m.p. 205—206° (Found: C, 42·7; H, 4·7; N, 25·0. $C_8H_{10}N_4O_2S$ requires C, 42·5; H, 4·5; N, 24·8%). This derivative is also formed when 4-amino-5-formamido-6-methyl-2-methylthiopyrimidine and formic acetic anhydride are heated together (0·75 h) on a water-bath.

4-Ethylamino-5-formamido-6-methyl-2-methylthiopyrimidine (12).—(a) *From 4,5-diformamido-6-methyl-2-methylthiopyrimidine.* A solution of the diformamidopyrimidine (0·6 g) in dimethylformamide (7 ml) containing potassium carbonate (0·6 g) and iodoethane (0·5 g) was stirred for 30 h. After removal of inorganic salts the solution was diluted with water (20 ml) and then evaporated to dryness giving the *4-ethylaminopyrimidine* (0·3 g), m.p. 173—174° (from ethanol) (Found: C, 47·7; H, 6·5; N, 24·5. $C_9H_{14}N_4OS$ requires C, 47·8; H, 6·2; N, 24·8%).

(b) *From 5-amino-4-ethylamino-6-methyl-2-methylthiopyrimidine.* Heating under reflux a solution of the diaminopyrimidine (0·25 g) in formic acid (99%; 8 ml) for 0·75 h followed by evaporation to dryness gave an oil. This was dissolved in water (5 ml) and the pH of the solution was adjusted to 7 with ammonia, to give the 4-ethylaminopyrimidine (0·16 g), m.p. 173—174°.

Attempted Conversion of the 4-Ethylamino-5-formamidopyrimidine (12) *into a Diformamido-derivative.*—The 5-formamidopyrimidine in formic acetic anhydride was heated on a water-bath for 1·5 h. The mixture was then evaporated to dryness to leave an oil which slowly crystallised. This was shown to be 9-ethyl-6-methyl-2-methylthiopurine by comparison (i.r. spectrum, m.p.) with an authentic sample.[5]

We thank Dr. D. J. Brown for his interest and for discussions.

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