Useful Preparations involving the Reactions of Nucleophiles with Some Trimethylammonio-derivatives of Nitrogen Heterocycles

By G. B. Barlin * and A. C. Young, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia 2600

Methods are described for the preparation of alkoxy-, amino-, n-propylamino-, hydrazino-, mercapto-, fluoro-, and cyano-derivatives of pyridine, pyrimidine, quinoline, quinazoline, and purine by treatment of the corresponding trimethylammonio-compound with the appropriate nucleophile.

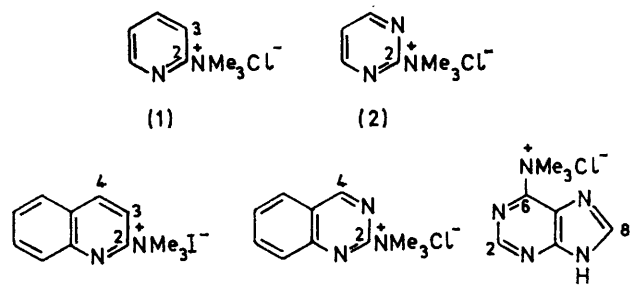
OUR recent work [1-3] on the kinetics of replacement by hydroxide ion of the trimethylammonio-group from substituted pyridines, pyrimidines, quinolines, quinazolines, and purines has shown that the trimethylammonio-compounds are 700—1600 times more reactive than the corresponding chloro-compounds but only 5—8 times less reactive than the methylsulphonyl analogues. These results suggested that the trimethylammonio-compounds, like the methylsulphonyl compounds,[4] might be useful in synthesis, and we have now examined their reactions with a range of nucleophiles.

Trimethylammonio-compounds have previously been used sporadically in a restricted variety of such syntheses. Thus the trimethylammonio-group has been displaced readily from substituted pyrimidines by hydroxide,[5,6] alkoxide,[5] cyanide,[5,7] phenoxide,[5] sulphonamide,[8-10] fluoride,[11] and azide [11] ions; from purines by fluoride [12] and hydroxide ions; [13] and from quinoline by hydroxide ions.[14] The use of the corresponding trimethylammonio-compounds with potassium cyanide in acetamide has permitted the preparation of 2-cyano-4,6-dimethyl- and 4-cyano-2,6-dimethyl-pyrimidine whereas these cyano-pyrimidines could not be prepared from their chloro-analogues with potassium or copper(I) cyanide.[5,7]

We now describe a much wider range of reaction between a variety of trimethylammonio-compounds and alcoholic sodium alkoxide, aqueous ammoniacal ammonium chloride, n-propylamine, hydrazine hydrate, sodium cyanide in *NN*-dimethylformamide, potassium hydrogen difluoride in ethanol, and aqueous sodium hydrogen sulphide.

With alcoholic sodium alkoxide, the trimethylammonio-compounds gave good yields of alkoxy-heterocycles in all cases (Table 1); with aqueous ammoniacal ammonium chloride reasonable yields of amino-compounds were obtained in seven of the eight reactions examined (Table 2), but 9-methylpurin-2-yltrimethylammonium chloride at 100°, gave a mixture of amino- and dimethylamino- (formed by demethylation) compounds.

With n-propylamine, eight of the nine reactions examined gave good yields of the corresponding n-propylamino-compounds (Table 3) but quinolin-2-yltrimethylammonium iodide furnished only 2-dimethylaminoquinoline. Similarly, reactions with hydrazine gave the hydrazino-compounds (Table 4) except that no product



Typical trimethylammonio-derivatives of: (1) pyridine, (2) pyrimidine, (3) quinoline, (4) quinazoline, (5) purine

could be isolated from 5-nitropyrimidin-2-yltrimethylammonium chloride. With sodium cyanide in dimethylformamide at 50° the two trimethylammonio-compounds studied gave their cyano-analogues. Attempted preparations with sodium cyanide in acetamide, similar to that described by Klötzer,[7] failed with these compounds.

Conversion of 9-methylpurin-6-yltrimethylammonium chloride into 6-fluoro-9-methylpurine was achieved under conditions similar to those used by Kiburis and Lister [12] with the unmethylated analogue.

The reaction of 5-nitro-2-pyridyltrimethylammonium chloride with aqueous sodium hydrogen sulphide proceeded smoothly at room temperature to give the corresponding mercapto-compound.

EXPERIMENTAL

Analyses were performed by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 20° and 20 mmHg unless otherwise stated. M.p.s were taken for samples in Pyrex glass capillaries. All compounds were examined for the presence of impurities by paper chromatography

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[3] G. B. Barlin and A. C. Young, *J. Chem. Soc.* (*B*), 1971, 2323.
[4] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*C*), 1967, 2473.
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[13] T. B. Walsh and R. Wolfenden, *J. Amer. Chem. Soc.*, 1967, **89**, 6221.
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on Whatman no. 1 paper with (*a*) aqueous 3% ammonium chloride and (*b*) butan-2-ol–5N-acetic acid (7 : 3) as solvents.

Reactions of Trimethylammonio-compounds with Alcoholic Sodium Alkoxide.—The trimethylammonio-compound (0·1 g) and alcoholic sodium alkoxide were heated together. The conditions of reaction, methods of isolation, and yields are summarised in Table 1.

Reactions of Trimethylammonio-compounds with Aqueous Ammoniacal Ammonium Chloride.—The results and conditions of reaction of the trimethylammonio-compounds (0·1 g) with a mixture of aqueous ammonium hydroxide (*d* 0·91; 3 ml) and ammonium chloride (0·32 g) are listed in Table 2 with the following exception.

Reaction of 9-Methylpurin-2-yltrimethylammonium Chloride with Aqueous Ammoniacal Ammonium Chloride.—9-Methylpurin-2-yltrimethylammonium chloride (0·020 g), ammonium hydroxide (*d* 0·91; 1 ml), and ammonium chloride (0·1 g) were heated in a sealed tube at 100° for 6 h. T.l.c. of the mixture (alumina; chloroform) gave 2-dimethylamino-9-methylpurine [0·007 g; from light petroleum (b.p. 60—80°)], m.p. 89—90° (lit.,[1] 89—90°), and 2-amino-9-methylpurine (0·004 g; sublimed at 150° and 0·02 mmHg), m.p. 239—241° (lit.,[15] 242—243°).

Reactions of Trimethylammonio-compounds with n-Propylamine.—The trimethylammonio-compound (0·020 g) and n-propylamine (1 ml) were heated in a sealed tube. The results and conditions of the reactions are given in Table 3 with the exception of the following reaction.

2-Dimethylaminoquinoline.— Quinolin-2-yltrimethylammonium iodide (0·020 g) and n-propylamine (1 ml) were heated in a sealed tube at 100° for 3 h. The mixture was filtered to remove unchanged starting material (0·003 g), m.p. and mixed m.p. 171°, and the filtrate evaporated to dryness. The residue was extracted with benzene and gave an oil which with ethanolic picric acid gave 2-dimethylaminoquinoline picrate (0·016 g), m.p. and mixed m.p. 219—220° (lit.,[16] 221—222°).

Reactions of Trimethylammonio-compounds with Hydrazine Hydrate at 20°.—The trimethylammonio-compound (0·020 g) and hydrazine hydrate were set aside at 20° for 15 min. The mixture was then evaporated to dryness and the product recrystallised. The quantities of reagent, solvent for recrystallisation, and results are in Table 4.

Reaction of Quinolin-2-yltrimethylammonium Iodide with Hydrazine Hydrate at 100°.—A mixture of quinolin-2-yltrimethylammonium iodide (0·020 g) and hydrazine hydrate (98%; 0·5 ml) was heated under reflux for 25 min, and then evaporated to dryness under reduced pressure. The residue was extracted with chloroform and treatment of the oil obtained with ethanolic picric acid gave 2-dimethylaminoquinoline picrate, m.p. and mixed m.p. 219—221° (lit.,[16] 221—222°). When the reaction was repeated at 60° for 2 h and 20° for 24 h only 2-dimethylaminoquinoline could be detected.

Reaction of 5-Nitro-2-pyridyltrimethylammonium Chloride with Aqueous Sodium Hydrogen Sulphide.—2-Mercapto-5-nitropyridine. 5-Nitro-2-pyridyltrimethylammonium chloride (0·40 g) was added to aqueous sodium hydrogen sulphide (1·2M; 10 ml) at room temperature; the mixture was shaken for 1 min, immediately acidified with hydrochloric acid, and chilled. The precipitate was filtered off and dissolved in dilute sodium hydroxide solution; the solution was acidified with hydrochloric acid to give 2-mercapto-5-nitropyridine (0·228 g, 79%), m.p. 190—191° (decomp.) (from aqueous methanol) [lit.,[17] 188—191° (decomp.)].

Reaction of 9-Methylpurin-6-yltrimethylammonium Chloride with Potassium Hydrogen Difluoride.—6-Fluoro-9-methylpurine. 9-Methylpurin-6-yltrimethylammonium chloride (0·020 g) and potassium hydrogen difluoride (0·070 g) in ethanol (2 ml) were heated at 50° for 2 h. The mixture was diluted with water and adjusted, by addition of aqueous sodium hydrogen carbonate, to pH 7. This solution was extracted with chloroform; the extract was dried (Na_2SO_4), the solvent distilled off, and the product recrystallised from

TABLE 1

Reactions of trimethylammonio-compounds (0·1 g) with alcoholic sodium alkoxide

Product	Alcoholic sodium alkoxide	Conditions of reaction	Method of isolation [a]	Product		
				% Yield	M.p. (°C)	Lit. m.p. (°C)
2-Methoxypyridine picrate	2M; 10 ml	100°, 12 h	A	51	159—160 [b]	159—160 [c]
2-Methoxy-5-nitropyridine	0·8M; 5 ml	20°, 10 min	B	98	106—108 [b]	109—110 [d]
2-Methoxypyrimidine picrate	0·25M; 20 ml	20°, 5 min	A	90	105—106 [b]	104—106 [e]
2-Methoxy-5-nitropyrimidine	0·5M; 20 ml	20°, 5 min	B	70	67—68	69—70 [f]
4-Methoxypyrimidine picrate	0·25M; 4 ml	20°, 5 min	A	74	126·5	123—124 [e]
2-Methoxyquinoline picrate	1·5M; 12·5 ml	100°, 30 min	B	77	184—185 [b]	182—183 [g]
2-Methoxyquinazoline picrate	1M; 5 ml	66°, 10 min	A	56	135—136 [h]	137—138 [i]
4-Methoxyquinazoline picrate	1M; 5 ml	20°, 5 min	A	98	174—175 [b]	174—175 [i]
2-Ethoxy-9-methylpurine	0·5M; 10 ml	50°, 5 min	B	64	111 [b]	111—112 [j]
6-Ethoxy-9-methylpurine	0·2M; 25 ml	77°, 15 min	A	64	115—116 [b,k]	107—108 [j]
6-Methoxypurine	0·1M; 10 ml	50°, 5 min	C	91	194—195	194—195 [l]

[a] Methods of isolation were as follows: A, the reaction mixture was diluted with water, adjusted to pH 7, and extracted with chloroform; the solvent was evaporated, giving the free base which furnished a picrate with ethanolic picric acid. B, As in A except that the free base was recrystallised from light petroleum (b.p. 60—80°). C, as in A except that the free base was recrystallised from chloroform–acetone. [b] No depression of m.p. was observed on admixture with an authentic specimen. [c] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 648. [d] W. Gruber, *Canad. J. Chem.*, 1953, **31**, 1020. [e] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1955, 211. [f] D. J. Brown and R. V. Foster, *Austral. J. Chem.*, 1966, **19**, 2321. [g] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 736. [h] Found: C, 46·3; H, 2·8; N. 17·8. Calc. for $C_{15}H_{11}N_5O_8$: C, 46·3; H, 2·9; N, 18·0%. [i] K. Adachi, *J. Pharm. Soc. Japan*, 1955, **75**, 1426. [j] G. B. Barlin, *J. Chem. Soc.* (*B*), 1967, 954. [k] Found: C, 53·6; H, 5·7. Calc. for $C_8H_{10}N_4O$; C, 53·9; H, 5·7%. [l] G. Huber, *Chem. Ber.*, 1957, **90**, 698.

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TABLE 2

Reactions of trimethylammonio-compounds (0·1 g) with ammonium hydroxide (*d* 0·91; 3 ml)–ammonium chloride (0·32 g)

Product	Conditions of reaction	Method of isolation [a]	Solvent for recrystallisation [b]	Product: % Yield	Product: M.p. (°C)	Product: Lit. m.p. (°C)
2-Amino-5-nitropyridine	50°, 3 h	A	1	63	184	184 [c]
2-Aminopyrimidine picrate	100°, 1 h	B	1	40	235—237 [d]	237—238 [e]
2-Amino-5-nitropyrimidine	50°, 15 min	C	2	47	235	236 [f]
4-Aminopyrimidine picrate	50°, 3 h	B	1	48	225	226 [g]
2-Aminoquinazoline	50°, 3 h	C	2	62	202—203	203—204 [h]
4-Aminoquinazoline	50°, 3 h	A	1	75	270	272—273 [h]
6-Amino-9-methylpurine	50°, 3 h	A	1	67	310	310 [i]

[a] Methods of isolation were as follows: A, the reaction mixture was chilled and the product filtered off; B, the reaction mixture was boiled and the picrate prepared with aqueous picric acid; C, the reaction mixture was evaporated to dryness and the product extracted into chloroform. [b] Solvents for recrystallisation were as follows: 1, water; 2, propan-2-ol. [c] A. Mangini and M. Colonna, *Gazzetta*, 1943, **73**, 313. [d] No depression of the m.p. was observed on admixture with an authentic specimen. [e] E. Büttner, *Ber.*, 1903, **36**, 2227. [f] W. J. Hale and H. C. Brill, *J. Amer. Chem. Soc.*, 1912, **34**, 82. [g] H. L. Wheeler, *J. Biol. Chem.*, 1907, **3**, 285. [h] H. J. Rodda, *J. Chem. Soc.*, 1956, 3509. [i] R. K. Robins and H. H. Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490.

TABLE 3

Reactions of trimethylammonio-compounds (0·020 g) with n-propylamine (1 ml)

Product	Conditions of reaction	Method of isolation [a]	Product: % Yield	Product: M.p. (°C)	Lit. m.p. (°C)	Analyses (%): Found C	Found H	Found N	Calc. C	Calc. H	Calc. N	Molecular formula
2-*n-Propylamino-5-nitropyridine*	50°, 3 h	A	60	91—92		53·4	6·4	23·1	53·0	6·1	23·2	$C_8H_{11}N_3O_2$
2-n-Propylaminopyrimidine picrate	100°, 1 h	B	32	150—151	151—152 [b]	42·4	4·0	23·0	42·6	3·85	22·95	$C_{13}H_{14}N_6O_7$
2-n-Propylamino-5-nitropyrimidine	20°, 5 min	C	72	116 [c]	119—119·5 [d]	45·9	5·7		46·15	5·5		$C_7H_{10}N_4O_2$
4-*n-Propylaminopyrimidine picrate*	50°, 3 h	B	71	160—161		42·4	3·9	22·9	42·6	3·85	22·95	$C_{13}H_{14}N_6O_7$
2-*n-Propylaminoquinazoline picrate*	50°, 3 h	B	67	187		49·0	4·1	20·1	49·0	3·9	20·2	$C_{17}H_{16}N_6O_7$
4-*n-Propylaminoquinazoline picrate*	50°, 3 h	B	67	205—206		47·4	3·9	19·2	47·0	4·2	19·4	$C_{17}H_{16}N_6O_7,H_2O$
9-*Methyl-2-n-propylaminopurine picrate*	100°, 6 h	B	60	226		42·65	4·1		42·9	3·8		$C_{15}H_{16}N_8O_7$
9-*Methyl-6-n-propylaminopurine picrate*	50°, 3 h	B	68	223—225		42·6	4·1		42·9	3·8		$C_{15}H_{16}N_8O_7$

[a] Methods of isolation were as follows: A, the reaction mixture was evaporated to dryness and the product extracted with, and recrystallised from, cyclohexane; B, the reaction mixture was evaporated to dryness and the product isolated as the picrate from ethanol; C, as in A except that the product was recrystallised from light petroleum (b.p. 60—80°). [b] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276. [c] Product dried at 80° for 1 hr. [d] E. Waletzky, U.S.P. 2,543,748 (*Chem. Abs.*, 1951, **45**, 5371).

TABLE 4

Reactions of trimethylammonio-compounds (0·020 g) with hydrazine hydrate

Product	Hydrazine hydrate: ml	Hydrazine hydrate: % soln.	Solvent for recryst. [a]	Product: % Yield	Product: M.p. (°C)	Lit. m.p. (°C)	Analyses (%): Found C	Found H	Found N	Calc. C	Calc. H	Calc. N	Molecular formua
2-Hydrazino-5-nitropyridine	1·0	49	1	73	207	205—206 [b]	39·1	4·2	36·4	39·0	3·9	36·4	$C_5H_6N_4O_2$
2-Hydrazinopyrimidine	1·5	32	2	79	108 [c]	108—110 [d]							
4-Hydrazinopyrimidine	0·5	98	2	71	132—134 †	132—134 [d] †							
2-Hydrazinoquinazoline	0·5	98	3	69	130—131	132—133 [e]	60·2	5·4		60·0	5·0		$C_8H_8N_4$
4-Hydrazinoquinazoline	1·0	49	3	67	187	186 [f]	60·2	5·1	35·1	60·0	5·0	35·0	$C_8H_8N_4$
2-*Hydrazino-9-methylpurine*	1·0	98	3	90	184—185 [g]		44·0	5·1	50·7	43·9	4·9	51·2	$C_6H_8N_6$
6-Hydrazino-9-methylpurine	1·0	49	4	33	211—212	210—211 [h]							

[a] Solvents for recrystallisation were: 1, ethanol; 2, benzene; 3, propan-2-ol; 4, methanol. [b] A. Mangini and B. Frenguelli, *Gazzetta*, 1939, **69**, 86. [c] No depression of the m.p. was observed on admixture with an authentic specimen. [d] J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 1955, 3478. [e] M. Claesen and H. Vanderhaeghe, *Bull. Soc. chim. belges*, 1957, **68**, 220. [f] M. J. S. Dewar, *J. Chem. Soc.*, 1944, 619. [g] Dried at 120° for 2 h. [h] R. K. Robins and H. H. Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490. † Decomp.

hexane to give 6-fluoro-9-methylpurine (0·006 g), m.p. 130—131°, identical (mixed m.p.) with an authentic specimen (lit.,[18] 125—127°).

Reaction of Trimethylammonio-compounds with Sodium Cyanide in Dimethylformamide.—*9-Methylpurine-6-carbonitrile.* 9-Methylpurin-6-yltrimethylammonium chloride

[18] A. G. Beaman and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 2310.

(0·100 g), sodium cyanide (0·100 g), and *NN*-dimethylformamide (5 ml) were heated at 50° for 2 h. The mixture was filtered and the filtrate evaporated to dryness. The residue was extracted with boiling hexane and on concentration gave the nitrile (0·025 g), m.p. 153—154° (lit.,[19] 153—154·5°) [Found (material dried at 100° for 1 h): C, 52·7; H, 3·4; N, 43·9. Calc. for $C_7H_5N_5$: C, 52·8; H, 3·2; N, 44·0%].

Quinazoline-4-carbonitrile.—A mixture of quinazolin-4-yltrimethylammonium chloride (0·08 g), sodium cyanide (0·08 g), and *NN*-dimethylformamide (2·5 ml) was heated at 50° for 1 h, filtered, and evaporated to dryness. The residue was extracted with boiling light petroleum (b.p. 60—80°) and the solution concentrated to give quinazoline-4-carbonitrile (0·034 g), m.p. 118° (lit.,[20] 118—119°).

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