515. *The Preparation and Reactions of 4-Amino-2-(carboxymethylthio)pyrimidines.*

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4-Amino-2-(carboxymethylthio)pyrimidines are prepared by treatment of 4-amino-2-mercaptopyrimidines with chloroacetic acid. These compounds are shown to be useful intermediates in the preparation of 4-amino-2-hydroxy-, 4-amino-, and 2 : 4-diamino-pyrimidines from 2 : 4-dimercaptopyrimidines *via* the 4-amino-2-mercaptopyrimidines.

The preparation of a series of 4-amino-2-mercaptopyrimidines, by the reaction of 2 : 4-dimercaptopyrimidines with ammonia and amines, was described by Russell, Hitchings, Elion, and Falco (*J. Amer. Chem. Soc.*, 1949, in the press). When the hydrolysis of the thiol group of such compounds by means of chloroacetic acid (Wheeler and Liddle, *Amer. Chem. J.*, 1908, **40**, 547) was attempted, the formation of the relatively stable 4-amino-2-(carboxymethylthio)pyrimidines occurred regularly. This was unexpected since Wheeler and Liddle (*loc. cit.*) had shown 4-hydroxy-2-(carboxymethylthio)pyrimidine to be decomposed to thioglycollic acid and uracil even by hot water and subsequent experience had indicated chloroacetic acid to be a general reagent for the desulphurization of thiopyrimidines (Wheeler and Liddle, *loc. cit.*; Johnson and Hemingway, *J. Amer. Chem. Soc.*, 1915, **37**, 380) and thiohydantoins (Johnson, Pfau, and Hodge, *J. Amer. Chem. Soc.*, 1912, **34**, 1041). Only pyrimidine-2 : 4-bisthioglycollic acid (Wheeler and Liddle, *loc. cit.*) had been found to be resistant to hydrolysis. On the other hand, a number of purines had been found to give stable thioglycollic acids (Johns and Hogan, *J. Biol. Chem.*, 1913, **14**, 299; Johns and Baumann, *ibid.*, 1914, **15**, 515).

Quite recently Bendich, Tinker, and Brown (*J. Amer. Chem. Soc.*, 1948, **70**, 3109) found that 4 : 6-diamino-2-(carboxymethylthio)pyrimidine separated when the desulphurization of 4 : 6-diamino-2-mercaptopyrimidine by means of chloroacetic acid was attempted. It would appear, therefore, that the stability of the 2-carboxymethylthio-grouping is markedly increased by the presence of an amino-, rather than a hydroxyl, group in position 4 (6) of the pyrimidine nucleus.

The 4-amino-2-(carboxymethylthio)pyrimidines have been found to be useful intermediates for the preparation of the 4-hydroxy-2-amino-, 4-amino-, and 2 : 4-diamino-pyrimidines from the corresponding 4-amino-2-mercaptopyrimidines.

The 4-amino-2-(carboxymethylthio)pyrimidines are stable to hot dilute or cold concentrated mineral acid. However, they may be hydrolysed by hot concentrated hydrochloric acid to the corresponding 4-amino-2-hydroxypyrimidines. Cytosine (4-amino-2-hydroxypyrimidine), 5-methylcytosine (Hitchings, Elion, Falco, and Russell, *J. Biol. Chem.*, 1949, **177**, 357), *N*-phenylcytosine (Russell *et al.*, *loc. cit.*), N-*tetradecylcytosine*, and N-*benzylcytosine* were prepared by this means.

The replacement of the thiol group of 4-amino-2-mercaptopyrimidines by hydrogen may be carried out by treatment in alcoholic solution with Raney nickel. However, the solubility of many of the 2-mercapto-derivatives is rather limited and conversion into the 2-carboxymethylthio-derivatives before reduction facilitates the reaction. 4-n-*Amylaminopyrimidine* and 4-piperidino-6-methylpyrimidine (isolated as its *picrate*) were prepared directly from the corresponding 2-mercapto-derivatives whilst 4-anilino- (Russell *et al.*, *loc. cit.*) and 4-p-*methoxyanilino-pyrimidine* were prepared *via* the carboxymethylthio-compounds.

4-Amino-2-(carboxymethylthio)pyrimidines react readily with ammonia or primary amines at 140—150°. Since the 4-amino-2-mercaptopyrimidines do not react in this way (Russell

et al., loc. cit.) the carboxymethylthio-derivatives are essential intermediates for the preparation of 2 : 4-diaminopyrimidines from the dimercapto-derivatives. Thus 4-anilino-2-mercaptopyrimidines gave no reaction with ammonia during 24 hours at 140° whilst under the same conditions 4-anilino-2-(carboxymethylthio)pyrimidine gave an 80% yield of 2-amino-4-anilinopyrimidine. 4-*Anilino*-2-*methylaminopyrimidine*, 4-*anilino*-2-*benzylaminopyrimidine*, 2-*amino*-4-*piperidinopyrimidine*, 2-*amino*-4-N-*methylpiperazinopyrimidine*, and 2-*amino*-4-n-*amylaminopyrimidine* were prepared by the same general method.

Experimental.

4-*Amino*-2-(*carboxymethylthio*)*pyrimidines*.—These compounds, listed together with their properties in the table, were prepared by heating under reflux the 4-amino-2-mercaptopyrimidine (1 mol.) in an aqueous solution of chloroacetic acid (1 mol.) until dissolution was complete. On cooling the product usually separated in a crystalline condition. The products so obtained were essentially pure but were crystallised once from a suitable solvent before analysis. If the base did not separate the aqueous

2-Carboxymethylthio-pyrimidine.	M. p.	Cryst. form and solvent.	Formula.	Analysis. Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
4-Amino 4-Amino-5-methyl	}	Hitchings *et al., loc. cit.*					
4-*Amino*-6-*methyl*	256° (decomp.)	Needles, water	$C_7H_9O_2N_3S$	41·9	4·8	42·2	4·5
4-*Tetradecylamino*	118—119	Plates, aq. alcohol	$C_{20}H_{34}O_2N_3S$	63·2	8·9	63·3	9·0
4-*Benzylamino*	109—111	Needles, methanol	$C_{13}H_{13}O_2N_3S$	58·2	4·6	58·4	4·6
4-Piperidino *hydrochloride*	199 (decomp.)	Prisms, aq. acetone	$C_{11}H_{16}O_2N_3SCl$	45·8	5·9	45·6	5·5
4-4′-Methylpiperazino *hydrochloride*	203—204 (decomp.)	Prisms, aq. acetone	$C_{11}H_{17}O_2N_4SCl$	43·0	5·3	43·4	5·3
4-*Anilino*	197 (decomp.)	Needles, water	$C_{12}H_{11}O_2N_3S$	54·9	4·1	55·2	4·2
Hydrochloride of above	above 250	Needles, dil. HCl	$C_{12}H_{12}O_2N_3SCl$	48·8	4·0	48·5	4·2
4-Anilino-5-methyl *hydrochloride*	210 (decomp.)	Nedeles, dil. HCl	$C_{13}H_{14}O_2N_3SCl$	50·3	4·3	50·3	4·5
4-*Anilino*-6-*methyl*	188—189	Needles, water	$C_{13}H_{13}O_2N_3S$	56·3	4·8	56·7	4·7
4-*Anisidino*	118—119	Needles, water	$C_{13}H_{13}O_3N_3S$	54·3	4·3	54·6	4·5

solution was concentrated to a syrup in an open dish on the steam-bath, and concentrated hydrochloric acid added. The resulting hydrochloride was recrystallised from aqueous acetone (1 : 1) or dilute hydrochloric acid.

2-*Amino*-4-*anilinopyrimidine*.—4-Anilino-2-(carboxymethylthio)pyrimidine (1 g.) (Russell *et al., loc. cit.*) was heated with ammonia solution (10 c.c., *d* 0·9) in a sealed tube at 140—150° for 24 hours. The tube was cooled and the contents concentrated to small bulk and made strongly alkaline with saturated sodium hydroxide solution. After being left for 2 hours the product was filtered off and recrystallised from aqueous alcohol. It formed long colourless needles (0·6 g.), m. p. 156—157° (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1131, gives m. p. 155—156°).

4-*Anilino*-2-*methylaminopyrimidine*.—This was prepared in the same way using a 25% aqueous methylamine solution in place of ammonia. The *hydrochloride* crystallised as needles, m. p. 246° (decomp.), from aqueous alcohol (Found : C, 55·7; H, 5·4. $C_{11}H_{13}N_4Cl$ requires C, 55·5; H, 5·5%).

2-*Amino*-4-*piperidinopyrimidine*.—This was prepared from the hydrochloride of the corresponding 2-carboxymethylthio-compound and ammonia. After recrystallisation from water the *pyrimidine* formed elongated plates, m. p. 142° (Found : C, 61·1; H, 7·5. $C_9H_{14}N_4$ requires C, 60·8; H, 7·9%).

2-*Amino*-4-N-*methylpiperazinopyrimidine*.—This *compound*, m. p. 184°, was similarly prepared (Found : C, 56·4; H, 7·4. $C_9H_{15}N_5$ requires C, 56·0; H, 7·8%).

4-*Anilino*-2-*benzylaminopyrimidine*.—4-Anilino-2-(carboxymethylthio)pyrimidine (1·5 g.) was heated with benzylamine (2 g.) at the boiling point for 20 hours. On cooling the mass solidified, and, after dilution with water and extraction with ether, a small amount of an unidentified crystalline product, m. p. 223—225° (after recrystallisation from alcohol) (Found : C, 71·7; H, 5·9%), remained undissolved. The ether solution was dried, and the ether removed, whereupon the resultant oil slowly solidified. After being washed with light petroleum (b. p. 40—60°) the *pyrimidine* was recrystallised from methyl alcohol and formed plates, m. p. 112—113° (1·2 g.; 75%) (Found : C, 73·6; H, 5·5. $C_{17}H_{16}N_4$ requires C, 73·7; H, 5·8%).

2-*Amino*-4-n-*amylamino*-6-*methylpyrimidine*.—4-*n*-Amylamino-2-mercapto-6-methylpyrimidine (1·5 g.) was heated under reflux with chloroacetic acid (0·7 g.) and water (10 c.c.) until dissolution was complete, and the solution was then concentrated to a syrup in an open dish on a steam-bath. The syrup was dissolved in concentrated ammonia (20 c.c.) and heated in a sealed tube at 140° for 24 hours. On cooling an oil separated which soon crystallised (1·2 g.). After recrystallisation from aqueous alcohol the *pyrimidine* formed colourless needles, m. p. 99°(Found : C, 61·8; H, 9·1. $C_{10}H_{18}N_4$ requires C, 61·8; H, 8·9%).

4-p-*Methoxyanilinopyrimidine*.—4-*p*-Methoxyanilino-2-(carboxymethylthio)pyrimidine (2·2 g.) was

heated under reflux in absolute alcohol (75 c.c.) with Raney nickel (6 g.) and sodium carbonate (0·5 g.) for 3 hours. The nickel was removed by filtration, the alcoholic solution concentrated to small bulk, and the residue diluted with water (100 c.c.) and left in the cold. The *product* (1·7 g.) separated as colourless needles which melted at 136—137° after recrystallisation from aqueous alcohol (Found: C, 65·6; H, 5·4. $C_{11}H_{11}ON_3$ requires C, 65·6; H, 5·5%).

4-n-*Amylaminopyrimidine*.—4-*n*-Amylamino-2-mercaptopyrimidine (0·9 g.) was heated under reflux with Raney nickel (2·5 g.) and sodium carbonate (0·5 g.) in absolute alcohol (25 c.c.) for 3 hours. The alcohol was removed by evaporation on a steam-bath and the residual oil solidified. It was distilled at 100—110° (bath temperature)/5×10^{-2} mm.; the distillate solidified to colourless rectangular prisms of the *pyrimidine* (0·5 g.), m. p. 61—62° (Found: C, 65·7; H, 9·0. $C_9H_{15}N_3$ requires C, 65·5; H, 9·1%).

4-*Piperidino*-6-*methylpyrimidine*.—This was prepared similarly. The oily product (65% yield) could not be obtained crystalline and so was converted into its *picrate*. This compound was recrystallised from alcohol containing some picric acid; it formed yellow needles, m. p. 172—173° (Found: C, 47·6; H, 4·4. $C_{16}H_{18}O_7N_6$ requires C, 47·3; H, 4·4%).

N-*Tetradecylcytosine* (4-*Tetradecylamino*-2-*hydroxypyrimidine*).—4-Tetradecylamino-2-(carboxymethylthio)pyrimidine (0·5 g.) was heated under reflux with concentrated hydrochloric acid (5 c.c.) for 3 hours. The cooled solution was made strongly alkaline with ammonia and the product separated. The precipitate crystallised from alcohol in colourless plates (0·3 g.), m. p. 178—180°, of the *cytosine* derivative (Found: C, 70·1; H, 10·5. $C_{18}H_{33}ON_3$ requires C, 70·4; H, 10·8%).

N-*Benzylcytosine* (4-*Benzylamino*-2-*hydroxypyrimidine*).—This was prepared in a similar manner, in 67% yield. Crystallised from water N-*benzylcytosine* formed colourless plates, m. p. 224° (Found: C, 65·3; H, 5·4. $C_{11}H_{11}ON_3$ requires C, 65·6; H, 5·5%).

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