PURINE DERIVATIVES. III.*

7-(2-ISOTHIOCYANATOETHYL)-8-ALKYLTHEOPHYLLINES

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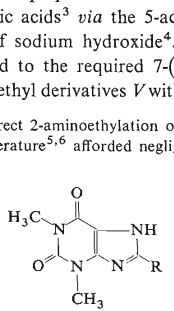
Numerous 7-(2-isothiocyanatoethyl)-8-alkyltheophyllines have been prepared by a multistep procedure from 8-alkyltheophyllines *via* the 7-cyanomethyl and 7-(2-aminoethyl) derivatives or *via* the 7-(2-hydroxyethyl)-, 7-(2-chloroethyl)-, and 7-(2-aminoethyl)-8-alkyltheophyllines. Ultraviolet and infrared spectra of these isothiocyanates and the corresponding intermediates have been recorded and interpreted.

In earlier papers[1,2] of this Series, the preparation and properties of some isothiocyanates have been reported, the isothiocyanato group of which was attached to a side chain placed at position 8 of the xanthine ring system. In compounds described in the present paper, the isothiocyanato group is attached to a side chain placed at position 7 of the xanthine system. The synthesis of the title 7-(2-isothiocyanatoethyl)-8-alkyltheophyllines has been effected as follows. The starting 8-alkyltheophyllines *I* have been prepared from 1,3-dimethyl-4,5-diaminouracil and the corresponding carboxylic acids[3] *via* the 5-acylamino derivatives which have been cyclized by the action of sodium hydroxide[4]. The thus-obtained 8-alkyltheophyllines *I* have been converted to the required 7-(2-isothiocyanatoethyl)-8-alkyltheophyllines *VI* *via* the 2-aminoethyl derivatives *V* with the use of several procedures.

The direct 2-aminoethylation of theophylline by means of ethyleneimine as reported in the patent literature[5,6] afforded negligible yields of the required amines *Vb* and *Vc* when applied



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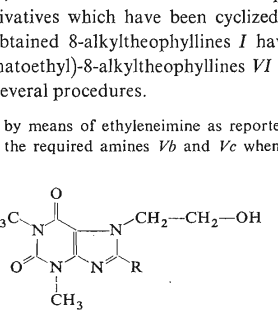
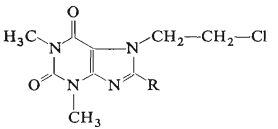


II

* Part II: This Journal *37*, 2630 (1972).



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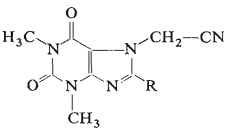

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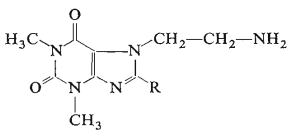

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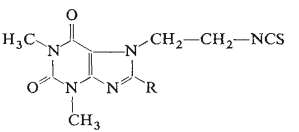


VI

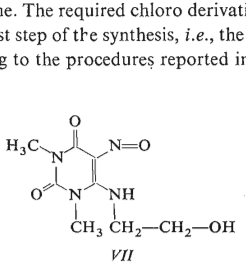
to 8-methyl- and 8-ethyltheophylline. The attempted introduction of the 2-aminoethyl group into the 8-alkyltheophylline ring system by means of the 2-bromoethylphthalimide method consisting in heating the reaction components[7] above 200°C or with the use of dimethylformamide as the reaction medium, at a lower temperature, also did not meet with success. In the presence of bulky substituents at position 8 (*e.g.*, n-butyl or benzyl), the 2-bromoethylphthalimide reaction does not take place at all. In those cases, when some 8-substituted 7-(2-phthalimidoethyl)theophylline was obtained, additional difficulties were encountered in its hydrazinolysis. Thus, the hydrazinolysis of 7-(2-phthalimidoethyl)-8-methyltheophylline affords only about 10% of the corresponding 2-aminoethyl derivative. The procedure consisting in ammonolysis of the corresponding 8-substituted 7-(2-chloroethyl)theophyllines *III* led to the amines *Va*, *Vb* and *Vc* the yields of which strongly decreased with the increasing bulk of the substituent at position 8. In comparison with 7-(2-aminoethyl)theophylline (*Va*) and the 8-methyl derivative *Vb*, the preparation of 7-(2-aminoethyl)-8-ethyltheophylline (*Vc*) required the use of strongly concentrated ethanolic ammonia (43—45% instead of 13—14%) and a longer reaction period of time. When a lower concentration of the ethanolic ammonia was used, the yield rapidly decreased. The attempted ammonolysis of 8-n-propyl-(*IIId*) and 8-n-butyl-7-(2-chloroethyl)theophylline (*IIIe*) failed under various reaction conditions investigated, *e.g.* with the use of 58—60% ammonia solution, prolonged reaction periods of time or at temperatures of 40—130°C, only the starting chlorides *IIId* and *IIIe* being recovered.

The best results were obtained by the fourth route, namely, by hydrogenation of 7-cyanomethyl-8-alkyltheophyllines *IV* over Raney cobalt in the medium of ethanol. The yields of the resulting 7-(2-aminoethyl) derivatives *V* varied in the range of 30 to 53%. The susceptibility of the nitrile group of the cyanomethyl derivatives *IV* to hydrogenation does not appear to depend to such an extent on the bulk of substituents at position 8 of the 7-cyanomethyltheophylline system as in the case of the preceding three method, except for the benzyl derivative *IVf*. The cyanomethyl intermediates *IV* were prepared by two routes. The first route consisted in cyanomethylation of 8-alkyltheophyllines with chloroacetonitrile in dimethylformamide in the presence of potassium carbonate. This route has been reported in the patent literature[8] for the parent

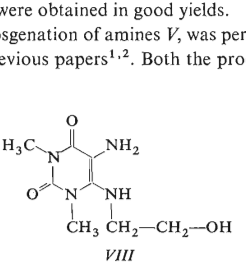
7-cyanomethyltheophylline. The second route comprised conversion (by the action of sodium methoxide) of the corresponding 8-alkyltheophylline to the sodium salt and reaction of the latter with chloroacetonitrile in dimethylformamide. Comparison of yields obtained by the potassium carbonate method and the sodium methoxide method is given in the Experimental Part. In the case of 8-benzyltheophylline, the sodium methoxide procedure is unequivocally the method of choice.

The required 7-(2-chloroethyl)-8-alkyltheophyllines for the ammonolysis to amines *V* were prepared from 8-alkyltheophyllines *via* 7-(2-hydroxyethyl)-8-alkyltheophyllines. The 2-hydroxyethylation of theophylline, theobromine and other 1,3- or 3,7-dialkylxanthines with ethylene chlorohydrin and ethylene oxide has been reported in detail by several authors[9–11]. These procedures, however, did not prove satisfactory with higher 8-alkyltheophyllines, especially because of the difficult isolation and separation of the resulting 7-(2-hydroxyethyl)-8-alkyltheophyllines from the starting material. As determined by chromatography of the 2-hydroxyethylation products, the quantitative alkylation of 8-alkyltheophyllines (alkyl = methyl to n-butyl) may be achieved in those cases when ethylene chlorohydrin is added in a 100% excess together with aqueous sodium hydroxide in small portions or at least in two portions. Other alkylation methods did not meet with success, *e.g.*, treatment of 8-alkyltheophyllines with ethylene chlorohydrin in dimethylformamide in the presence of potassium carbonate or of sodium salts of 8-alkyltheophyllines in dimethylformamide. The 7-(2-hydroxyethyl) derivatives were converted successfully into the 7-(2-chloroethyl)-8-alkyltheophyllines *III* analogously to the preparation of 7-chloroethyltheophylline[9], namely, by the action of thionyl chloride on the hydroxy derivatives *II* in benzene. The required chloro derivatives *III* were obtained in good yields.

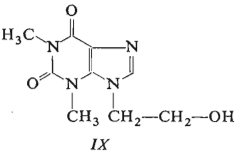
The last step of the synthesis, *i.e.*, the thiophosgenation of amines *V*, was performed according to the procedures reported in our previous papers[1,2]. Both the procedures



VII



VIII



IX

starting either from the amine hydrochloride or from the free base afforded the required 7-(2-isothiocyanatoethyl)-8-alkyltheophyllines *VI* in yields higher than 62% except for the n-butyl (*VIe*) and the benzyl (*VIf*) derivatives where the lower yields are due to a great solubility in all suitable solvents.

Formation of the 7-substituted (and not of the 9-substituted) 8-alkyltheophylline derivatives in alkylations of 8-alkyltheophyllines with ethylene chlorohydrin or chloroacetonitrile was proved by the synthesis of the authentic 9-(2-hydroxyethyl)isotheophylline (*IX*) and comparison of its ultraviolet spectrum with those of caffeine, the cyanomethyl derivatives and the 2-hydroxyethyl derivatives. The close resemblance of ultraviolet spectra of the cyanomethyl and 2-hydroxyethyl derivatives with that of caffeine and their difference from that of the 9-substituted derivative *IX* clearly prove that the substituted hydrocarbon residue is attached to position 7 of the 8-alkyltheophylline system (and not to position 9).

The synthesis of compound *IX* is reported in the patent literature[12]. Thus, reduction of 1,3-dimethyl-4-(2-hydroxyethylamino)-5-nitrosouracil (*VII*) affords 1,3-dimethyl-4-(2-hydroxyethylamino)-5-aminouracil (*VIII*) which is condensed with carbon disulfide in pyridine to give, 1,3-dimethyl-8-mercapto-9-(2-hydroxyethyl)isotheophylline. Desulfurization of the latter compound over Raney nickel in an aqueous medium leads to the required compound *IX*. In our hands, this procedure gave the final product in yields less than 10%. A considerably higher yield of the 9-(2-hydroxyethyl) derivative *IX* was obtained by a modified procedure consisting in conversion of the amino derivative *VIII* to compound *IX* with the use of triethyl orthoformate.

The ultraviolet spectra of the hydroxy derivatives *II*, the chloro derivatives *III*, the nitriles *IV*, the amines *V*, and the isothiocyanates *VI* were recorded in the 200 to 360 nm region. The spectra exhibit two characteristic bands at 209–212 nm and at 274–279 nm. The first band corresponds to the "*y*" band of simple purines and the second band to the "*x*" band of simple purines[13]. It may be seen from Table I that replacement of the hydrogen atom at position 8 of compounds *II* to *VI* by a benzyl group results in a very low bathochromic shift (about 2–3 nm). The molar extinction coefficient value of the "*y*" band is about 2–3 times as great as with the "*x*" band. The differences between the "*y*" band values within the above groups of compounds are most striking on comparison of the theophylline derivatives (*Va*, *VIa*) with the remaining 8-alkyltheophylline derivatives (*Vb*, *Vc etc.*). The *y*-bands of theophylline derivatives show the lowest ε value; on the other hand, the 8-benzyltheophylline derivatives (*Vf*, *VIf etc.*) exhibit the highest ε value. An analogous but less pronounced dependence may be observed on comparison of the ε values of *x*-bands.

The infrared spectra of compounds *II*–*VI* (at 3700–650 cm^{-1}) exhibit several characteristic bands. Thus, the two bands at 1710–1690 cm^{-1} (vs)* are ascribable to ν(CO) at position 2 of the xanthine system, at 1660–1650 cm^{-1} (vs) are ascribed to ν(CO) at position 6, and the shoulder or band at 1610 cm^{-1} (w) is due to ν(C:C)

* Abbreviations: vs, very strong; s, strong; w, weak.

TABLE I

Properties of 7-Substituted 8-Alkyltheophyllines (alkyl: *a* H, *b* CH_3, *c* C_2H_5, *d* n-C_3H_7, *e* n-C_4H_9, *f* $C_6H_5CH_2$)

Compound	Formula (mol.weight)	Calculated/Found %C	%H	%N	%Cl or S	M.p., °C (solvent)	λ_{max}, nm ($\varepsilon . 10^{-3}$)	λ_{min}, nm ($\varepsilon . 10^{-3}$)	λ_{max}, nm ($\varepsilon . 10^{-3}$)
IIb	$C_{10}H_{14}N_4O_3$ (238·2)	50·49 / 50·70	5·92 / 5·76	23·52 / 23·44	—	181—182·5 (ethanol)	210 (21·8)	246 (2·6)	275 (10·7)
IIc	$C_{11}H_{16}N_4O_3$ (252·3)	52·37 / 52·69	6·39 / 6·17	22·21 / 22·04	—	162·5—163·5 (ethanol)	210 (22·5)	247 (2·5)	276 (10·8)
IId	$C_{12}H_{18}N_4O_3$ (266·3)	54·12 / 54·38	6·81 / 6·92	21·04 / 21·38	—	154—155·5 (benzene)	210 (23·0)	247 (2·5)	276 (11·1)
IIe	$C_{13}H_{20}N_4O_3$ (280·3)	55·70 / 55·63	7·19 / 7·09	19·99 / 19·74	—	149—150·5 (benzene)	210 (22·7)	247 (2·8)	276 (11·4)
IIIb	$C_{10}H_{13}ClN_4O_2$ (256·7)	46·79 / 46·60	5·10 / 5·02	21·83 / 21·90	13·81 / 13·99	173—174·5 (ethanol)	210 (21·8)	246 (2·4)	275 (10·2)
IIIc	$C_{11}H_{15}ClN_4O_2$ (270·7)	48·80 / 49·03	5·59 / 5·70	20·70 / 20·66	13·10 / 13·50	148—149 (ethanol)	210 (23·6)	247 (2·7)	276 (11·2)
IIId	$C_{12}H_{17}ClN_4O_2$ (284·7)	50·61 / 50·79	6·02 / 6·19	19·68 / 19·51	12·45 / 12·71	120—122 (tetrachloromethane)	210 (24·2)	247 (2·5)	276 (11·3)
IIIe	$C_{13}H_{19}ClN_4O_2$ (298·8)	52·26 / 52·50	6·41 / 6·70	18·75 / 18·61	11·87 / 11·97	157·5—159 (methanol)	210 (24·0)	247 (2·5)	277 (11·3)
IVb	$C_{10}H_{11}N_5O_2$ (233·2)	51·49 / 51·80	4·75 / 4·67	30·03 / 29·91	—	235·5—238 (chloroform)	210 (21·8)	246 (2·0)	276 (10·0)
IVc	$C_{11}H_{13}N_5O_2$ (247·3)	53·43 / 53·71	5·30 / 5·57	28·33 / 28·34	—	174·5—176·5 (benzene)	210 (22·6)	246 (2·1)	276 (10·4)
IVd	$C_{12}H_{15}N_5O_2$ (261·3)	55·16 / 54·99	5·79 / 5·92	26·81 / 26·71	—	137—139 (chloroform–heptane)	210 (24·2)	246 (2·4)	277 (10·6)
IVe	$C_{13}H_{17}N_5O_2$ (275·3)	56·71 / 56·53	6·22 / 6·08	25·44 / 25·42	—	128—130 (tetrachloromethane)	210 (24·0)	246 (2·4)	277 (10·9)

IVf	$C_{16}H_{15}N_5O_2$	62·12	4·89	22·64	—	141·5—142	212	247	278
	(309·3)	62·52	5·10	22·48		(tetrachloromethane)	(31·3)	(2·5)	(11·3)
Va	$C_9H_{13}N_5O_2$	48·42	5·87	31·38	—	143·5—145[c]	209	246	274
	(223·2)	48·62	5·86	31·54		(benzene)	(20·1)	(2·1)	(8·6)
Vb	$C_{10}H_{15}N_5O_2$	50·62	6·37	29·52	—	139·5—142	209	247	275
	(237·3)	50·71	6·45	29·41		(benzene)	(20·6)	(2·3)	(9·7)
Vc	$C_{11}H_{17}N_5O_2$	52·57	6·82	27·86	—	106—108·5	210	247	276
	(251·3)	52·72	6·66	28·03		(benzene)	(21·7)	(2·5)	(10·0)
Vd.HCl	$C_{12}H_{20}ClN_5O_2$	47·76	6·68	23·21	11·75	273—275·5[a]	211	248	277
	(301·8)	47·82	6·70	23·15	11·88	(ethanol)	(22·8)	(2·3)	(10·1)
Ve	$C_{13}H_{21}N_5O_2$	55·53	7·58	25·07	—	85·5—87·5[b]	211	248	277
	(279·3)	55·27	7·38	24·96		(tetrachloromethane)	(22·3)	(2·5)	(10·5)
Vf.HCl	$C_{16}H_{20}ClN_5O_2$	54·93	5·76	20·02	10·14	251—253	212	249	279
	(349·8)	54·75	5·57	20·03	10·12	(1-propanol)	(29·2)	(2·7)	(10·8)
VIa	$C_{10}H_{11}N_5O_2S$	45·27	4·18	26·40	12·09	186—188	209	245	274
	(265·3)	45·47	4·25	26·30	11·87	(tetrachloromethane)	(20·8)	(3·1)	(8·1)
VIb	$C_{11}H_{13}N_5O_2S$	47·30	4·69	25·08	11·48	188—189·5	210	246	275
	(279·3)	47·36	4·58	24·89	11·57	(tetrachloromethane)	(22·0)	(3·2)	(9·5)
VIc	$C_{12}H_{15}N_5O_2S$	49·13	5·15	23·88	10·93	158—158·5	210	247	276
	(293·3)	48·97	5·02	23·96	10·80	(tetrachloromethane)	(22·9)	(2·1)	(9·7)
VId	$C_{13}H_{17}N_5O_2S$	50·80	5·58	22·79	10·43	120·5—121·5	210	248	277
	(307·4)	50·41	5·58	22·57	10·69	(benzene)	(23·4)	(3·3)	(10·2)
VIe	$C_{14}H_{19}N_5O_2S$	52·32	5·96	21·79	9·98	133—134	210	248	277
	(321·4)	52·41	5·96	21·75	10·11	(tetrachloromethane-hexane)	(23·3)	(3·3)	(10·2)
VIf	$C_{17}H_{17}N_5O_2S$	57·45	4·82	19·17	9·02	156·5—158·5	211	249	278
	(355·4)	57·27	4·72	19·75	9·10	(benzene)	(30·7)	(3·4)	(10·3)

[a] The free base, m.p. 91·0—92·5°C; [b] the hydrochloride, m.p. 255·0—257·5°C; [c] reported, m.p. 143—144°C (ref.[6]) and 144—146°C (ref.[18]).

and ν(C:N), *cf.* refs[1,14]. The group of three bands in the 3000–2800 cm^{-1} (w) region is ascribed to the stretching vibrations of the C—H bond, *cf.* refs[15,16]. The nitriles *IV* exhibit a narrow band at 2380–2370 cm^{-1} (vw). The hydroxy derivatives *II* show a broad band at 3150 cm^{-1} (w) corresponding to the stretching vibrations of the associated O—H bond and a band at 3630 cm^{-1} (w) corresponding to the stretching vibrations of the free O—H bond. The broad band at 3150 cm^{-1} (w) of amines *V* is ascribable to the stretching vibrations of the associated N—H bond. With the isothiocyanates *VI*, the broad band at 2110–2100 cm^{-1} (s) and the narrow band at 2230–2220 cm^{-1} (w) are characteristic of isothiocyanates attached to an aliphatic hydrocarbon residue.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried over P_2O_5 or 5 h at 70°C and at less then 1 Torr. IR spectra were recorded on a Zeiss UR-20 apparatus. UV spectra were measured on a Zeiss Specord UV VIS apparatus.

7-(2-Hydroxyethyl)-8-alkyltheophyllines (*II*)

The corresponding 8-alkyltheophylline *I* (50 mmol) was dissolved in 45 ml of aqueous sodium hydroxide (2·0 g; 50 mmol). The solution was treated dropwise through the reflux condenser with ethylene chlorohydrin (4·1 g; 3·4 ml; 50 mmol). The mixture was refluxed for 90 min, cooled down to room temperature, and treated with additional sodium hydroxide (2·0 g; 50 mmol) in a minimum of water and then (through the reflux condenser) with additional ethylene chlorohydrin (4·1 g; 3·4 ml; 50 mmol). The refluxing was continued for further 90 min. The content of the flask was evaporated under diminished pressure to dryness and the residue extracted with boiling benzene. The benzenic extract was evaporated to deposit the crystalline product. The following compounds were obtained by this procedure (alkyl at position 8 and % yield given): methyl (*IIb*), 50·9%; ethyl (*IIc*), 38·8%; n-propyl (*IId*); 77·6%; n-butyl (*IIe*), 29·1%. The analytical samples were obtained by an additional crystallisation from a suitable solvent.

7-(2-Chloroethyl)-8-alkyltheophyllines (*III*)

A mixture of thionyl chloride (12·0 g; 7·4 ml; 0·10 mol) and benzene (15 ml) was added portionwise to the corresponding 7-(2-hydroxyethyl)-8-alkyltheophylline (*II*; 27 mmol) in benzene and the resulting mixture refluxed for 3 h. The excess thionyl chloride and benzene were distilled off under diminished pressure. The crude residue was recrystallised from ethanol. The following chloro derivatives *III* were obtained by this procedure (alkyl at position 8 and % yield given): methyl (*IIIb*), 75·5%; ethyl (*IIIc*), 76·7%; n-propyl (*IIId*), 89·9%; n-butyl (*IIIe*), 69·4%. The analytical samples were obtained by an additional crystallisation from a suitable solvent.

7-Cyanomethyl-8-alkyltheophyllines (*IV*)

Procedure A. Chloroacetonitrile (10·0 g; 8·4 ml; 0·13 mol) was added to a suspension of the appropriate 8-alkyltheophylline *I* (0·1 mol), potassium carbonate (6·9 g; 0·05 mol), and dimethylformamide (90 ml) and the temperature of the mixture was raised in the course of 40–45 minutes to the value of 140°C. At this temperature, the heating bath was removed, the mixture allowed to cool to about 100°C, and the inorganic salts filtered off. The material on the filter was washed

with hot dimethylformamide (100 ml). The filtrate and washings were combined and evaporated under diminished pressure to dryness. The residue was crystallised from chloroform (compounds *IVb* and *IVc*) or chloroform–heptane (*IVd*, *IVe*).

Procedure B. The appropriate 8-alkyltheophylline *I* (10 mmol) was dissolved in the necessary amount of refluxing ethanol or 2-propanol. The resulting solution was cooled down to about 40°C and treated with 5 ml of methanolic sodium methoxide (10 mmol). The reaction mixture was evaporated under diminished pressure to dryness. A suspension of the residual salt in dimethylformamide (40 ml) was then treated under stirring with chloroacetonitrile (8·3 g; 0·77 ml; 11 mmol). The resulting mixture was heated under continuous stirring at 100°C for one hour and then evaporated under diminished pressure. The dry residue was then extracted with hot benzene or hot chloroform. The required cyanomethyl derivatives were obtained by evaporation of the benzenic (compounds *IVc*, *IVd*, *IVf*) or chloroform (*IVb*) extract to a small volume. With compound *IVe*, the benzenic extract was concentrated and the concentrate precipitated by the addition of hexane.

The following nitriles *IV* were obtained by these general procedures (alkyl at position 8, procedure, and % yield given): methyl (*IVb*), *A*, 37·3%, *B*, 69·5%; ethyl (*IVc*), *A*, 70·6%, *B*, 5·2%; n-propyl (*IVd*), *A*, 81·7%, *B*, 59·7%; n-butyl (*IVe*), *A*, 42·1%, *B*, 42·5%; benzyl (*IVf*), *B*, 40·7%. The analytical samples were prepared by an additional crystallisation from a suitable solvent.

7-(2-Aminoethyl)-8-alkyltheophyllines (*V*)

Procedure A. The appropriate 7-cyanomethyl-8-alkyltheophylline *IV* (25 mmol) was hydrogenated in a rocking autoclave (volume 250 ml) in ethanol (130 ml) over Raney cobalt (2·0—6·0 g) for 10—12 hours at 70—120°C/120—150 atm. The content of the autoclave was allowed to cool, the catalyst was filtered off, and the filtrare was evaporated under dimished pressure to dryness. The crude amine was purified either in the form of the free base or *via* the hydrochloride. The free base was recrystallised from benzene (compound *Vb*) or chromatographed on a column of alumina (Brockman activity VI) and eluted with chloroform (*Va*), benzene (*Ve*), 1 : 1 chloroform–tetrachloromethane (*Vc*), or 99 : 1 benzene–methanol (*Vd*). Purification through hydrochlorides: The crude amine was dissolved in a little ethanol, the solution acidified to pH 2 with concentrated hydrochloric acid, evaporated under diminished pressure to dryness, the residue dissolved in water, the aqueous solution filtered with active charcoal, the filtrate evaporated under diminished pressure to dryness, and the residual hydrochloride recrystallised from 1-propanol (*Ve*.HCl; *Vf*.HCl) or first extracted with 1-propanol and then recrystallised from ethanol (*Vd*.HCl). The following amines were obtained by this procedure (substituent at position 8, temperature, pressure, time, and % yield given): hydrogen (*Va*), 70—80°C, 120 atm, 52·4% (base); methyl (*Vb*), 80—90°C, 130 atm, 10 hours, 47·4% (base); ethyl (*Vc*), 90—100°C, 130 atm, 12 hours, 30·7% (base); n-propyl (*Vd*), 100—110°C, 140 atm, 12 hours, 47·7% (base), 48·6% (hydrochloride); n-butyl (*Ve*), 100—110°C, 150 atm, 10 hours, 53·4% (base), 30·0% (hydrochloride); benzyl (*Vf*), 110—120°C, 140 atm, 12 hours, 32·6% (hydrochloride).

Procedure B. A precooled autoclave was charged with the appropriate 7-(2-chloroethyl)-8-alkyltheophylline *III* (23 mmol) and ethanolic ammonia (120 ml). The content was heated at 125—135°C (c. 30 atm), allowed to cool, evaporated under diminished pressure to dryness, the residue dissolved in aqueous ammonia (40 ml), the solution filtered, the filtrate extracted with five 30 ml portions of chloroform, the extract dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on a column of alumina (Brockman activity VI) and the purified product eluted with chloroform (compounds *Va* and *Vb*) or with 88 : 11 : 1 benzene–chloroform–methanol (*Vc*). The following amines *V* were obtained by this procedure (substituent at position 8, concentration of ethanolic ammonia, time of heating, and % yield given): hydrogen

(*Va*), 13—14% NH_3, 3 h, 80·1%; methyl (*Vb*), 13—14% NH_3, 3 h, 31·5%; ethyl (*Vc*), 43—45% NH_3, 12 h, 19·8%. For the properties of all compounds see Table I.

7-(2-Isothiocyanatoethyl)-8-alkyltheophyllines (*VI*)

Procedure A. A solution of the appropriate 7-(2-aminoethyl)-8-alkyltheophylline *V* (7·3 mmol) in chloroform (10—15 ml) was added over 5 minutes under cooling with ice-cold water and stirring to a mixture of thiophosgene (7·4 mmol; 0·89 g; 0·60 ml), calcium carbonate (11 mmol; 1·1 g), chloroform (15—10 ml), and water (5—6 ml). The resulting emulsion was stirred at room temperature for 6 hours and kept overnight. The excess calcium carbonate was filtered off and the layers were separated. The chloroform layer was evaporated under diminished pressure to dryness and the residue chromatographed on a column of alumina (Brockman activity VI) and eluted with benzene (compounds *VIb*, *VIc*, and *VId*).

Procedure B. A solution of the corresponding 7-(2-aminoethyl)-8-alkyltheophylline hydrochloride *V*.HCl (10 mmol) in water (25—35 ml) was added over 5 minutes under cooling with ice-cold water and stirring to a mixture of thiophosgene (10·05 mmol; 1·22 g; 0·82 ml), calcium carbonate (16 mmol; 1·6 g), and chloroform (70 ml), and the whole was stirred at room temperature for 6 h. The excess calcium carbonate was then filtered off and the layers were separated. The chloroform layer was dried over calcium chloride, evaporated to dryness under diminished pressure, and the residue either crystallised from tetrachloromethane (compound *VIa*) or purified by chromatography on a column of alumina (Brockman activity VI) with the use of benzene as eluant (*VIe*, *VIf*).

The following isothiocyanates were obtained by these procedures (substituent at position 8, procedure, and % yield given): hydrogen (*VIa*), *B*, 56·2%; methyl (*VIb*), *A*, 77·1%; ethyl (*VIc*), *A*, 62·7%; n-propyl (*VId*), *A*, 82·5%; n-butyl (*VIe*), *B*, 33·1%; benzyl (*VIf*), *B*, 41·7%. For the properties see Table I.

1,3-Dimethyl-4-(2-hydroxyethylamino)-5-nitrosouracil (*VII*)

1,3-Dimethyl-4-(2-hydroxyethylamino)uracil[17] (8·2 g; 41 mmol) was dissolved in refluxing methanol (30 ml), the solution cooled to 35°C, and treated portionwise through the reflux condenser with freshly distilled n-propyl nitrite (16·1 g; 17·6 ml; 0·181 mol) and two drops of concentrated hydrochloric acid. The resulting mixture was heated for 30 min at 40°C to deposit red needles. The next day, the product was collected with suction, washed at 0°C with precooled methanol, and dried under diminished pressure. Yield, 6·3 g (67·4%) of compound *VII*, m.p. 175—177°C (reported[17], m.p. 180—181°C).

9-(2-Hydroxyethyl)isotheophylline (*IX*)

1,3-Dimethyl-4-(2-hydroxyethylamino)-5-nitrosouracil (6·1 g; 0·268 mol) was hydrogenated at ordinary pressure in methanol (150 ml) over Raney nickel (2·8 g of the moist specimen). When the theoretical amount of hydrogen was taken up, the catalyst was filtered off and the filtrate evaporated under diminished pressure to dryness to afford the crude glassy amine *VIII* in an almost quantitative yield. A mixture of the crude amine *VIII* (428 mg; 2·0 mmol) and triethyl orthoformate (6·6 g; 5·9 ml; 44·8 mmol) was treated under cooling with tap water and stirring with conc. HCl (0·15 ml), the whole shaken at room temperature for 50 h, and evaporated under diminished pressure. The residue was crystallised from a minimum amount of water to deposit after prolonged standing light yellow needles of compound *IX*, m.p. 271·5—273°C (reported[12],

m.p. 271—273°C); yield, 192 mg; 42·7%. Ultraviolet spectrum (water), λ_{max} in nm ($\varepsilon \cdot 10^{-3}$): 206 (26·8), 239 (9·4), 269 (11·6).

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