PURINE DERIVATIVES. IV.*

7-(3-ISOTHIOCYANATOPROPYL)-8-ALKYLTHEOPHYLLINES

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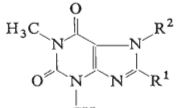
A series of 7-(3-isothiocyanatopropyl)-8-alkyltheophyllines was synthetized from 8-alkyltheophyllines *via* 7-(2-cyanoethyl) and 7-(3-aminopropyl) derivatives. The IR and UV spectra of the prepared substances were measured and interpreted.

In connection with the study of isothiocyanates of the xanthine series we also prepared and investigated the substances which have, in contrast to earlier prepared isothiocyanates of this series, the isothiocyanate group bound to the purine nucleus by means of a chain of three methylene groups. Their preparation was carried out as follows:



I, $R^2 = H$
II, $R^2 = CH_2CH_2CN$
III, $R^2 = CH_2CH_2CH_2NH_2$
IV, $R^2 = CH_2CH_2CH_2—N=C=S$
V, $R^2 = CH_2CH_2CH_2OH$
VI, $R^2 = CH_2CH_2CH_2Cl$

In formulae *I*—*IV*: for *a*, $R^1 = H$; *b*, $R^1 = CH_3$; *c*, $R^1 = C_2H_5$; *d*, $R^1 = n\text{-}C_3H_7$; *e*, $R^1 = n\text{-}C_4H_9$; *f*, $R^1 = C_6H_5CH_2$.

The starting 8-alkyltheophyllines *I* were prepared according to[1,2]. By their cyanoethylation we obtained 7-(2-cyanoethyl)-8-alkyltheophyllines *II* which gave on reduction 7-(3-aminopropyl)-8-alkyltheophyllines *III* necessary for the synthesis of final isothiocyanates *IV*. In literature cyanoethylation of theophylline itself is described. It was carried out by heating theophylline and acrylonitrile at 150°C in pyridine, in the presence of sodium methoxide and copper(II) sulfate[4], as well as by refluxing theophylline in excess acrylonitrile under catalysis with Triton B. In the case of

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8-alkyltheophyllines (where alkyl is methyl to n-butyl or benzyl) the first procedure (*A*) generally afforded lower yields (nitriles *IIb*, *IIc*, *IId* < 20%). The second procedure could not be used in the case of 8-alkyltheophyllines because the 8-substituted 7-(2-cyanoethyl)theophylline formed separated from the reaction mixture before the remaining 8-alkyltheophylline could dissolve in acrylonitrile. For this reason we dissolved the corresponding 8-alkyltheophylline first in pyridine or dimethyl sulfoxide (in the case of 8-n-propytheophylline also dioxan) and only then added acrylonitrile and the catalyst to this solution (procedure *B*). As we intended to transform the 7-(2-cyanoethyl) derivate *II* formed to the corresponding 7-(3-aminopropyl) derivative *III* by hydrogenation, we abandoned the use of dimethyl sulfoxide as solvent, although the yields of nitriles *II* were good when it was employed.

In the literature[3] hydrogenation of 7-(2-cyanoethyl)theophylline on Raney nickel in methanolic ammonia has been described. This procedure gave lower yields in the case of 8-alkyl derivatives *II* than the hydrogenation on Raney cobalt in the absence of ammonia, described earlier for the preparation of 7-(3-aminopropyl)theophylline[4] itself. The nitrile group in 7-(2-cyanoethyl)-8-alkyltheophyllines is reduced with relative difficulty (8–12 hours, 90–120°C, 100–150 atm). In addition to the mentioned procedures we also tried hydrogenation on PtO_2 and lithium aluminum hydride reduction. Here, however, mixtures of amine, the by-products and the unreacted nitrile are formed, which do not separate well. The applied hydrogenation on Raney cobalt gave 43–78% yields of 7-(3-aminopropyl)-8-alkyltheophyllines in the form of hydrochlorides. Lower yields of 8-methyl (*IIIb*) and 8-benzyl derivative (*IIIf*) are not caused by imperfect reduction of the starting nitrile, but by the difficult isolation of these substances. Free bases of these amines could be isolated only in several cases; even then the purity was low, mainly due to unusual solubility and low thermal stability in common solvents.

The final 7-(3-isothiocyanatopropyl)-8-alkyltheophyllines *IV* were prepared from amines or aminehydrochlorides *III* by thiophosgene method in aqueous chloroformic medium in the presence of an excess of calcium carbonate which bound the liberated hydrogen chloride. In order to obtain pure products crude isothiocyanates *IV* had to be chromatographed on alumina.

The second method of synthesis of the required 7-(3-aminopropyl) derivatives was employed only in the case of theophylline itself. From the sodium salt of theophylline we prepared 7-(3-hydroxypropyl)theophylline *V* with its subsequent conversion to the 7-(3-chloropropyl)theophylline *VI*. On its ammonolysis amine *IIIa* was formed, identical with the product obtained on reduction of 7-(2-cyanoethyl)-theophylline. Alkylation of the sodium salt of theophylline was carried out using a small excess of 3-chloropropanol in dimethylformamide at 90–100°C (4 hours). At lower temperatures the yields of hydroxy derivative *V* drop rapidly (for example, at 40°C the yield was only approx. 7% even at a 20 h reaction time). The transformation of hydroxy derivative *V* to chlorine derivative *VI* was carried out with thionyl

chloride in benzene in good yield. Unfortunately, the last step – ammonolysis of chloro derivative *VI* to 7-(3-aminopropyl)theophylline *IIIa* – did not take place as satisfactorily. In order to achieve at least a 60% yield of amine *IIIa*, it was necessary to carry out the ammonolysis of chloro derivative with at least 30% ethanolic ammonia at 125–135°C. In view of this fact, as well as with respect to the poor experiences with the ammonolysis of 7-(2-chloroethyl)-8-alkyltheophyllines[8] we did not carry out the preparation and the ammonolysis of 7-(3-chloropropyl)-8-alkyltheophyllines.

With the synthetised compounds the UV spectra in the 200–360 nm region and the IR spectra in the 3700–650 cm^{-1} region were measured. The UV spectra are characterised by two typical absorption bands in the 209–211 nm and 274–278 nm regions. The first corresponds to the *y*-band of simple purines and its molar extinction coefficient value ε is about 2–3 times higher than the second band which corresponds to the *x*-band of simple purines[5]. When comparing the *y*-bands of the mentioned substances it can be observed that the lowest ε value is found for the bands of substances which have in the position 8 a hydrogen atom (*i.e. IIa–IVa*). The ε value of this absorption band increases with increasing alkyl group in the position 8 until it achieves its maximum value in the case of 8-benzyl derivatives (*i.e. IIf–IVf*) approx. 30% higher than in the preceding n-butyl derivatives (*IIe–IVe*). A similar dependence may be also observed for *x*-bands. However their ε value is not so prominent in substances *IIf–IVf*.

The IR spectra of the prepared compounds are characterised by several common bands. These are especially the band at 1695–1685 cm^{-1} and the band at 1670 to 1660 cm^{-1} (both very strong). We assign the first one to ν(CO) in the position 2 of the theophylline nucleus, and the second to ν(CO) in the position 6 and together with the small peak at 1610 cm^{-1} to ν(C=C) and ν(C=N) (ref.[6]). Further the spectra contain a group of three weak bands in the 3000–2890 cm^{-1} region which we assign to stretching vibrations of the C—H bond (*cf.*[7–9]). Nitriles *II* are characterised by a weak narrow band at 2260 cm^{-1}. Amines *III* display a weak broad band at 3150 cm^{-1}, corresponding to the stretching vibrations of the associated N—H bond. In the spectra of isothiocyanates *IV* a strong broad band is present at 2110–2100 cm^{-1} and a weak narrow band at 2210–2200 cm^{-1}, typical of aliphatic isothiocyanates.

EXPERIMENTAL

Melting points were measured on a Kofler block. Analytical samples were dried in a vacuum (below 1 Torr) for 5 h and at 70°C, over phosphorus pentoxide. The IR spectra were measured on a Zeiss UR-20 apparatus and the UV on Zeiss Specord UV VIS apparatus.

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

Procedure A: A mixture of the corresponding 8-alkyltheophyllines *I* (20 mmol), acrylonitrile 2·1 g; 2·6 ml; 40 mmol), and sodium methoxide (0·3 g) in pyridine (25 ml) was heated in an auto-

TABLE I
Properties of 7-Substituted 8-Alkyltheophyllines

Compound	Formula (m.w.)	Calculated/Found % C	% H	% N	% Cl (S)	M.p., °C (solvent)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	λ_{min}, nm ($\varepsilon \cdot 10^{-3}$)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)
						7-(2-Cyanoethyl)-8-alkyltheophyllines			
IIa	$C_{10}H_{11}N_5O_2$	51·49	4·75	30·03		155—157[a]	209	245	274
	(233·2)	51·60	4·85	29·90		(ethanol)	(19·5)	(1·7)	(8·0)
IIb	$C_{11}H_{13}N_5O_2$	53·43	5·30	28·33		201—202·5	209	246	275
	(247·3)	53·60	5·43	28·13		(ethanol)	(21·4)	(2·1)	(9·6)
IIc	$C_{12}H_{15}N_5O_2$	55·16	5·79	26·81		191·5—193·5	210	247	276
	(261·3)	55·30	5·84	26·66		(ethanol)	(21·1)	(2·1)	(10·0)
IId	$C_{13}H_{17}N_5O_2$	56·71	6·22	25·44		149—150	210	247	277
	(275·3)	56·93	6·36	25·35		(tetrachloromethane–heptane)	(22·8)	(2·1)	(10·5)
IIe	$C_{14}H_{19}N_5O_2$	58·11	6·62	24·21		130—131	210	247	277
	(289·3)	58·30	6·65	24·13		(ethanol)	(23·4)	(2·1)	(10·9)
IIf	$C_{17}H_{17}N_5O_2$	63·14	5·30	21·66		175·5—176·5	210	248	278
	(323·3)	63·44	5·58	21·47		(benzene–tetrachloromethane)	(30·4)	(2·3)	(11·0)
						7-(3-Aminopropyl)-8-alkyltheophyllines			
IIIa	$C_{10}H_{16}ClN_5O_2$	43·88	5·89	25·59	12·95	265·5—267·5	209	246	275
	(273·7)	43·69	5·81	25·67	13·05	(methanol–ethanol)	(18·1)	(1·6)	(7·7)
IIIb	$C_{11}H_{18}ClN_5O_2$	46·07	5·98	24·43	12·37	245—247	210	247	276
	(286·7)	46·30	6·13	24·15	12·19	(methanol)	(19·8)	(1·9)	(9·4)

IIIc	$C_{12}H_{20}ClN_5O_2$ (301·8)	47·76 47·97	6·68 6·87	23·23 23·00	11·75 11·88	232—234 (n-propanol)	210 (21·0)	247 (2·0)	277 (9·7)
IIId	$C_{13}H_{22}ClN_5O_2$ (315·8)	49·45 49·59	7·01 7·12	22·20 22·19	11·23 11·15	225—227 (n-propanol)	210 (22·3)	247 (2·2)	277 (10·5)
IIIe	$C_{14}H_{24}ClN_5O_2$ (329·8)	51·00 51·04	7·33 7·24	21·24 21·33	10·75 10·83	219—221 (n-propanol)	210 (23·5)	247 (2·2)	277 (10·8)
IIIf	$C_{17}H_{22}ClN_5O_2$ (363·8)	56·11 56·03	6·09 6·15	19·25 19·08	9·75 9·99	294·5—296·5 (ethanol)	211 (30·6)	248 (2·5)	278 (11·1)
				7-(3-Isothiocyanatopropyl)-8-alkyltheophyllines					
IVa	$C_{11}H_{13}N_5O_2S$ (279·3)	47·30 47·63	4·69 4·80	25·08 24·87	11·48 11·38	135·5—137·5 (chloroform–tetrachloromethane)	209 (19·2)	246 (2·7)	274 (7·8)
IVb	$C_{12}H_{15}N_5O_2S$ (293·3)	49·13 49·32	5·15 5·02	23·88 23·74	10·93 10·83	153—155 (tetrachloromethane)	210 (21·5)	247 (2·9)	276 (9·6)
IVc	$C_{13}H_{17}N_5O_2S$ (307·4)	50·80 50·53	5·58 5·45	22·79 22·75	10·43 10·53	127·5—128·5 (tetrachloromethane)	210 (22·5)	248 (3·1)	277 (10·2)
IVd	$C_{14}H_{19}N_5O_2S$ (321·4)	52·32 52·16	5·96 6·14	21·78 21·98	9·98 10·08	136·5—138 (tetrachloromethane)	210 (23·6)	248 (3·1)	277 (10·5)
IVe	$C_{15}H_{21}N_5O_2S$ (335·4)	53·71 53·56	6·31 6·16	20·88 21·04	9·56 9·67	119—121 (tetrachloromethane–hexane)	210 (24·6)	248 (3·3)	277 (10·7)
IVf	$C_{18}H_{19}N_5O_2S$ (369·4)	58·52 58·26	5·18 5·06	18·96 18·71	8·68 8·56	176·5—178·5 (tetrachloromethane)	211 (31·4)	249 (3·7)	278 (11·0)

[a] Literature[3] gives m.p. 156—158°C.

clave at 150°C for 5 hours. The mixture was evaporated in a vacuum and the distillation residue was recrystallised from n-butanol (compound *IIc*), ethanol (compound *IIa*), or methanol (compound *IIb*).

Procedure B: The corresponding 8-alkyltheophylline *I* (40 mmol) was dissolved in pyridine (120—300 ml) by short boiling and the solution formed was cooled to 25—30°C. Acetonitrile (15·9 g; 20 ml; 0·30 mol) was added to it followed by 0·5 ml of a 40% Triton B. The mixture was refluxed for 15—20 min, then cooled and evaporated *in vacuo* to dryness. The product was separated from the polymers formed by boiling with a suitable solvent and evaporation of the ensuing solution to a small volume (for compounds *IIa*, *IIb*, *IIc*, *IIe* ethanol was used, for compound *IIf* acetone, and for compound *IId* a concentrated tetrachloromethane solution was precipitated with n-heptane). Applying these general procedures we prepared the following cyanoethyl derivatives *II* [substituent in the position 8 yield (procedure)]: hydrogen (*IIa*), 66·5% (A), 82·1% (B); methyl (*IIb*), 10·9% (A), 76·8% (B); ethyl (*IIc*), 9·6% (A), 77·5% (B); n-propyl (*IId*), 17·4% (A), 40·3% (B); n-butyl (*IIe*), 61·4% (B); benzyl (*IIf*), 29·2% (B). The samples for analysis were prepared by an additional crystallisation from a suitable solvent. The properties of substances *II* are listed in Table I.

7-(3-Aminopropyl)-8-alkyltheophyllines *III*

To the corresponding 7-(2-cyanoethyl)-8-alkyltheophylline *II* (10 mmol) in ethanol (65—90 ml) Raney cobalt (2—3 g) was added and the mixture hydrogenated in an autoclave at 90—120°C and 100—150 atm pressure for 8—12 h. After cooling the catalyst was filtered off and the filtrate evaporated *in vacuo* to a small volume. The acidity of the reaction mixture was adjusted with concentrated hydrochloric acid to pH 2. The obtained solution was evaporated *in vacuo* to dryness. The residue was dissolved in a small amount of water, the solution filtered with charcoal, and evaporated to dryness. The residue was either crystallised from ethanol (compound *IIIf*), methanol–ethanol mixture 1 : 1 (*IIIa*), and n-propanol (*IIId*), or digested with tetrachloromethane and crystallised from chloroform–heptane mixture (*IIe*). For compound *IIIc* digestion with benzene and crystallisation from n-propanol was applied and for substance *IIIa* digestion with chloroform and crystallisation from methanol. Using this procedure we obtained the following amine hydrochlorides *III* (substituent in the position 8, temperature, pressure, reaction time, yield): hydrogen (*IIIa*), 90—100°C, 100 atm, 8 h, 68·0%; methyl (*IIIb*), 90—100°C, 110 atm, 10 hours, 42·6%; ethyl (*IIIc*), 100—110°C, 110 atm, 10 h, 64·7%; n-propyl (*IIId*), 100—110°C, 130 atm, 10 h, 78·6%; n-butyl (*IIIe*), 100—110°C, 140 atm, 12 h, 74·3%; benzyl (*IIIf*), 110—120°C, 150 atm, 10 h, 47·6%. When isolating the free base *IIIa* we evaporated the filtrate after filtration off of the catalyst to dryness and chromatographed the residue on alumina (40-fold amount, activity II), using benzene for elution. The recovery of base was 60%. Samples for analysis were prepared by an additional crystallisation from a suitable solvent, see Table I.

7-(3-Isothiocyanatopropyl)-8-alkyltheophyllines (*IV*)

Procedure A: A solution of amine *III* (16·2 mmol) in 25 ml of chloroform was added in small portions under stirring and cooling to a mixture of thiophosgene (1·86 g; 1·23 ml; 16·2 mmol) and calcium carbonate (2·0 g; 20 mmol) in water (10 ml) and chloroform (10 ml). The stirring was continued at room temperature for another 5 h. The unreacted calcium carbonate was filtered off under suction, the chloroform layer was separated, dried over calcium chloride and evaporated to dryness under reduced pressure. The residue was purified by chromatography on alumina (20-fold amount, activity VI), using benzene for elution.

Procedure B: The corresponding amine hydrochloride (5·5 mmol) dissolved in water (14 ml) was added in small portions under stirring and cooling to a mixture of thiophosgene (0·633 g; 0·44 ml; 5·5 mmol) and calcium carbonate (1·6 g; 16 mmol) in chloroform (20 ml) and the stirring was continued at room temperature for another 6 h. The unreacted calcium carbonate was filtered off, the chloroform layer was separated and dried over calcium chloride and evaporated *in vacuo* to dryness. The residue was chromatographed on alumina (20-fold amount, activity VI) with benzene (for *IVb—IVf*) or chloroform (for *IVa*). Using these procedures we prepared the following isothiocyanates *IV* (substituent in the position 8, yield): hydrogen (*IVa*), 60·0% (A), or 57·8% (B); methyl (*IVb*), 54·9% (B); ethyl (*IVc*), 73·7% (B); n-propyl (*IVd*), 52·4% (B), n-butyl (*IVe*), 60·1% (B); benzyl (*IVf*), 61·4% (B). Samples for analysis were prepared by crystallisation of chromatographically pure compounds from suitable solvents. The properties of the prepared isothiocyanates *IV* are listed in Table I.

7-(3-Hydroxypropyl)theophylline *V*

A mixture of theophylline (1·80 g; 10 mmol), water (40 ml), and an equivalent amount of 10M-NaOH was stirred at 40°C until theophylline was dissolved. The solution was evaporated *in vacuo* at 40—50°C and the residue dried at 50°C and 1 Torr. The residue was suspended in dimethylformamide (40 ml), 3-chloropropanol (1·145 g; 0·875 ml; 12 mmol) was added, and the mixture was heated at 100°C under stirring for 4 h. Dimethylformamide was then distilled off in a vacuum. The dry residue was crystallised from ethanol; yield 1·21 g (50·8%), m.p. 150—152°C. For analysis the product was recrystallised from ethanol, m.p. 151—152·5°C. For $C_{10}H_{14}N_4O_3$ (238·2) calculated: 50·41% C, 5·92% H, 23·5% N; found: 50·65%C, 5·85% H, 23·83% N.

7-(3-Chloropropyl)theophylline *VI*

Hydroxy derivative *V* (952 mg; 4 mmol) was suspended in benzene (15 ml), and thionyl chloride (2·0 g; 1·25 ml; 16·7 mmol) was added to it in small portions. The mixture was refluxed for 3·5 hours under exclusion of moisture (calcium chloride tube). Volatile components were distilled off and the residue was crystallised from ethanol. Yield 692 mg (64·8%), m.p. 119—120°C. For analysis the sample was recrystallised from ethanol, m.p. 120·5—121°C. For $C_{10}H_{13}ClN_4O_2$ (256·7) calculated: 46·79% C, 5·10% H, 21·83% N, 13·81% Cl; found: 47·03% C, 5·26% H, 21·76% N, 13·78% Cl.

7-(3-Aminopropyl)theophylline *IIIa*

A mixture of chloro derivative *VI* (1·28 g; 5·4 mmol) and 30% ethanolic ammonia (40 ml) was heated in an autoclave at 123—135°C for 3 hours and then evaporated to dryness. The residue was dissolved in aqueous ammonia (20 ml), charcoal was added, and the mixture filtered. The aqueous filtrate was evaporated to dryness, the residue dissolved in ethanol, acidified with concentrated hydrochloric acid, and allowed to crystallise. Yield 388 mg (26·3%) of amine hydrochloride, m.p. 258—260°C. A sample crystallised from n-propanol melted at 265—267°C. Mixture melting point with the product of reduction of nitrile *IIa* was 265—267°C.

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REFERENCES

1. Speer J. H., Raymond A. L.: J. Am. Chem. Soc. *75*, 114 (1953).
2. Mokrý J., Kostolanský A.: Chem. zvesti *10*, 170 (1956).
3. Zelnik R., Pesson M.: Bull. Soc. Chim. France *1959*, 1667.
4. Doebel K., Spiegelberg H.: US-Pat. 2 761 862 (1956); Chem. Abstr. *51*, 3676 (1957).
5. Mason S. F.: J. Chem. Soc. *1954*, 2071.
6. Angell C. L.: J. Chem. Soc. *1961*, 511.
7. Montgomery J. A., Holum L. B.: J. Am. Chem. Soc. *80*, 407 (1958).
8. Rybár A., Štibrányi L., Uher M.: This Journal *37*, 3936 (1972).
9. Montgomery J. A.: J. Am. Chem. Soc. *78*, 1928 (1956).

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