PURINE DERIVATIVES. II.*

8-(2-ISOTHIOCYANATOETHYL)-7-ALKYLTHEOPHYLLINES

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A series of 8-(2-isothiocyanatoethyl)-7-alkyltheophyllines has been prepared from the corresponding aminoethyl and cyanomethyl derivatives. The appropriate 8-cyanomethyl-7-alkyltheophyllines have been prepared on alkylation of 8-cyanomethyltheophylline sodium salt. The latter compound has been obtained from 1,3-dimethyl-4-(2-cyanoethylamino)uracil by nitrosation and thermal cyclisation of the 5-nitroso intermediate. Ultraviolet and infrared spectra of the synthesized compounds have been investigated.

The isothiocyanates derived from purines have not been investigated so far in detail with the exception of 7-substituted 8-isothiocyanatomethyltheophyllines and 7-substituted 8-isothiocyanatomethyl-1,3-diethylxanthines[1]. In the present paper we wish to report compounds the isothiocyanate group of which is distant by two carbon atoms from position 8 of the purine nucleus.

For the preparation of the title isothiocyanatoethyl derivatives, the 7-substituted 8-(2-aminoethyl)theophyllines were required. Of these amines, only the 7-methyl derivative[2] has been prepared, namely, by the Hofmann degradation of 3-(caffein-8-yl) propionic acid[3]. To circumvent this rather complicated route, we wanted to prepare the required amines by reduction of 7-substituted 8-cyanomethyltheophyllines but the search in the literature was again disappointing. Only one representative of this series of compounds has been prepared by Golovčinskaja[4], namely, 8-cyanomethylcaffeine, by a multistep synthesis from 8-chlorocaffeine *via* diethyl (caffein-8-yl)-malonate, (caffein-8-yl)acetic acid, methyl ester and by dehydratation of the corresponding amide with phosphorus oxychloride. The attempted shorter preparation of 8-cyanomethylcaffeine from 8-chloromethylcaffeine and sodium cyanide failed[4].

In the present paper we report a simple and convenient synthesis of 8-cyanomethylcaffeine as well as some 7-substituted 8-cyanomethylcaffeines. In this method, we have utilized the earlier observations[5] on cyclisation of 1,3-dimethyl-5-nitrosouracils substituted at position 4 by a —NH—CH_2—R group (R designates electron-donating substituents or the ethoxycarbonyl group from the electron-withdrawing substituents). Thermal cyclisation of these 5-nitroso derivatives leads under removal of water

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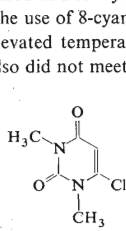
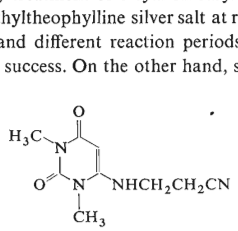
in toluene, xylene, butanol and the like to theophyllines substituted at position 8 by the group R. With the use of 1,3-dimethyl-4-(2-cyanoethylamino)-5-nitrosouracil, we have obtained 8-cyanomethyltheophylline (*III*), the alkylation of which led to the required 8-cyanomethyl-7-alkyltheophyllines *IV*.

The starting 1,3-dimethyl-4-chlorouracil (*I*) was prepared from 1,3-dimethylbarbituric acid by the action of phosphorus oxychloride[6]. Condensation of compound *I* with 3-aminopropionitrile afforded 1,3-dimethyl-4-(2-cyanoethylamino)uracil (*II*), a portion of 3-aminopropionitrile being converted to the hydrochloride. With the use of a 4-molar excess of 3-aminopropionitrile, the yield of compound *II* was 70%. Treatment of the uracil derivative *II* with n-propyl nitrite in methanol under catalysis of hydrogen chloride afforded 1,3-dimethyl-4-(2-cyanoethylamino)-5-nitrosouracil. The use of other nitrosating agents resulted in a contaminated product or low yields. Thus, after the treatment with sodium nitrite in hydrochloric acid, only the impure starting compound was isolated while the reaction with pentyl nitrite and isopentyl nitrite in ethanol under catalysis of hydrochloric acid had a satisfactory course but the isolation of the product by distillation *in vacuo* was accompanied by resinification. The crude nitroso derivative was cyclised by refluxing in butanol (the use of toluene or xylene as cyclisation medium led to resinification). The reaction mixture deposited directly the required 8-cyanomethyltheophylline (*III*).

The alkylation of compound *III* to 8-cyanomethyl-7-alkyltheophyllines *IV* when performed analogously[1] to the alkylation of 8-hydroxymethyltheophylline or 8-hydroxymethyl-1,3-diethylxanthine (*i.e.*, on heating of 8-cyanomethyltheophylline with alkyl bromides or alkyl iodides in dimethylformamide and in the presence of potassium carbonate as receptor of hydrogen chloride set free by the reaction) did not give satisfactory results since only the 7-methyl derivative *IVa* was obtained by this method (the yield, however, was low). The 7-n-butyl derivative *IVd* was prepared in a low yield by treatment of 8-cyanomethyltheophylline with 1-diazobutane. The use of 8-cyanomethyltheophylline silver salt at room temperature as well as at an elevated temperature and different reaction periods of time (from 0·5 to 14 hours) also did not meet with success. On the other hand, satisfactory results were obtained



I



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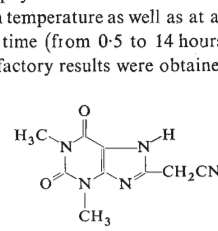
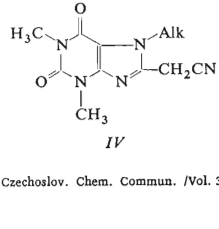
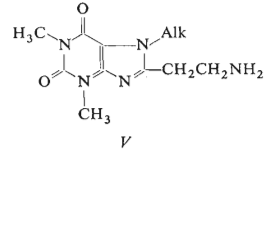


III



IV



V

TABLE I

Properties of 8-Substituted 7-Alkyltheophyllines (*a* CH_3; *b* C_2H_5; *c* n-C_3H_7; *d* n-C_4H_9; *e* $C_6H_5CH_2$; *f* $CH_2{=}CHCH_2$)

Compound	Formula (M. weight)	Calculated/Found				M.p., °C (solvent)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	λ_{min}, nm ($\varepsilon \cdot 10^{-3}$)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)
		% C	% H	% N	% Cl or % S				
				8-Cyanomethyl-7-alkyltheophyllines					
IVa	$C_{10}H_{11}N_5O_2$ (233·2)	51·49 51·27	4·75 4·60	30·03 30·13	—	232–234[a] (methanol)	207 (28·1)	246 (2·3)	276 (10·1)
IVb	$C_{11}H_{13}N_5O_2$ (247·3)	53·43 53·20	5·30 5·17	28·33 28·60	—	196–197 (CCl_4)	208 (27·3)	246 (2·9)	276 (10·2)
IVc	$C_{12}H_{15}N_5O_2$ (261·3)	55·16 54·90	5·79 5·68	26·81 26·99	—	135–136 (CCl_4)	209 (30·8)	246 (2·7)	276 (10·4)
IVd	$C_{13}H_{17}N_5O_2$ (275·3)	56·71 56·52	6·22 6·12	25·44 25·52	—	111–112 (CCl_4–hexane)	208 (27·8)	247 (2·4)	276 (10·0)
IVe	$C_{16}H_{15}N_5O_2$ (309·3)	62·12 62·00	4·89 4·65	22·64 22·72	—	171–173 (CCl_4)	208 (32·7)	248 (2·6)	277 (9·6)
IVf	$C_{12}H_{13}N_5O_2$ (259·3)	55·59 55·82	5·05 5·18	27·01 26·87	—	152–154 (chloroform–hexane)	208 (26·4)	246 (2·4)	276 (9·9)
				8-(2-Aminoethyl)-7-alkyltheophyllines					
Va . HCl	$C_{10}H_{16}ClN_5O_2$ (273·7)	43·88 44·08	5·89 5·80	25·59 25·55	12·95 13·07	308–310 (methanol–chloroform)	210 (23·1)	247 (2·6)	276 (10·6)
Vb . HCl	$C_{11}H_{18}ClN_5O_2$ (287·8)	45·91 45·80	6·30 6·18	24·34 24·53	12·32 12·37	254–225 (extd. with chloroform)	209 (22·7)	247 (2·6)	276 (10·2)

Vc	$C_{12}H_{19}N_5O_2$	54·32	7·22	26·40	—	100—103	209	248	277
	(265·3)	54·40	7·24	26·48		(CCl_4–hexane)	(26·3)	(2·9)	(11·2)
Vd . HCl	$C_{13}H_{22}ClN_5O_2$	49·44	7·02	22·18	11·23	231—232·5	210	247	276
	(315·8)	49·33	6·95	22·19	11·52	(extd. with chloroform)	(23·2)	(2·6)	(10·5)
Ve . HCl	$C_{16}H_{20}ClN_5O_2$	54·93	5·76	20·02	10·14	227—229	211	248	278
	(349·8)	55·17	6·00	20·24	10·28	(1-propanol)	(28·9)	(2·9)	(10·4)
				8-(2-Isothiocyanatoethyl)-7-alkyltheophyllines					
VIa	$C_{11}H_{13}N_5O_2S$	47·30	4·69	25·08	11·48	173—174	208	247	278
	(279·3)	47·48	4·99	24·96	11·53	(benzene)	(25·5)	(3·7)	(10·3)
VIb	$C_{12}H_{15}N_5O_2S$	49·13	5·15	23·88	10·93	137—139	208	247	277
	(293·3)	48·94	5·24	23·79	10·89	(benzene)	(28·1)	(3·8)	(11·5)
VIc	$C_{13}H_{17}N_5O_2S$	50·80	5·58	22·79	10·43	117—118	209	248	277
	(307·4)	50·65	5·56	22·70	10·40	(chloroform–hexane)	(26·7)	(3·9)	(11·6)
VId	$C_{14}H_{19}N_5O_2S$	52·32	5·96	21·79	9·98	149—151	209	248	276
	(321·4)	52·20	5·95	21·71	9·95	(benzene)	(27·1)	(3·9)	(11·3)
VIe	$C_{17}H_{17}N_5O_2S$	57·45	4·82	19·71	9·02	183—184·5	209	250	279
	(355·4)	57·70	4·88	19·65	8·90	(benzene–hexane)	(35·7)	(3·3)	(9·9)

[a]Reported[4], m.p. 228—229°C.

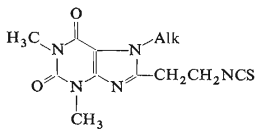
TABLE II
UV Spectra of Model Substances and of Compounds *III*, *VIII* and *IX*

Compound	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)
8-Methylcaffeine	206 (24·8); 273(10·2);
1,3,8,9-Tetramethylxanthine	203 (17·7); 238 (7·5); 269 (7·2)
VIII	208 (26·0); 275 (10·9)
IX	208 (25·4); 278 (9·7)
III	207 (23·7); 275 (10·2)

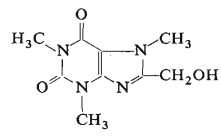
with the sodium salt which was prepared by treatment of 8-cyanomethyltheophylline with methanolic sodium methoxide. The sodium salt was alkylated with alkyl halides in dimethylformamide at 40°C or 70°C. The reaction course was checked by the pH value measurements of the reaction medium. With methyl iodide, the reaction of the sodium salt was completed within 15 min at 40°C and almost instantly at 70°C. Since the use of higher alkyl iodides led to strongly contaminated products, the remaining alkylations were performed with alkyl bromides and benzyl chloride at 70°C. The unreacted parent 8-cyanomethyltheophylline was highly more polar than the corresponding 7-alkyl derivatives *IV* and was removed by column chromatography on alumina.

The reduction of the above 8-cyanomethyl-7-alkyltheophyllines *IV* to 8-(2-aminoethyl)-7-alkyltheophyllines gave unsatisfactory results when performed with lithium aluminium hydride in diethyl ether or tetrahydrofuran, powdered sodium in dioxane and in the presence of ethanol, or, by hydrogenation over palladium on active carbon in the presence of hydrochloric acid at 90°C and 120 atm. With the use of Urushibara Raney nickel catalyst (80 – 90°C, 120 – 140 atm, 8 – 12 hours), the yields considerably increased but, notwithstanding, did nit exceed 50% (based on the starting nitrile); from amines prepared by this procedure only the 7-methyl (*Va*) and 7-n-propyl derivative (*Vc*) have achieved the analytical purity. Finally, the hydrogenation over Raney cobalt at 90 – 100°C and 100 – 110 atm for 10 – 12 hours was successfully used as the general method. The 2-aminoethyl derivatives *V* were then converted to 8-(2-isothiocyanatoethyl)-7-alkyltheophyllines *VI* by the thiophosgene method in aqueous chloroform and in the presence of calcium carbonate as receptor of hydrogen chloride liberated by the reaction.

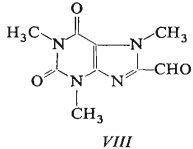
Another route for the preparation of isothiocyanates *VI* might involve reduction of the corresponding 2-nitrovinyl derivatives. This method was used only in the case of the 7-methyl derivative *VIa*. Thus, 8-hydroxymethylcaffeine[1] (*VII*) was oxidized with manganese dioxide in dioxane to caffeine-8-carbaldehyde (*VIII*). This procedure



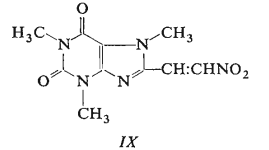
VI



VII



VIII



IX

is more advantageous than the earlier method consisting in chlorination of 8-methylcaffeine and hydrolysis of the mixture of chlorinated products[7]. Condensation of the aldehyde *VIII* with nitromethane gave only poor yields of 8-(2-nitrovinyl)caffeine (*IX*) when performed under catalysis of butylamine. Reasonable yields were obtained with the use of sodium hydroxide in aqueous ethanol. The 2-nitrovinyl derivative *IX* was converted to 8-(2-aminoethyl)caffeine (*Va*) by hydrogenation over Raney nickel (70°C, 100 atm, 10 hours). Treatment of the 2-aminoethyl derivative *Va* with thiophosgene afforded the final 8-(2-isothiocyanatoethyl)caffeine *VIa*, identical with the specimen obtained from 8-cyanomethylcaffeine.

To confirm the assumption that the alkylation of 8-cyanomethyltheophylline occurs at position 7 (and not 9) of the purine nucleus, we have compared the ultraviolet spectra of the alkyl derivatives *IV* with those of 8-methylcaffeine and 1,3,8,9-tetramethylxanthine. Thus, the ultraviolet spectrum of the 9-substituted derivatives considerably differs from that of 8-methylcaffeine or those of the alkyl derivatives *IV*. On the other hand, the ultraviolet spectra of 8-methylcaffeine and compounds *IV* are very similar. Consequently, 8-cyanomethyltheophylline sodium salt is alkylated or aralkylated at the nitrogen atom in position 7.

Ultraviolet spectra of the synthesized substances (Table I and II) exhibit two bands in the 273–278 nm and 206–209 nm region. The first absorption band of 8-cyanomethyl-7-alkyltheophyllines is located at 276–277 nm and corresponds to the x-band of simpler purines[8]. From comparison of positions of this maximum in the case of 8-cyanomethyltheophylline and the 7-substituted derivatives it may be seen that introduction of an alkyl or aralkyl group into position 7 does not result in any appreciable bathochromic shift. The shift of the x-band due to replacement of one hydrogen atom in the 8-methyl group of 8-methylcaffeine by the nitrile, aminomethyl, and isothiocyanatomethyl group is somewhat more distinct (3–4 nm, 3–4 nm, and 3–5 nm, resp.). The second absorption band corresponding to the y-band of simpler purines lies with all synthesized xanthine derivatives in the 207–209 nm region. The corresponding extinction coefficient is from two times to three times higher than that of the x-band. When compared with the

y-band of 8-methylcaffeine, the y-bands of the synthesized compounds show a lower bathochromic shift (max. 3 nm) similar to x-bands.

The infrared spectra of all synthesized compounds show the following absorption bands: two bands at 1715—1710 cm^{-1} (vs*) attributable to ν(CO) at position 2 and at 1680—1670 cm^{-1} (vs) attributable to ν(CO) at position 6, ν(C=C), and ν(C=N) (ref.[1,9]). Furthermore, the group of three bands at 2900—3000 cm^{-1} (w) may be attributed to stretching vibrations of the C—H bond (ref.[10,11]). The particular compounds exhibit additional characteristic bands, namely, the nitriles *IV* a narrow band at 2260—2254 cm^{-1} (w), the amines *V* a broad band at 3150 cm^{-1} (w), and the isothiocyanates *VI* a broad split band with a maximum at 2110—2100 cm^{-1} (s) and at 2210 cm^{-1} (w). Caffeine-8-carbaldehyde (*VIII*) exhibits an additional absorption band at 1730 cm^{-1} (vs) attributable to the aldehydic group at position 8. From the two bands at 1350 cm^{-1} (s) and 1560 cm^{-1} (s) of 8-(2-nitrovinyl)caffeine (*IX*), the former may be attributed to symmetrical and the latter to asymmetrical stretching vibrations of the nitro group.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried over phosphorus pentoxide for 5 h at 70°C under diminished pressure below 1 Torr. IR spectra were taken on a Zeiss UR-10 apparatus. UV spectra were measured on a Perkin-Elmer Model 137 apparatus.

1,3-Dimethyl-4-(2-cyanoethylamino)uracil (*II*)

A mixture of 1,3-dimethyl-4-chlorouracil (*I*; 38·5 g; 0·217 mol), water (80 ml), and 3-aminopropionitrile (76 g; 1·08 mol) was heated under reflux condenser on a steam bath for 30 min and allowed to stand at room temperature overnight to deposit the product which was collected with suction, washed with water, and air-dried. Yield, 33·0 g (70%) of compound *II*, m.p. 213—215°C. The analytical sample was recrystallised from water; m.p. 215—216°C. For $C_9H_{12}N_4O_2$ (222·2) calculated: 48·64% C, 5·44% H, 31·52% N; found: 48·51% C, 5·38% H, 31·68% N.

8-Cyanomethyltheophylline (*III*)

A solution of compound *II* (34·0; 0·162 mol) in methanol (1300 ml) was treated at 35°C with n-propyl nitrite (63·2 g; 69 ml; 0·710 mol) and 2—4 drops of conc. HCl. A vigorous reaction set in and the color changed to deep red. The mixture was allowed to stand for 30 min and the methanol was evaporated under diminished pressure at temperature below 40°C. The residual sirup, without any purification, was dissolved in butanol (100 ml) and the solution heated 3—5 min to 140—150°C to deposit almost immediately 8-cyanomethyltheophylline. The mixture was then cooled down to about 30°C, diluted with acetone (100 ml), stirred for 30 min, and the solid collected with suction. The mother liquors were concentrated to about $^1/_4$ of the original volume and the concentrate diluted with an equal volume of acetone to deposit an additional crop of the product. Overall yield of compound *III*, 23.1 g (64·1%); m.p. 270—273°C. The analytical sample was recrystallised from acetone; m.p. 274—276°C. For $C_9H_9N_5O_2$ (219·2) calculated: 49·32% C, 4·14% H, 31·93% N; found: 49·53% C, 4·19% H, 32·02% N.

8-Cyanomethyl-7-alkyltheophyllines *IV*

Methanolic sodium methoxide (20·8 mmol; 11 ml) was added to a suspension of 8-cyanomethyltheophylline (*III*; 4·56 g; 20·8 mmol) in methanol (21 ml). After a while, the mixture solidified.

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

The solvent was evaporated under diminished pressure. The residual sodium salt (5·0 g; 18 mmol; 99·2%) was dissolved in dimethylformamide (40 ml), the solution treated with the appropriate alkyl halide, and the whole heated under stirring at 70°C until the pH value of a sample (diluted with water) dropped from 12 to 7. The solvent was evaporated under diminished pressure and the residue crystallised from ethanol (with compound *IVa*) or extracted with hot chloroform. The crude product was purified by column chromatography on alumina (Brockmann activity II) in chloroform. The prepurified product was crystallised from chloroform and hexane (compounds *IVc*, *IVe*, *IVf*) or ethanol (compound *IVb*). Compound *IVd* was chromatographed in tetrachloromethane and then crystallised from tetrachloromethane and hexane. This general procedure was used in the preparation of the following compounds *IV* (alkyl, alkyl halide and its amount, reaction time, and yield given): methyl (*IVa*), methyl iodide (22·5 mmol), 15 min at 40°C, 47·2%; ethyl (*IVb*), ethyl bromide (23·4 mmol), 1 hour, 73·0%; n-propyl (*IVc*), n-propyl bromide (27·0 mmol), 90 min, 65·2%; n-butyl (*IVd*), n-butyl bromide (30·0 mmol), 2 hours, 63·2%; benzyl (*IVe*), benzyl chloride (25·2 mmol), 45 min, 53·%; allyl (*IVf*), allyl bromide (23·5 mmol), 30 min, 64·4%. The analytical sample were obtained by additional crystallisations from suitable solvents. For the analytical data, melting points, and ultraviolet spectral data see Table I.

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

A. A mixture of the appropriate alkyl derivative *IV* (10 mmol), Urushibara Raney nickel (2—3 g), and 30% methanolic ammonia (20 ml) was hydrogenated at 80—90°C and 120—130 atm for 8—10 hours, the catalyst filtered off, the filtrate evaporated under diminished pressure, and the residual amine recrystallised from methanol (compound *Va*) or chloroform–hexane (compound *Vc*).

B. A mixture of the appropriate alkyl derivative *IV* (7 mmol), Raney cobalt (its weight was equal to that of compound *IV*), and ethanol (60—70 ml) was hydrogenated at 90—100°C and 100—110 atm for 10—12 hours, the catalyst filtered off, the filtrate concentrated to the volume of about 15—20 ml, the concentrate adjusted with concentrated hydrochloric acid to pH 2, evaporated to dryness under diminished pressure, and the residual amine hydrochloride dissolved in water (about 15—20 ml). A small amount of the unreacted nitrile was filtered off under the addition of active charcoal and the aqueous amine hydrochloride was evaporated to dryness under diminished pressure. The residue was crystallised from 2-propanol (compound *Ve*) or extracted with hot chloroform (compounds *Vb*, *Vd*). The above procedures were used to prepare the following amines *V* or their hydrochlorides (alkyl, temperature, pressure, time of hydrogenation, yield, and procedure *A* or *B* given): methyl (*Va*), 80°C, 120 atm, 8 hours, 40·9% *A*; ethyl (*Vb* . HCl), 90°C, 100 atm, 10 hours, 57·2%, *B*; n-propyl (*Vc*), 90°C, 130 atm, 10 hours, 49·5%, *A*; n-butyl (*Vd* . HCl), 100°C, 100 atm, 11 hours, 31·6%, *B*; benzyl (*Ve* . HCl), 100°C, 110 atm, 12 hours, 41·9%, *B*. Hydrogenation of 8-cyanomethyl-7-allyltheophylline (*IVf*) at 80°C and 130 atm for 10 hours by procedure *A* gave 46·0% of the n-propyl derivative *Vc*, identical with the specimen obtained from the nitrile *IVc*. The analytical samples were recrystallised from suitable solvents.

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

A solution of 8-(2-aminoethyl)-7-alkyltheophylline *V* (6 mmol) in chloroform (30—40 ml) was added portionwise to a mixture of calcium carbonate (0·5 g), thiophosgene (0·76 g; 0·51 ml; 6·6 mmol), and water (15 ml) under stirring and cooling with ice-cold water. The stirring was then continued at room temperature for 12 hours. The unreacted calcium carbonate was filtered off, the chloroform layer separated from the filtrate, dried over sodium sulfate, and evaporated

to dryness under diminished pressure. The crude isothiocyanate was purified by column chromatography on alumina. The elution was performed with benzene at 60°C (compounds *VIa*, *VIb*, *VIe*) or chloroform (compounds *VIc*, *VId*). The isothiocyanates *VI* were obtained in the following yields: methyl (*VIa*), 27·5%; ethyl (*VIb*), 17·2%; n-propyl (*VIc*), 33·3%; n-butyl (*VId*), 26·1%; benzyl (*VIe*), 20·5%.

Caffeine-8-carbaldehyde (*VIII*)

Active manganese dioxide (41 g; 0·48 mol) was added to a suspension of 8-hydroxymethylcaffeine[1] (*VII*; 10·3 g; 45·6 mmol) in dioxane (450 ml) and the whole mixture was heated at 70°C for 4 hours under stirring. The manganese oxides were then filtered off and extracted with two 200 ml portions of boiling dioxane. The filtrate and extracts were combined and concentrated to deposit the product which was recrystallised from ethanol. Yield, 5·8 g (57%) of the aldehyde *VIII*, m.p. 167 to 169°C (reported[7], m.p. 165—167°C).

8-(2-Nitrovinyl)caffeine (*IX*)

A solution of compound *VIII* (1·70 g; 7·6 mmol) in methanol (100 ml) was treated with nitromethane (0·51 g; 8·4 mmol) and then portionwise under stirring at 0—5°C with a solution of sodium hydroxide (0·35 g; 8·4 mmol) in 10 ml of water. The mixture was stirred below 10°C for 30 min and then adjusted with dilute (1 : 1) hydrochloric acid to pH value 1 to deposit immediately a yellow precipitate which was collected with suction and dried. Yield, 0·92 g (45%) of compound *IX*, m.p. 216—219°C. The analytical sample was recrystallised from ethanol; m.p. 216—219°C. For $C_{10}H_{11}N_5O_4$ (265·2) calculated: 45·27% C, 4·17% H, 26·38% N; found: 45·03% C, 4·25% H, 26·48% N.

8-(2-Aminoethyl)caffeine (*Va*)

A solution of compound *IX* (0·90 g; 3·4 mmol) in methanol (30 ml) was hydrogenated over Raney nickel W-6 (0·3 g) at 70°C and 100 atm for 10 hours, the catalyst filtered off, and the filtrate evaporated under diminished pressure. The crude residue was recrystallised from methanol to afford 45% of the amine *Va*, identical with the specimen obtained from the nitrile *IVa*.

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