1,3-DIPOLAR CYCLOADDITION REACTIONS OF 7-ALKENYL- OR 7-ALKYNYL-8-AZIDOMETHYLTHEOPHYLLINES

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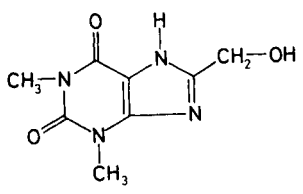
Received May 6th, 1987

Dedicated to Prof. W. Pfleiderer on the occasion of his 60th birthday.

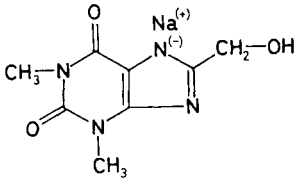
8-Azidomethyltheophyllines *XI*—*XIV*, containing dipolarophilic alkenyl or alkynyl (i.e. allyl, 2-butenyl, cinnamyl, and 2-propynyl) groups in position 7, undergo thermally induced 1,3-dipolar intramolecular cycloaddition under formation of 7-substituted 1,3-dimethyl-2,4-dioxo-1,2,3,4,6,6a,7,11-octahydro(1,2,3)triazolo[1′,5′ : 1,2]pyrazino[5,4-*f*]purines *XV*—*XVII* and 1,3-dimethyl-2,4-dioxo-1,2,3,4,6,11-hexahydro(1,2,3)triazolo[1′,5′ : 1,2]pyrazino[5,4-*f*]purine (*XVIII*), respectively. The compounds were synthesized starting from 8-hydroxymethyltheophylline (*I*) which was alkylated to give 7-alkenyl- and 7-alkynyl-8-hydroxymethyltheophyllines *III*—*VI* and these were converted into the corresponding 8-halogenomethyl derivatives *VII*—*X* by treatment with thionyl chloride or phosphorus tribromide. Reaction of *VII*—*X* with sodium azide afforded the 8-azidomethyl derivatives *XI*—*XIV*.

Xanthine derivatives with another fused heterocyclic ring have interesting effects on the cardiovascular system. They exhibit particularly antianginous and antiarrhythmic activities and they also affect the blood pressure. Recently, many compounds of this type are in advanced stages of pharmacological or clinical testing[1-9].

Our present work describes the synthesis of condensed heterocyclic derivatives of theophylline and the corresponding intermediates, 7-substituted 8-azidomethyltheophyllines, obtained from 8-hydroxymethyltheophylline (*I*) by a four-step synthesis. The starting compound *I* was prepared according to ref.[10].



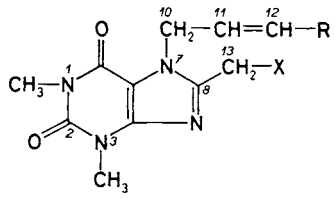
I



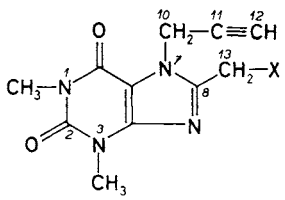
II

In the first synthetic step, compound *I* is converted into 7-alkenyl- or 7-alkynyl-8--hydroxymethyltheophyllines *II*–*VI*. We used two methods of alkylation. The first consisted in substitution reaction of sodium salt of 8-hydroxymethyltheophylline (*II*) with alkynyl or alkenyl halides in aprotic solvents, preferably in dimethylformamide. The sodium salt *II* is formed from compound *I* on reflux with sodium methoxide or ethoxide in an excess of the corresponding alcohol. The potassium salt may be prepared in an analogous way. As alkynyl and alkenyl halides we used 3-bromopropyne, 3-bromopropene, 1-bromo-2-butene, and 3-chloro-1-phenyl-1--propene. The introduction of these substituents into position 7 of theophylline skeleton creates a dipolarophilic center for 1,3-dipolar cycloaddition reactions. The reaction of sodium salt *II* with the mentioned alkynyl and alkenyl halides was monitored by following the change in pH value of the reaction mixture. The reaction times ranged from 1 to 4 hours. According to the second alkylation method, compound *I* reacted with the mentioned halides in the presence of anhydrous potassium carbonate in dimethylformamide according to ref.[10]. We used only catalytic amounts of sodium iodide which resulted in purer products (particularly *IV* and *V*) and in somewhat higher yields.

The second step of the synthesis was conversion of derivatives *III*–*VI* into the 7-alkenyl or 7-alkynyl-8-halogenomethyl derivatives *VII*–*X*. We used thionyl chloride or phosphorus tribromide as the halogenation reagents. Compounds *III* and *IV* were treated with an excess of thionyl chloride, which served simultaneously as the reaction medium, to give 7-allyl- and 7-(2-propynyl)-8-chloromethyltheophylline (*VII* and *VIII*, respectively). The reaction of compounds *V* and *VI* was carried out with an excess of phosphorus tribromide in benzene, toluene or halogenated hydrocarbons under formation of the respective 7-(2-butenyl)- and 7-cinnamyl-8--bromomethyltheophyllines (*IX* and *X*).



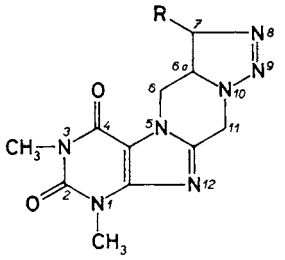
III, R = H; X = OH
V, R = CH_3; X = OH
VI, R = C_6H_5; X = OH
VII, R = H; X = Cl
IX, R = CH_3; X = Br
X, R = C_6H_5; X = Br
XI, R = H; X = N_3
XIII, R = CH_3; X = N_3
XIV, R = C_6H_5; X = N_3



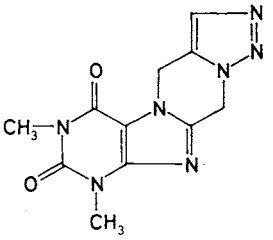
IV, X = OH
VIII, X = Cl
XII, X = N_3

In the third step of the synthetic scheme, 8-halogenomethyl derivatives *VII*–*X* were converted into the corresponding 8-azidomethyl derivatives *XI*–*XIV*. Although

we tried several procedures in various solvents, only two were used for the preparation. The first, employed in the preparation of 7-allyl-8-azidomethyltheophylline (*XI*), consisted in preceding transformation of the 8-halogenomethyl derivatives *VII*–*X* into the corresponding 8-iodomethyl derivatives which without isolation were reacted with sodium azide in aqueous acetone at room temperature and finally at slightly elevated temperature. The second procedure was the direct reaction of 8-halogenomethyl derivatives *VII*–*X* with sodium azide at elevated temperature, preferably in boiling aqueous acetone. In both the procedures, we followed the reaction by thin-layer chromatography after derivatization of the azide group with triphenylphosphine. The reaction mixture was heated until the starting halogenomethyl derivative disappeared. The acetone : water ratio was chosen so as to obtain a homogeneous solution at the reaction temperature from the originally two-phase system at room temperature. With anhydrous aprotic solvents, the reaction mixture remained heterogeneous even at high temperature and the reaction required much longer reaction times. Consequently, the reaction did not stop at the stage of the corresponding 8-azidomethyl derivatives *XI*–*XIV* and these products partially underwent further cycloaddition to the final compounds *XV*–*XVIII* or decomposed under elimination of nitrogen (followed volumetrically).



XV, R = H
XVI, R = CH_3
XVII, R = C_6H_5



XVIII

The fourth step of the synthesis represented the thermally induced intramolecular 1,3-dipolar cycloaddition of 7-alkenyl-8-azidomethyl derivatives *XI*, *XIII*, and *XIV* to 7-substituted 1,3-dimethyl-2,4-dioxo-1,2,3,4,6,6a,7,11-octahydro(1,2,3)triazolo[1′, 5′ : 1,2]pyrazino[5,4-*f*]purines *XV*–*XVII*. Cycloaddition of the azide group to the 2,3-double bond of the alkenyl group formed thus the triazolino[1,5-*a*]pyrazine grouping fused to the original theophylline system. With the 7-allyl derivative *XI*, the cycloaddition afforded compound *XV* with hydrogen atom in position 7; with the 7-(2-butenyl) derivative *XIII*, the product *XVI* contained methyl group in position 7. Analogously, derivative *XIV* gave compound *XVII* with 7-phenyl group.

When the cycloaddition was performed with the 7-propargyl derivative *XII*, the tetracyclic 1,3-dimethyl-2,4-dioxo-1,2,3,4,6,11-hexahydro(1,2,3)triazolo[1',5' : 1,2]-pyrazino[5,4-*f*]purine (*XVIII*) was obtained.

The intramolecular cycloaddition was effected by heating the azidomethyl derivatives *XI*–*XIV* to about 110°C in dioxane as the solvent of choice (concerning the purity of the desired compounds *XV*–*XVIII*). Reaction temperatures higher than 130°C (e.g. reflux in xylene) led to elimination of nitrogen and further decomposition of the products (see e.g. ref.[11]). The intramolecular cycloaddition also occurred by standing of solid 8-azidomethyl derivatives *XI*–*XIV* alone at room temperature for several months.

The structure of the synthesized intermediates as well as the final products was confirmed by elemental analyses and UV, IR, ^{1}H NMR, and mass spectra. These data (except IR spectra) for intermediates *III*–*XIV* are given in Tables I and II. The IR spectra of the studied compounds exhibited the following common bands: a very strong band at 1 655–1 670 cm^{-1}, ascribed to ν(CO) in position 6, ν(C=C), and ν(C=N), and a very strong band at 1 690–1 710 cm^{-1} due to ν(CO) in position 2 (see also ref.[10]). Bands at 1 490–1 500, 1 545–1 550, and 1 600–1 610 cm^{-1} correspond to skeletal vibrations of the purine nucleus. In addition to these common bands, derivatives *III*–*VI* exhibited a weak broad hydroxyl band at about 3 400 to 3 500 cm^{-1}. Similarly, compounds *XI*–*XIV* displayed a band at 2 103–2 110 cm^{-1} due to the N_3 group. The UV spectra show two maxima (except for *XIV*), at 207 to 215 nm (log ε 4·26–4·69) and at 273–291 nm (log ε 3·91–4·00). Replacement of the hydroxyl in compounds *III*–*VI* by halogen (in *VII*–*X*) results in a bathochromic shift of both absorption bands.

From the ^{1}H NMR spectra the following conclusions can be drawn. The 7-cinnamyl derivatives *VI*, *X*, and *XIV* have the *E*-configuration; for the 7-(2-butenyl) compounds *V*, *IX*, and *XIII* we were not able to determine the configuration of the CH=CH bond. The signals of H-10 and H-12 protons of the propargyl group in compounds *IV*, *VIII*, and *XII* have coupling constant ^4J = 2·5 Hz. Substituents X in compounds *III*–*XIV* do not affect significantly the chemical shifts (δ) of the protons in the alkynyl or alkenyl groups, except the value for H-13, vicinal to the mentioned substituents X. In accord with ref.[12], neither introduction of an alkynyl or alkenyl group into position 7 of the theophylline nucleus nor annelation of the above-mentioned heterocyclic systems alters significantly chemical shifts of the methyl groups bonded to the nitrogen atoms in positions 1 and 3. The differences between the chemical shifts for the N(1)—CH_3 and N(3)—CH_3 are caused by the anisotropic effect of carbonyl groups in positions 2 and 4 of the purine nucleus. For the tetracyclic compound *XVII* we found the coupling constant J(6a, 7) = 3 Hz which, according to the Karplus relationship[13], corresponds to the dihedral angle of 140° between the protons on the carbon atoms 6a and 7. This indicates that the cycloaddition leading to compound *XVII* is a concerted process (see e.g. ref.[14]).

TABLE I

7,8-Disubstituted theophyllines *III*—*XIV*

Compound	Formula (mol. w.)	Calculated/found				M.p., °C[a] (yield, %)	λ_{max}, nm (log ε)			M^+ *m/z*
		% C	% H	% N	% Cl/Br					
III	$C_{11}H_{14}N_4O_3$	52·79	5·64	22·39	—	133—134[b]	208	275		250
	(250·2)	52·88	5·69	22·18	—	(75—77)	(4·41)	(3·99)		
IV	$C_{11}H_{12}N_4O_3$	53·23	4·87	22·57	—	149—152	—	—		248
	(248·2)	53·20	4·85	22·59	—	(81)				
V	$C_{12}H_{16}N_4O_3$	54·53	6·10	21·20	—	174—176[c]	209	277		264
	(264·3)	54·07	6·33	21·45	—	(40)	(4·40)	(3·94)		
VI	$C_{17}H_{18}N_4O_3$	59·98	5·32	20·58	—	146—148	—	—		340
	(340·3)	59·80	5·17	21·04	—	(53)				
VII	$C_{11}H_{13}ClN_4O_2$	49·17	4·88	20·85	13·20	130—132[d]	213	285		268
	(268·7)	48·88	4·72	20·71	13·71	(82)	(4·39)	(3·96)		
VIII	$C_{11}H_{11}ClN_4O_2$	49·53	4·15	21·01	13·29	166—168	212	284		266
	(266·7)	49·50	4·25	21·13	13·30	(73)	(4·41)	(3·95)		
IX	$C_{12}H_{15}BrN_4O_2$	44·04	4·58	17·12	24·42	151—153[e]	215	291		327
	(327·2)	44·12	4·38	17·39	24·48	(42)	(4·26)	(3·91)		
X	$C_{17}H_{17}BrN_4O_2$	50·63	4·25	17·36	19·81	147—148	—	—		403
	(403·2)	50·69	4·22	17·16	19·75	(55)				
XI	$C_{11}H_{13}N_7O_2$	47·99	4·74	35·62	—	94—95	207	273		—
	(275·2)	47·80	4·42	35·84	—	(89)	(4·37)	(3·97)		
XII	$C_{11}H_{11}N_7O_2$	48·34	4·05	35·88	—	132 (decomp.)	210	278		—
	(273·2)	48·17	4·32	35·70	—	(80)	(4·48)	(4·04)		
XIII	$C_{12}H_{15}N_7O_2$	49·81	5·22	33·89	—	102—103	211	279		—
	(289·3)	49·98	5·03	34·16	—	(85)	(4·40)	(4·00)		
XIV	$C_{17}H_{17}N_7O_2$	58·10	4·87	27·90	—	119·5—122 (decomp.)	209	254	276	—
	(351·3)	57·93	4·99	27·61	—	(76)	(4·69)	(4·36)	(3·93)	

[a] From ethanol; [b] reported[10] m.p. 131·5—133°C; [c] from acetone, from acetone, reported[10] m.p. 130—132°C; [e] from ethanol–water.

TABLE II

Proton NMR spectra of the prepared intermediates

Compound	H-(R)	H-12	J(11, 12) Hz	H-11	J(11, 10) Hz	H-10	H-13	N(3)—CH_3	N(1)—CH_3	Other signals
III	—	5·23 dd, 2 H	8·0	6·00 m, 1 H	5·0	5·10 d, 2 H	4·78 s, 2 H	3·53 s, 3 H	3·40 s, 3 H	3·88 s, 1 H(OH)
V[a]	1·70 d, 3 H	5·68 m, 1 H	—	5·68 m, 1 H	—	5·00 m, 2 H	4·75 s, 2 H	3·53 s, 3 H	3·40 s, 3 H	3·70 s, 1 H(OH)
VI	7·27 s, 5 H	6·60 d, 1 H	16·0	6·28 td, 1 H	5·0	5·20 d, 2 H	4·81 s, 2 H	3·52 s, 3 H	3·42 s, 3 H	3·50 s, 1 H(OH)
VII	—	5·26 dd, 2 H	8·0	6·00 m, 1 H	5·1	5·23 d, 2 H	4·69 s, 2 H	3·60 s, 3 H	3·40 s, 3 H	—
VIII[b]	—	3·05 t, 1 H	—	—	—	5·28 d, 2 H	4·88 s, 2 H	3·38 s, 3 H	3·19 s, 3 H	—
IX	1·60 d, 3 H	5·70 m, 1 H	—	5·70 m, 1 H	4·5	5·03 d, 2 H	4·50 s, 2 H	3·55 s, 3 H	3·40 s, 3 H	—
X	7·25 s, 5 H	6·60 d, 1 H	16·0	6·28 td, 1 H	5·0	5·19 d, 2 H	4·49 s, 2 H	3·50 s, 3 H	3·33 s, 3 H	—
XI	—	5·20 dd, 2 H	10·0	6·00 m, 1 H	5·0	5·05 d, 2 H	4·48 d, 2 H	3·59 s, 3 H	3·39 s, 3 H	—
XII[b,c]	—	3·35 t, 1 H	—	—	—	5·25 d, 2 H	4·71 s, 2 H	3·39 s, 3 H	3·19 s, 3 H	—
XIII[a]	1·68 d, 3 H	5·65 m, 1 H	—	5·65 m, 1 H	4·5	4·98 d, 2 H	4·46 s, 2 H	3·55 s, 3 H	3·38 s, 3 H	—
XIV	7·20 s, 5 H	6·56 d, 1 H	16·0	6·18 td, 1 H	5·0	5·09 d, 2 H	4·40 s, 2 H	3·49 s, 3 H	3·31 s, 3 H	—

[a] J(12, H-(R)) = 4·5 Hz; [b] J(10, 12) = 2·5 Hz; [c] in hexadeuteriodimethyl sulfoxide.

EXPERIMENTAL

The melting points are uncorrected. Analytical samples were crystallized from appropriate solvents and dried at 100°C/65 Pa for 8—10 h over phosphorus pentoxide, compounds *XI*—*XIV* at 40°C. Compounds *V*, *IX*, and *XIII* were purified by column chromatography (silica gel, 50 : 1) in chloroform prior to crystallization. UV spectra were measured in methanol (concentration $30-5{\cdot}0 \cdot 10^{-5}$ mol l^{-1}) on a UV-VIS Specord M-40 (Carl Zeiss) spectrophotometer, IR spectra in chloroform or KBr on a Perkin-Elmer 457 instrument. ^1H and ^{13}C NMR spectra (in deuteriochloroform) were obtained with a JEOL FX-100 (100 MHz and 25·05 MHz, respectively) instrument, using tetramethylsilane as internal standard. Mass spectra were measured on an MS-902S spectrometer. Thin-layer chromatography was carried out on Silufol UV_{254} (Kavalier) in chloroform or dichloromethane–acetone (10 : 1). The filtrates and other solutions were concentrated under diminished pressure on a rotatory evaporator.

7-Alkynyl- and 7-Alkenyl-8-hydroxymethyltheophyllines *III*—*VI*

A) 8-Hydroxymethyltheophylline[10] (*I*, 210 g; 1·0 mol) was added to a solution of sodium (23·5 g) in methanol (600 ml) and the suspension was refluxed for 1 h. After cooling to room temperature, the solid sodium salt *II* was filtered, the filtrate was concentrated under diminished pressure to half of the original volume, cooled and the second crop of *II* was collected. The combined portions of *II* were dried at 90°C/0·26 kPa; yield 208 g (90%) of a white powder, not melting up to 360°C.

The corresponding alkynyl or alkenyl halide (0·12—0·15 mol) was added to a suspension of *II* (23·3 g; 0·10 mol) and sodium iodide (1·5 g; 0·01 mol) in dimethylformamide (150 ml) and the mixture was stirred at 80°C until its pH dropped from 12 to 7—8. After cooling, the inorganic salts were removed by filtration, the filtrate was taken down under diminished pressure and the residue was mixed with ether (150—200 ml). The separated solid was filtered and crystallized from an appropriate solvent.

B) A mixture of *I* (21·0 g; 0·10 mol), potassium carbonate (14·0 g; 0·10 mol), dimethylformamide and the alkenyl halide (0·12—0·15 mol) was heated to 100°C with stirring until the pH of the mixture dropped from 12 to 7—8. After cooling to room temperature, the inorganic salts were filtered and the filtrate was taken down under diminished pressure. The crude product was crystallized from an appropriate solvent.

According to these procedures, the following 8-hydroxymethyl derivatives were prepared (the amount of the alkynyl or alkenyl halide, procedure, and reaction time are given): *III* (3-bromopropene, 14·5 g, 10·4 ml; *B*, 2 h); *IV* (3-bromopropyne, 17·8 g, 11·3 ml; *A*, 1 h; *B*, 2 h); *V* (1-bromo-2-butene, 18·9 g, 14·4 ml; *A*, 1 h; *B*, 4 h); *VI* (cinnamyl chloride, 19·8 g; *A*, 2 h).

7-Allyl- or 7-(2-Propynyl)-8-chloromethyltheophylline (*VII* or *VIII*)

Thionyl chloride (60 ml) was added in small portions to *III* (25·0 g; 0·1 mol) or *IV* (24·8 g; 0·1 mol) (initially a vigorous reaction) and the mixture was refluxed for 3 h (or 1 h) under exclusion of moisture. The excess thionyl chloride was distilled off, finally under diminished pressure and the residue was crystallized from acetone.

7-(2-Butenyl)-8-bromomethyltheophylline (*IX*)

Phosphorus tribromide (28·8 g; 10 ml; 100 mmol) was added to *V* (7·95 g; 30 mmol) in benzene (100 ml) and the mixture was refluxed for 3 h. After evaporation of the solvent, the residue was stirred with chloroform (80 ml), the chloroform solution was washed with water, 5% sodium

hydroxide and water and dried over sodium sulfate. The solvent was evaporated and the residue crystallized from ethanol–water (8 : 2).

7-Cinnamyl-8-bromomethyltheophylline (*X*)

Compound *VI* (10·2 g; 30 mmol) was treated with phosphorus tribromide in benzene for 1 h as described in the preparation of *IX*. After end of the reaction, the cold benzene solution was decanted, washed with water, 5% sodium hydroxide solution and water and dried over sodium sulfate. The solvent was evaporated and the residue crystallized from ethanol.

7-Allyl-8-azidomethyltheophylline (*XI*)

A mixture of *VII* (2·70 g; 10 mmol), sodium iodide (3·0 g; 20 mmol), and acetone (50 ml) was refluxed with stirring for 3 h. After cooling, the inorganic salts were filtered off and the filtrate was stirred with a solution of sodium azide (1·0 g; 15 mmol) in water (10 ml) at 30°C for 2 h and then at 45°C for 0·5 h. The mixture was concentrated to a minimum volume under diminished pressure and the product was taken up in tetrachloromethane (35 ml). The extract was dried over sodium sulfate, filtered with charcoal and the solvent was evaporated under diminished pressure in the dark.

7-(2-Propynyl)-8-azidomethyltheophylline (*XII*)

A solution of sodium azide (1·0 g; 15 mmol) in water (10 ml) was added to a solution of *VIII* (2·66 g; 10 mmol) in acetone (45 ml) and the stirred mixture was heated to 55°C for 2 h. The obtained solution was filtered with charcoal and the filtrate was mixed with water (100 ml). The crystalline product was dried in the dark.

7-(2-Butenyl)-8-azidomethyltheophylline (*XIII*)

A solution of sodium azide (2·5 g; 38 mmol) in water (30 ml) was added to *IX* (6·50 g; 20 mmol) in acetone (50 ml). The mixture was refluxed for 2 h under stirring and the obtained solution was filtered, the filtrate was mixed with water (50 ml) and the product was allowed to crystallize.

7-Cinnamyl-8-azidomethyltheophylline (*XIV*)

A solution of sodium azide (4·0 g; 60 mmol) in water (20 ml) was added to *X* (8·0 g; 20 mmol) in acetone (120 ml). After reflux for 0·5 h, the originally two-phase mixture became homogeneous. Acetone was evaporated under reduced pressure, water (30 ml) was added to the residue and the separated solid product was collected on filter and crystallized from ethanol. For the physical, analytical, and spectral data of the intermediates *III*—*XIV* see Tables I and II.

1,3-Dimethyl-2,4-dioxo-1,2,3,4,6,6a,7,11-octahydro(1,2,3)triazolo[1′,5′ : 1,2]pyrazino-[5,4-*f*]purine (*XV*) and Derivatives *XVI* and *XVII*

A solution of *XI* (2·75 g; 10 mmol) in dioxane (35 ml) was refluxed for 1 h. After cooling, the cycloadduct *XV* was filtered and crystallized from dioxane; yield 2·6 g (94·5%) of *XV*, m.p. 174·5 to 177°C. For $C_{11}H_{13}N_7O_2$ (275·2) calculated 47·81% C, 4·63% H, 35·21% N; found: 47·99% C, 4·75% H, 35·62% N. Mass spectrum, *m/z*: 275 (M^+). UV spectrum, λ_{max}, nm (log ε): 205 (4·39), 271 (4·07). ^{1}H NMR spectrum: 5·66 d, 1 H (H-6, $J(6, 6) = 18·5$); 4·97 d, 1 H (H-6); 4·60 dd, 1 H (H-11, $J(11, 11) = 13$, $J(11, 6a) = 5·2$); 4·34 dd, 1 H (H-7, $J(7, 7) = 15·6$, $J(7, 6a) = 5·2$);

4·24 dd, 1 H (H-7, J(7, 6a) = 10·4); 3·93 m, 1 H (H-6a); 3·71 d, 1 H (H-11); 3·56 s, 3 H (N(3)—CH_3); 3·38 s, 3 H (N(1)—CH_3). ^{13}C NMR spectrum: 154·97 (C-4); 151·52 (C-2); 148·70 (C-12a); 145·32 (C-11a); 106·32 (C-4a); 68·68 (C-7); 50·31 (C-6a); 44·98 (C-6 or C-11); 43·78 (C-11 or C-6); 29·83 (N(1)—CH_3); 27·90 (N(3)—CH_3).

Compound XVI: From *XIII* (2·90 g; 10 mmol) in dioxane (40 ml). After reflux for 4 h, the solvent was driven off under reduced pressure, the oily residue was triturated with ether and the separated compound was purified by column chromatography on silica gel (50 : 1) in chloroform. Yield 1·20 g (41·5%) of *XVI*, m.p. 156—158°C (decomp.). For $C_{12}H_{15}N_7O_2$ (289·3) calculated: 49·86% C, 5·10% H, 33·78% N; found: 49·81% C, 5·22% H, 33·89% N. UV spectrum, λ_{max}, nm (log ε): 207 (4·31), 272 (4·01). ^{1}H NMR spectrum: 5·58 d, 1 H (H-6, J(6, 6) = 18·3); 4·95 d, 1 H (H-7, J(7, CH_3) = 7·0); 4·90 d, 1 H (H-6); 4·65 dd, 1 H (H-11, J(11, 11) = 11·5, J(11, 6a) = = 3·5); 4·43 m, 1 H (H-6a); 3·68 d, 1 H (H-11); 3·53 s, 3 H (N(3)—CH_3); 3·33 s, 3 H (N(1)—CH_3); 1·35 d, 3 H (C(7)-CH_3). ^{13}C NMR spectrum: 155·02 (C-4); 151·45 (C-2); 148·69 (C-12a); 145·60 (C-11a); 106·64 (C-4a); 75·96 (C-7); 56·65 (C-6a); 45·28 (C-6 or C-11); 44·31 (C-11 or C-6); 29·86 (N(1)—CH_3); 27·92 (N(3)—CH_3); 15·58 (C(7)—CH_3).

Compound XVII: From *XIV* (3·51 g; 10 mmol) in dioxane (50 ml). After reflux for 1 h, the reaction mixture was concentrated under reduced pressure to half of the original volume, mixed with ether (10 ml) and the precipitate was crystallized from ethanol–ether (4 : 1) affording 2·30 g (63%) of *XVII*, m.p. 163—165°C. For $C_{17}H_{17}N_7O_2$ (351·3) calculated: 58·26% C, 4·93% H, 27·62% N; found: 58·10% C, 4·87% H, 27·90% N. Mass spectrum, m/z: 323 (M — 28). UV spectrum, λ_{max}, nm (log ε): 208 (4·35), 277 (3·79). ^{1}H NMR spectrum: 7·40 s, 5 H (H-arom.); 4·96 d, 1 H (H-7, J(7, 6a) = 3·5); 4·86 d, 2 H (H-6, J(6, 6a) = 3·7); 4·44 m, 1 H (H-6a); 3·75 s, 2 H (H-11); 3·53 s, 3 H (N(3)—CH_3), 3·33 s, 3 H (N(1)—CH_3).

1,3-Dimethyl-2,4-dioxo-1,2,3,4,6,11-hexahydro(1,2,3)triazolo[1′,5′ : 1,2]pyrazino-[5,4-*f*]purine (*XVIII*)

8-Azidomethyl derivative *XII* (2·73 g; 10 mmol) was dissolved at room temperature in dioxane (40 ml), the solution was filtered with charcoal and the filtrate was refluxed for 1 h. The title compound *XVIII* began to separate from the mixture already after about 15 min. After the end of the reaction, the product was filtered, the filtrate was concentrated under diminished pressure to half of the original volume, cooled and another portion of the product was obtained by filtration. Total yield of *XVIII*, m.p. 306—309°C (decomp.) was 1·80 g (65·4%). For $C_{11}H_{11}N_7O_2$ (273·2) calculated: 48·32% C, 4·15% H, 35·44% N; found: 48·34% C, 4·05% H, 35·88% N. Mass spectrum, m/z: 273 (M^+). UV spectrum, λ_{max}, nm (log ε): 209 (4·55), 273 (3·99). ^{1}H NMR, spectrum ($C^2H_3SOC^2H_3$): 7·89 s, 1 H (H-7); 5·86 s, 2 H (H-6); 5·64 s, 2 H (H-11); 3·45 s, 3 H (N(3)—CH_3); 3·31 s, 3 H (N(1)—CH_3).

The authors are indebted to Dr X. Svobodová for the elemental analyses, to Dr I. Skačáni for the IR *and* UV *spectral measurements and to Dr J. Bella for the* ^{1}H *and* ^{13}C NMR *spectra.*

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Translated by M. Tichý.