3,7-DIALKYL-8-ALKYL- OR -ARYL-3,7-DIHYDROPURINE-2,6-DIONES

Alfonz RYBÁR[a], Dušan HESEK[b], Fridrich SZEMES[b], Juraj ALFÖLDI[a] and Marian TEGZA[b]

[a] *Institute of Chemistry, Slovak Academy of Sciences, 842 38 Bratislava and*
[b] *Drug Research Institute, 900 01 Modra*

Received January 2, 1990
Accepted January 30, 1990

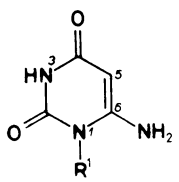
3,7-Dialkyl-8-alkyl- or -aryl-3,7-dihydropurine-2,6-diones *XII*—*XIV* were synthesized from 5-alkylamino-6-amino-1-alkyl-2,4(1*H*, 3*H*)-pyrimidinediones *VII*—*IX* by three methods: the first is based upon an acid catalyzed cyclization of the starting derivatives *VII*—*IX* with orthoesters of carboxylic acids in dimethylformamide. In the second and third methods the 5-((N-acyl)(N-alkyl)amino) derivatives *X*, *XI*, obtained by acylation of *VII*—*IX* were cyclized either in aqueous solution of alkali metal hydroxides, or in dimethylformamide in the presence of alkali metal carbonates. Intermediates *VII*—*IX* were prepared from 6-amino-1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones *I*—*III* via the corresponding 5-bromo derivatives *IV*—*VI* and by their aminolysis with the appropriate alkylamines.

This paper concerns the synthesis of new 3,7-dialkyl-8-alkyl- or -aryl-3,7-dihydropurine-2,6-diones *XII*—*XIV* suitable for preparation of further substituted xanthine derivatives potentially active against cardiovascular disorders. So far, only 8-methyl and 8-benzyl-3.7-dimethyl derivatives[1,2] have been the representatives of purines having an unsubstituted hydrocarbon residue. The above-mentioned products were obtained by a partial methylation of 8-substituted 3-methyl-3,7-dihydropurine-2,6-diones into position 7 (refs[1,3]). This method is disadvantageous because of formation of a 1,3,7-trimethyl derivative in addition to the required 3,7-dimethylated one regardless of the excess of the methylating agent.

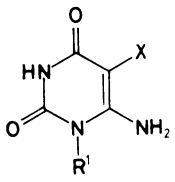
The presented synthesis affords compounds *XII*—*XIV* without by-products; the starting 6-amino-1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones *I*—*III* were brominated in position 5 (compounds *IV*—*VI*), which, on nucleophilic substitution with primary alkylamines gave 5-alkylamino-6-amino-1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones *VII* to *IX*. These were acylated with aliphatic carboxylic acids to yield the corresponding 5-((N-alkyl)(N-acyl)amino) derivatives *X*, *XI*, and cyclized to the final dioxopurines *XII*—*XIV*.

5-Bromo derivatives *IV*—*VI*, the initial step of this synthesis, were obtained by bromination of the starting substances *I*—*III* either in acetic acid in the presence of alkali metal acetates, or in lower aliphatic alcohols in the presence of alkali metal

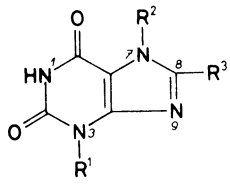
carbonates or hydrocarbonates. Compounds *I*–*III* were also brominated in water in the presence of alkali metal carbonates or hydrocarbonates at about 5°C, but the products *IV*–*VI* were, in accordance with ref.[4], partially contaminated by barbituric acid derivatives. As found, these by-products did not originate when alkali metal carbonates were replaced by calcium carbonate at temperatures between 5 and 10°C; consequently, this procedure proved suited for preparation of *IV*–*VI*.



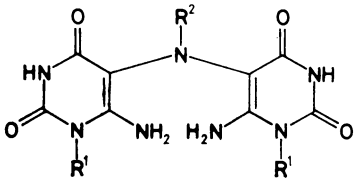
I—*III*



IV-*XI*



XII-*XIV*



XV

For explanation of substituents R^2 and R^3, see Table I (compounds *IV*–*XI*) and Table II (compounds *XII*–*XIV*). For compouds *I*, *IV*, *VII*, *X*, *XII* $R^1 = CH_3$; *II*, *V*, *VIII*, *XIII* $R^1 = C_2H_5$; *III*, *VI*, *IX*, *XI*, *XIV* $R^1 = n\text{-}C_3H_7$. For compounds: *IV*–*VI* X = Br; *VII*–*IX* X = NHR^2; *X*, *XI* X = N (R^2)COR^3.

5-Alkylamino derivatives *VII*–*IX* were prepared by reacting 5-bromo derivatives *IV*–*VI* with alkylamines, or their aqueous solutions in excess at 60–100°C. The by-product of this reaction is the corresponding tertiary amine *XV* formed even at a great excess of the alkylamine. Tertiary amines *XV*, where R^1 and R^2 are methyl or ethyl groups could be purified by acetylation of the crude reaction mixture giving 5-(N-acetyl)amino derivative *X*, separable by dissolution in water. Separation of tertiary amines *XV* with greater akyl groups is based on their lower solubility in ethanol; they are lacking a characteristic melting point, nevertheless, they revealed a molecular radical ion in their mass spectra.

Intermediates *X*–*XI* (5-(N-acyl)amino derivatives) were obtained from *VII*–*IX* on reflux with carboxylic acids in excess; accordingly, the reflux time depends on the size of R^2 and R^3. Yields and analytical data of intermediates *IV*–*XI* are listed in Table I.

The last step of this synthesis was the cyclization of 5-(N-acyl)amino derivatives *X*–*XI* to the final products *XII*–*XIV*. Two methods were employed: *a*) Reflux in aqueous alkali metal hydroxide or carbonate and acidification of the alkali metal salt of *XII*–*XIV* either with acetic acid, or carbon dioxide. Yields of this cyclization depend on the substituent bulkiness: the greater is R^2 the lesser is the yield. *b*) Heating in an aprotic solvent as e.g. dimethylformamide at 80–120°C in the presence of alkali metal carbonate.

The best yields of dioxopurines *XII*–*XIV* afforded cyclization of 5-alkylamino derivatives *VII*–*IX* with orthoesters of carboxylic acids in dimethylformamide under catalysis of *p*-toluenesulfonic acid at temperatures up to 100°C. Yields and analytical data of dioxopurines *XII*–*XIV* are listed in Table II.

The ^{1}H NMR chemical shift data of *XII*–*XIV* are listed in Table III; signals of the CH_3 group at N-3 appearing at δ 3·50–3·65 were found to be little influenced by the nature of substituents at N-7 and N-8. Similarly, signals due to N-7—CH_3 group occur at δ 3·90–3·93 except those of *XIIIb* and *XIVc*, which were seen, as a result of a deshielding effect of the aromatic ring, at δ 4·10. Signals of other CH_3 and CH_2 groups were assigned according to their multiplicity. Coupling constants for compounds bearing an allyl group at C-7 (*XIIp*, *XIIIc*, *XIIId*, *XIVf*) *J*(H,H)-*trans* = 16·93 Hz, *J*(H,H)-*cis* = 10·26 Hz, whilst that for the N-7—CH_2 was splitted into a doublet (4·1 Hz). The N-1—H signal for all compounds *XII*–*XIV* under study is a broad singlet at δ 8·15–9·65.

EXPERIMENTAL

The melting points are uncorrected, crystallized samples were dried at 100°C/65 Pa prior to analyses over phosphorus pentoxide for 8–10 h. Intermediates *VIIb*, *VIIIb*, *IXa* were purified with charcoal via aqueous solutions of hydrochlorides and recovered by basification with ammonia. The ^{1}H NMR spectra of deuterochloroform solutions containing tetramethylsilane as an internal reference were measured with a Bruker AM-300 spectrometer, the electron impact mass spectra were recorded with a Jeol 100 D apparatus at an ionization energy 70 eV. The reaction course and the purity of products were monitored by thin-layer chromatography on Silufol UV_{254} (Kavalier, Czechoslovakia) in solvent systems chloroform–methanol 9 : 1, or chloroform–ethanol–triethylamine 3 : 1 : 0·1 (compounds *IV*–*IX*).

6-Amino-5-bromo-1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones *IV*–*VI*

A) To a stirred and to 15–17°C cooled mixture consisting of compound *I*–*III* (0·20 mol), sodium hydrogencarbonate (17·64 g, 0·21 mol) and methanol (200 ml) bromine (33·60 g, 10·8 ml, 0·21 mol) was added to the bottom of the flask during 30 min. The reaction was finished after further 30 min and the product was filtered off and crystallized from water.

B) To a stirred solution obtained by a short heating of compound *I* (28·20 g, 0·20 mol) and sodium acetate trihydrate (29·90 g, 0·22 mol) in acetic acid (1 500 ml) bromine (35·16 g, 11·3 ml, 0·22 mol) was added to the bottom of the flask at about 90°C. Stirring had been continued for

TABLE I

Yields and analytical data of intermediates *IV*—*XI*

Compound	R^2	R^3	Yield, % (method)	M.p., °C solvent	Formula (M.w.)	Calculated/Found			M^+ *m/z*
						% C	% H	% N	
IV	—	—	70 (*A*) 83 (*B*) 62 (*C*)	286—288[a] water	$C_5H_6BrN_3O_2$ (220·0)	27·29 26·99	2·75 2·64	19·10[b] 19·15	219 221
V	—	—	56 (*A*) 57 (*C*)	248—249 methanol	$C_6H_8BrN_3O_2$ (234·1)	30·79 30·76	3·45 3·36	19·75[c] 18·05	233 235
VI	—	—	52 (*A*) 34 (*C*)	255—257[d] methanol	$C_7H_{10}BrN_3O_2$ (248·1)	33·89 34·10	4·06 4·25	16·94[e] 17·22	247 249
VIIa	CH_3	—	66	238—240 water	$C_6H_{10}N_4O_2$ (170·2)	42·35 42·07	5·92 6·03	32·93 32·98	170
VIIb	C_2H_5	—	55	208—210 ethanol	$C_7H_{12}N_4O_2$ (184·2)	45·64 45·76	6·57 6·51	30·42 30·28	184
VIIc	n-C_3H_7	—	57	230—232 ethanol	$C_8H_{14}N_4O_2$ (198·2)	48·47 48·18	7·12 7·29	28·27 28·36	198
VIId	n-C_4H_9	—	80	193—195 ethanol	$C_9H_{16}N_4O_2$ (212·3)	50·93 51·03	7·60 7·68	26·40 26·63	212
VIIe	$CH_2CH:CH_2$	—	61	185—186 ethanol	$C_8H_{12}N_4O_2$ (196·2)	48·97 48·69	6·17 6·36	28·56 28·55	196
VIIf	$CH_2C_6H_5$	—	50	236—237 ethanol	$C_{12}H_{14}N_4O_2$ (246·3)	58·52 58·33	5·73 5·60	22·75 23·01	246

VIIIa	CH_3	—	93	219—222 ethanol	$C_7H_{12}N_4O_2$ (184·2)	45·64 45·52	6·57 6·51	30·42 30·33	184
VIIIb	$CH_2CH:CH_2$	—	65	218—221 ethanol	$C_9H_{14}N_4O_2$ (210·2)	51·42 51·35	6·71 6·99	26·65 26·46	210
IXa	CH_3	—	73	205—207 ethanol	$C_8H_{14}N_4O_2$ (198·2)	48·47 48·43	7·12 7·38	28·27 28·43	198
IXb	n-C_3H_7	—	80	227—229 ethanol	$C_{10}H_{18}N_4O_2$ (226·3)	53·08 53·18	8·02 8·22	24·76 24·83	226
IXc	$CH_2CH:CH_2$	—	52	214—216 methanol	$C_{10}H_{16}N_4O_2$ (224·3)	53·55 53·29	7·19 7·01	24·98 25·19	224
Xa	CH_3	CH_3	68	315—316 water–ethanol	$C_8H_{12}N_4O_3$ (212·2)	45·28 45·33	5·70 5·80	26·40 26·49	212
Xb	CH_3	C_2H_5	83	316—317 water	$C_9H_{14}N_4O_3$ (226·2)	47·78 47·90	6·24 6·28	24·77 25·00	226
Xc	CH_3	n-C_3H_7	85	328—329 water	$C_{10}H_{16}N_4O_3$ (240·3)	49·99 50·05	6·71 6·78	23·32 23·59	240
Xd	CH_3	n-C_5H_{11}	77	280—282 ethanol	$C_{12}H_{20}N_4O_3$ (268·3)	53·71 53·84	7·51 7·52	20·88 21·22	268
Xe	C_2H_5	CH_3	81	326—327 water	$C_9H_{14}N_4O_3$ (226·2)	47·78 47·55	6·24 6·28	24·77 25·03	226
Xf	C_2H_5	C_2H_5	70	328—330 water	$C_{10}H_{16}N_4O_3$ (240·3)	49·99 50·21	6·71 6·73	23·32 23·57	240
Xg	C_2H_5	n-C_3H_7	64	316—318 water	$C_{11}H_{18}N_4O_3$ (254·3)	51·95 52·01	7·13 7·18	22·03 22·30	254

TABLE I
(*Continued*)

Compound	R^2	R^3	Yield, % (method)	M.p., °C solvent	Formula (M.w.)	Calculated/Found % C	% H	% N	M^+ *m/z*
Xh	C_2H_5	n-C_5H_{11}	60	258–259 water	$C_{13}H_{22}N_4O_3$ (282·3)	55·30 55·52	7·86 7·90	19·84 19·63	282
Xi	n-C_3H_7	CH_3	44	312–314 water	$C_{10}H_{16}N_4O_3$ (240·3)	49·99 49·80	6·71 6·58	23·32 23·57	240
Xj	n-C_3H_7	C_2H_5	87	300–302 water	$C_{11}H_{18}N_4O_3$ (254·3)	51·95 51·96	7·13 7·29	22·03 22·19	254
Xk	n-C_3H_7	n-C_3H_7	89	302–303 water	$C_{12}H_{20}N_4O_3$ (268·3)	53·71 53·87	7·51 7·67	20·88 21·16	268
Xl	n-C_3H_7	n-C_5H_{11}	65	275–277 ethanol	$C_{14}H_{24}N_4O_3$ (296·4)	56·74 56·90	8·16 8·30	18·91 18·66	296
XIa	n-C_3H_7	CH_3	68	288–289 methanol	$C_{12}H_{20}N_4O_3$ (268·3)	53·71 53·60	7·51 7·80	20·88 21·11	268
XIb	n-C_3H_7	n-C_5H_{11}	62	239–241 ethanol	$C_{16}H_{28}N_4O_3$ (324·4)	59·23 59·37	8·70 8·68	14·27 14·45	324

[a] Reported m.p. 265°C (ref.[4]), 278–280°C (ref.[5]); [b,c] % Br calculated/found 36·32/36·02, 34·14/33·98, respectively; [d] reported m.p. 237 to 239°C (ref.[6]); [e] % Br calculated/found 32·21/32·05.

c. 2 h till the temperature dropped to about 20°C, the product was filtered off and crystallized from water.

C) To a stirred and to 5—7°C cooled mixture of compound *I*—*III* (50 mmol), calcium carbonate (3·0 g, 30 mmol) and water (50 ml), bromine (8·15 g, 2·6 ml, 51 mmol) was introduced to the bottom of the flask during 10 min. The mixture was stirred at this temperature for additional 50 min, the crude product was filtered off and crystallized from water.

5-Alkylamino-6-amino-1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones *VII*—*IX*

Compound *IV*—*VI* (0·2 mol) was heated with concentrated aqueous solution or anhydrous alkylamine (2·0 mol) in a closed vessel as follows: compounds *VIIa*—*VIIc*, *VIIIa* at 65°C for 3 h, *VIIe*, *IXa* for 4 h, *VIIIb*, *IXb*, *IXc* for 5 h, and compounds *VIId* and *VIIf* at 80°C for 7 h. The excess of the amine was distilled off under reduced pressure, the residue was suspended in ethanol (50 ml — compounds *VIIa*—*VIIc*, *VIIIa*, *IXa*) or water (50 ml — compounds *VIId*—*VIIf*, *VIIIb*, *IXb*, *IXc*) and pH of the suspension was adjusted to 7 by addition of acetic acid. The ethanol containing flasks were allowed to stand at 0°C for c. 5 h, the aqueous suspensions at room temperature for c. 1 h; during this time the alkylammonium bromide being formed dissolved, the desired product was filtered off and crystallized from ethanol (compounds *VIIc*—*VIIf*, *VIIIa*, *VIIIb*, *IXa*—*IXc*) or water (compounds *VIIa*, *VIIb*).

5-((N-Alkyl)(N-acyl)amino)-6-amino-1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones *X*—*XI*

Compound *VII*—*IX* (40 mmol) was either refluxed or heated to 160°C with the respective aliphatic acid (0·4 mol) with stirring as follows: compounds *Xa*—*Xc*, *Xe*, *Xf* for 3 h, *Xd*, *Xi*, *XIa* for 4 h, *Xg*, *Xj* for 5 h, *Xk* for 6 h, *Xh*, *Xl* for 7h, and *Xb* for 8 h. Excess of the acid was then distilled off under reduced pressure and the residue was crystallized from water (*Xa*, *Xe*, *Xf*, *XIi*, *XIa*) or ethanol (*Xb*, *Xg*, *Xj*, *Xk*), or extracted with ether at elevated temperature and crystallized from water (*Xc*), ethanol (*Xd*, *Xl*), methanol (*Xh*), or aqueous ethanol (*XIb*).

3,7-Dialkyl-8-alkyl- or -aryl-3,7-dihydropurine-2,6-diones *XII*—*XIV*

A) Sodium hydroxide (1 mol l^{-1}, 20 ml, 20 mmol) was added to a suspension of 5-acylamino derivatives *X* (20 mmol) in water (40 ml) the pH of which was adjusted to 7. The mixture with compound *XIIa* was refluxed and stirred for 1 h, with *XIIb*—*XIIe* 3 h, with *XIIk* 4 h, and with *XIIf* 5 h. The undissolved impurities were filtered off and dilute acetic acid (1 : 1) was added to the cooled filtrate; alternatively, the cooled filtrate was saturated with carbon dioxide. The mixture was left to stand at about 0°C for 2—3 h, the precipitated product was filtered off, dried at 100°C under diminished pressure and crystallized from ethanol. The not-cyclized starting material *X* had to be removed from compounds *XIIk*, *XIIl* with hot toluene or tetrachloromethane in which only the products are soluble.

B) 5-Acylamino derivative *X*—*XI* (40 mmol), anhydrous potassium carbonate (6·63 g, 48 mmol) and dimethylformamide (100 ml) were heated at 120°C for 3 h (*XIIa*), 5 h (*XIIg*), 6 h (*XIId*, *XIIl*), 7 h (*XIIe*), 10 h (*XIIf*, *XIVc*), 12 h (*XIIh*, *XIVd*, *XIVe*), 14 h (*XIIm*). Dimethylformamide was distilled off under reduced pressure, the dry residue was dissolved in water (50 to 150 ml), the turbidity was removed by filtration with charcoal and the filtrate was saturated with carbon dioxide. The mixture was allowed to stand at 0°C for 2—3 h, the precipitate was filtered off, dried at 100°C under diminished pressure and crystallized from ethanol.

C) 5-Alkylamino derivative *VII*—*IX* (10 mmol), dimethylformamide (15 ml), triethyl- or trimethylorthoester of carboxylic acid (15 mmol) and *p*-toluenesulfonic acid monohydrate

TABLE II

Yields and analytical data of 3,7-disubstituted 8-alkyl-, or -aryl-3,7-dihydropurine-2,6-diones *XII*—*XIV*

Compound	R^2	R^3	Yield, % (method)	M.p. °C	Formula (M.w.)	Calculated/Found			M^+ *m/z*
						% C	% H	% N	
XIIa	CH_3	CH_3	53 (*A*) 82 (*B*)	309—311[a]	$C_8H_{10}N_4O_2$ (194·2)	49·48 49·63	5·19 5·28	28·85 29·06	194
XIIb	CH_3	C_2H_5	54 (*A*)	262—263	$C_9H_{12}N_4O_2$ (208·2)	51·91 51·97	5·81 5·73	26·91 27·11	208
XIIc	CH_3	n-C_3H_7	51 (*A*)	244—245	$C_{10}H_{14}N_4O_2$ (222·2)	54·04 54·10	6·35 6·42	25·21 25·47	222
XIId	CH_3	n-C_5H_{11}	54 (*A*) 43 (*B*)	220—222	$C_{12}H_{18}N_4O_2$ (250·3)	57·58 57·30	7·25 7·27	22·39 22·47	250
XIIe	C_2H_5	CH_3	25 (*A*) 68 (*B*), 89 (*C*)	267—268	$C_9H_{12}N_4O_2$ (208·2)	51·91 51·94	5·81 5·82	26·91 27·13	208
XIIf	C_2H_5	C_2H_5	45 (*A*) 82 (*B*), 94 (*C*)	237—238	$C_{10}H_{14}N_4O_2$ (222·2)	54·04 54·20	6·35 6·44	25·21 25·37	222
XIIg	C_2H_5	n-C_3H_7	69 (*B*) 93 (*C*)	211—213	$C_{11}H_{16}N_4O_2$ (236·3)	55·91 56·00	6·83 6·93	23·71 23·84	236
XIIh	C_2H_5	n-C_5H_{11}	91 (*B*)	165—166	$C_{13}H_{20}N_4O_2$ (264·3)	59·07 59·13	7·63 7·61	21·20 21·14	264
XIIi	C_2H_5	C_6H_5	56 (*C*)	227—228	$C_{14}H_{14}N_4O_2$ (270·3)	62·21 62·47	5·22 5·16	20·73 20·58	270
XIIj	n-C_3H_7	CH_3	93 (*C*)	218—219	$C_{10}H_{14}N_4O_2$ (222·2)	54·04 54·12	6·35 6·31	25·21 25·46	222

XIIk	n-C_3H_7	C_2H_5	29 (*A*)	180–181[b]	$C_{11}H_{16}N_4O_2$ (236·3)	55·91 56·13	6·83 6·96	23·71 24·04	236
XIIl	n-C_3H_7	n-C_3H_7	34 (*B*)	172–174[b]	$C_{12}H_{18}N_4O_2$ (250·3)	57·58 57·28	7·25 7·47	22·39 22·22	250
XIIm	n-C_3H_7	n-C_5H_{11}	78 (*B*)	167–168	$C_{14}H_{22}N_4O_2$ (278·4)	60·41 60·70	7·97 7·83	20·13 20·34	278
XIIn	n-C_4H_9	CH_3	63 (*C*)	231–232	$C_{11}H_{16}N_4O_2$ (236·3)	55·91 55·92	6·83 6·88	23·71 24·04	236
XIIo	n-C_4H_9	C_6H_5	69 (*C*)	221–223	$C_{16}H_{18}N_4O_2$ (298·3)	64·41 64·48	6·08 6·09	18·78 18·97	298
XIIp	$CH_2CH:CH_2$	CH_3	41 (*C*)	214–215	$C_{10}H_{12}N_4O_2$ (220·2)	54·53 54·67	5·49 5·45	25·44 25·62	220
XIIr	$CH_2C_6H_5$	CH_3	77 (*C*)	243–245	$C_{14}H_{14}N_4O_2$ (270·3)	62·21 62·20	5·22 5·26	20·73 20·98	270
XIIIa	CH_3	CH_3	59 (*C*)	268–270[c]	$C_9H_{12}N_4O_2$ (208·2)	51·91 51·77	5·81 6·03	26·91 27·20	208
XIIIb	CH_3	C_6H_5	50 (*C*)	267–269	$C_{14}H_{14}N_4O_2$ (270·3)	62·21 62·01	5·52 5·49	20·73 21·00	270
XIIIc	$CH_2CH:CH_2$	CH_3	78 (*C*)	200–202	$C_{11}H_{14}N_4O_2$ (234·3)	56·40 56·33	6·02 6·30	23·92 24·03	234
XIIId	$CH_2CH:CH_2$	C_6H_5	45 (*C*)	238–239	$C_{16}H_{16}N_4O_2$ (296·3)	64·85 64·59	5·44 5·39	18·91 19·03	296
XIVa	CH_3	CH_3	32 (*C*)	255–257	$C_{10}H_{14}N_4O_2$ (222·2)	54·04 53·83	6·35 6·10	25·21 25·40	222

TABLE II
(*Continued*)

Compound	R^2	R^3	Yield, % (method)	M.p. °C	Formula (M.w.)	Calculated/Found			M^+ *m/z*
						% C	% H	% N	
XIVb	CH_3	n-C_3H_7	18 (*C*)	228–229	$C_{12}H_{18}N_4O_2$ (250·3)	57·58 57·78	7·25 7·45	22·39 22·68	250
XIVc	CH_3	C_6H_5	44 (*C*)	250–251	$C_{15}H_{16}N_4O_2$ (284·3)	63·36 63·38	5·67 5·91	19·71 19·69	284
XIVd	n-C_3H_7	CH_3	67 (*B*)	187–189	$C_{12}H_{18}N_4O_2$ (250·3)	57·58 57·40	7·25 7·13	22·39 22·45	250
XIVe	n-C_3H_7	n-C_5H_{11}	69 (*B*)	115–116	$C_{16}H_{26}N_4O_2$ (306·4)	62·72 62·99	8·55 8·70	18·29 18·48	306
XIVf	$CH_2CH:CH_2$	CH_3	35 (*C*)	180–181	$C_{12}H_{16}N_4O_2$ (248·3)	58·05 57·91	6·49 6·28	22·57 22·81	248

[a] In sealed capillary; [b] from toluene; [c] from water.

TABLE III

^{1}H NMR chemical shifts (δ, ppm) of compounds *XII*—*XIV*

Compound	N(3)-R^1	N(7)-R^2	C(8)-R^3	N(1)-H[a]
XIIa	3·55 s, 3 H (CH_3)	3·90 s, 3 H (CH_3)	2·50 s, 3 H (CH_3)	8·15
XIIb	3·55 s, 3 H (CH_3)	3·90 s, 3 H (CH_3)	1·40 t, 3 H (CH_3) 2·80 q, 2 H (CH_2)	8·80
XIIc	3·55 s, 3 H (CH_3)	3·90 s, 3 H (CH_3)	1·03 t, 3 H (CH_3) 1·80 se, 2 H (CH_2) 2·72 t, 2 H (CH_2)	9·20
XIId	3·55 s, 3 H (CH_3)	3·93 s, 3 H (CH_3)	0·92 t, 3 H (CH_3) 1·40 ov, 4 H (2 × CH_2) 1·78 q, 2 H (CH_2) 2·75 t, 2 H (CH_3)	9·00
XIIe	3·55 s, 3 H (CH_3)	1·40 t, 3 H (CH_3) 4·30 q, 2 H (CH_2)	2·50 s, 3 H (CH_3)	9·35
XIIf	3·58 s, 3 H (CH_3)	1·45 t, 3 H (CH_3) 4·30 q, 2 H (CH_2)	1·50 t, 3 H (CH_3) 2·80 q, 2 H (CH_2)	9·10
XIIg	3·55 s, 3 H (CH_3)	1·45 t, 3 H (CH_3) 4·30 q, 2 H (CH_2)	1·02 t, 3 H (CH_3) 1·82 se, 2 H (CH_2) 2·70 t, 2 H (CH_2)	9·40
XIIh	3·55 s, 3 H (CH_3)	1·45 t, 3 H (CH_3) 4·30 q, 2 H (CH_2)	0·93 t, 3 H (CH_3) 1·40 ov, 4 H (2 × CH_2) 1·80 qi, 2 H (CH_2) 2·75 t, 2 H (CH_2)	9·20
XIIi	3·62 s, 3 H (CH_3)	1·52 t, 3 H (CH_3) 4·40 q, 2 H (CH_2)	7·58—7·68 m, 5 H (arom.)	8·92
XIIj	3·50 s, 3 H (CH_3)	0·92 t, 3 H (CH_3) 1·82 se, 2 H (CH_2) 4·18 t, 2 H (CH_2)	2·45 s, 3 H (CH_3)	9·58
XIIk	3·50 s, 3 H (CH_3)	0·90 t, 3 H (CH_3) 1·78 se, 2 H (CH_2) 4·15 t, 2 H (CH_2)	1·30 t, 3 H (CH_3) 2·72 q, 2 H (CH_2)	8·95
XIIl	3·48 s, 3 H (CH_3)	0·90 t, 3 H (CH_3) 1·78 ov, 2 H (CH_2) 4·12 t, 2 H (CH_2)	0·98 t, 3 H (CH_3) 1·78 ov, 2 H (CH_2) 2·65 t, 2 H (CH_2)	9·05
XIIm	3·58 s, 3 H (CH_3)	0·95 t, 3 H (CH_3) 1·82 ov, 2 H (CH_2) 4·20 t, 2 H (CH_2)	0·92 t, 3 H (CH_3) 1·38 ov, 4 H (2 × CH_2) 2·73 t, 2 H (CH_2) 2·80 ov, 2 H (CH_2)	9·18

TABLE III
(*Continued*)

Compound	N(3)-R^1	N(7)-R^2	C(8)-R^3	N(1)-H[a]
XIIn	3·50 s, 3 H (CH_3)	0·92 t, 3 H (CH_3) 1·35 se, 2 H (CH_2) 1·75 qi, 2 H (CH_2) 4·20 t, 2 H (CH_2)	2·45 s, 3 H (CH_3)	9·62
XIIo	3·63 s, 3 H (CH_3)	0·90 t, 3 H (CH_3) 1·30 se, 2 H (CH_2) 1·84 qi, 2 H (CH_2) 4·40 t, 2 H (CH_2)	7·55—7·65 m, 5 H (arom)	8·60
XIIp	3·53 s, 3 H (CH_3)	4·90 d, 2 H (CH_2) 5·05 d, 1 H (CH *trans*) 5·25 d, 1 H (CH *cis*) 5·93 o, 1 H (CH)	2·44 s, 3 H (CH_3)	9·65
XIIr	3·55 s, 3 H (CH_3)	5·50 s, 2 H (CH_2) 7·15—7·35 m, 5 H (arom.)	2·45 s, 3 H (CH_3)	9·20
XIIIa	1·35 t, 3 H (CH_3) 4·13 q, 2 H (CH_2)	3·90 s, 3 H (CH_3)	2·48 s, 3 H (CH_3)	8·83
XIIIb	1·35 t, 3 H (CH_3) 4·18 q, 2 H (CH_2)	4·00 s, 3 H (CH_3)	7·50—7·65 m, 5 H (arom.)	8·80
XIIIc	1·35 t, 3 H (CH_3) 4·13 q, 2 H (CH_2)	4·90 d, 2 H (CH_2) 5·10 d, 1 H (CH *trans*) 5·28 d, 1 H (CH *cis*) 5·98 o, 1 H (CH)	2·45 s, 3 H (CH_3)	9·18
XIIId	1·35 t, 3 H (CH_3) 4·18 q, 2 H (CH_2)	4·90 d, 2 H (CH_2) 5·08 d, 1 H (CH *trans*) 5·26 d, 1 H (CH *cis*) 6·03 o, 1 H (CH)	7·45—7·65 m, 5 H (arom.)	8·78
XIVa	0·95 t, 3 H (CH_3) 1·80 se, 2 H (CH_2) 4·02 t, 2 H (CH_2)	3·90 s, 3 H (CH_3)	2·45 s, 3 H (CH_3)	9·20
XIVb	0·95 t, 3 H (CH_3) 1·80 se, 2 H (CH_2) 4·09 t, 2 H (CH_2)	3·92 s, 3 H (CH_3)	1·05 t, 3 H (CH_3) 1·80 se, 2 H (CH_2) 2·75 t, 3 H (CH_2)	8·92
XIVc	1·02 t, 3 H (CH_3) 1·88 se, 2 H (CH_2) 4·15 t, 2 H (CH_2)	4·10 s, 3 H (CH_3)	7·65—7·75 m, 5 H (arom.).	8·80

TABLE III
(*Continued*)

Compound	N(3)–R^1	N(7)–R^2	C(8)–R^3	N(1)–H[a]
XIVd	0·90 ov, 3 H (CH_3) 1·75 se, 2 H (CH_2) 3·92 t, 2 H (CH_2)	0·94 ov, 3 H (CH_3) 1·75 se, 2 H (CH_2) 4·12 t, 2 H (CH_2)	2·40 s, 3 H (CH_3)	9·30
XIVe	0·95 t, 3 H (CH_3) 1·80 ov, 2 H (CH_2) 4·08 t, 2 H (CH_2)	0·95 t, 3 H (CH_3) 1·82 ov, 2 H (CH_2) 4·20 t, 2 H (CH_2)	0·98 t, 3 H (CH_3) 1·80 ov, 4 H (2 × CH_2) 1·82 ov, 2 H (CH_2) 2·75 t, 2 H (CH_2)	8·65
XIVf	0·93 t, 3 H (CH_3) 1·77 se, 2 H (CH_2) 3·99 t, 2 H (CH_2)	4·88 d, 2 H (CH_2) 5·03 d, 1 H (CH *trans*) 5·21 d, 1 H (CH *cis*) 5·92 o, 1 H (CH)	2·41 s, 3 H (CH_3)	9·36

[a] bs, 1 H; ov overlapped, se sextet.

(10—15 mg) were heated with stirring as follows: *XIIe* — 60°C, 2 h; *XIIf*, *XIVa* — 60°C, 3 h; *XIIg*, *XIIj*, *XIIn*, *XIIp* — 60°C, 4 h; *XIIi*, *XIIIc* — 60°C, 6 h; *XIVb*, *XIVf* — 60°C, 11 h; *XIIr* — 70°C, 5 h; *XIIo*, *XIIIa* — 70°C, 12 h; *XIVc*, *XIIIb*, *XIIId* — 85°C, 10 h. The mixture was cooled to ambient temperature and *p*-toluenesulfonic acid was neutralized by methanolic ammonia. Volatile portions were removed in vacuo, the residue was dissolved in water (5—15 ml), sodium hydroxide (1 mol l^{-1}, 11 ml) and charcoal were added, and carbon dioxide was introduced to the filtered solution till be product ceased to separate. After standing at 0°C for 2—3 h, the product was filtered off, dried at 100°C under reduced pressure and crystallized from ethanol.

The authors are indebted to Mr. V. Hladký, Miss A. Gembická and Mr. K. Paule for their assistance with preparation of intermediates, measuring the mass spectra and for elemental analyses, respectively.

REFERENCES

1. Golovchinskaya E. S.: Zh. Prikl. Khim. (Leningrad): *30*, 1374 (1957); Chem. Abstr. *52*, 5425 (1958).
2. Kostolanský A., Mokrý J., Tamchyna J.: Chem. Zvesti *10*, 96 (1956); Chem. Abstr. *50*, 13947 (1956).
3. Bedereck H., Siegel E., Föhlish B.: Chem. Ber. *95*, 407 (1962).
4. Wojciechowski J.: Acta Pol. Pharm. *18*, 409 (1961); Chem. Abstr. *57*, 11193 (1962).
5. Barker G. R., Luthy N. G.: J. Chem. Soc. *1956*, 920.
6. Schroeder E. F.: U.S. 2731465 (1956); Chem. Abstr. *51*, 1257 (1957).

Translated by Z. Votický.