STUDIES IN THE IMIDAZOLE SERIES

LIV. SYNTHESIS OF IMIDAZO[1,2-f]XANTHINE DERIVATIVES BASED ON 8-AMINO(ALKYLAMINO, ARYLAMINO)THEOPHYLLINES

A. A. Tkachenko, P. M. Kochergin,
and F. A. Zubkov

UDC 547.857.4'781.07:543.422.4'544

A number of 1H-imidazo[1,2-f]xanthine derivatives were obtained by the reaction of 8-amino(alkylamino, arylamino)theophyllines with α-haloketones and subsequent cyclization of the 7-acylalkyl-8-amino(alkylamino, arylamino)theophyllines.

In developing the research in [1] we have made a more detailed investigation of the reaction of 8-aminocaffeine (I) and 8-amino(alkylamino, arylamino)theophyllines (II-V) with α-haloketones. It was found that I, in contrast to 2-aminopyridine [2] and other nitrogenous 2-amino heterocycles [3], does not react with α-bromoketones, which is apparently explained by the low basicity of this compound. Compounds II-V do not react with α-haloketones in the absence of an alkaline agent. However, the reaction with bromomethyl aryl ketones proceeds very rapidly in aqueous alcohol solutions in the presence of KOH or NaOH, and even more rapidly when their potassium salts (IIa-Va) are heated in methanol to form 7-acylmethyl-8-amino(alkylamino, arylamino) theophyllines (VII-XIII, Table 1). It should be noted that the constants for X and XII do not agree with the literature data for these compounds, which were previously synthesized by the reaction of 7-phenacyl-8-bromotheophylline (VI) with butylamine and aniline [4, 5].

When II is heated in an aqueous alcohol solution of alkali or IIa is heated in methanol with α-bromoketones containing bromine attached to a secondary carbon atom, the reaction does not stop at the step involving the formation of 7-acylalkyl-8-aminotheophyllines but proceeds further with the splitting out of a molecule of water and the formation of the corresponding substituted imidazo[1,2-f]xanthines (XIV-XVII).

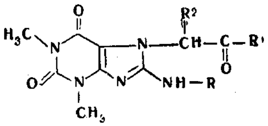
The 7-acylmethyl-8-amino(alkylamino, arylamino)theophyllines (VII-XIII) are smoothly converted to imidazoxanthine derivatives (XVIII-XXIV) only when they are heated in organic or mineral acids (HCOOH, CH_3COOH, HCl, HBr, H_3PO_4) and also by the action of dehydrating agents ($POCl_3$ and concentrated H_2SO_4). It is interesting to note that XII and XIII, which have aryl substituents attached to the exocyclic nitrogen atom which reduce the nucleophilicity of the imino group, do not change on refluxing in glacial acetic acid, but are cyclized to XXIII and XXIV when they are heated in 60-70% acetic acid. This is evidence that the cyclization of 7-acylmethyl-8-aminotheophyllines depends not only on the character of the substituent in the 8-position but also on the acidity of the medium.

Another more convincing proof of the catalytic effect of hydrogen ions on the closing of the imidazole ring is that 7-phenacyl-8-aminotheophylline (VII) does not change on prolonged refluxing in ethanol or butanol, but is rapidly converted to 2-phenyl-6,8-dimethylimidazo[1,2-f]xanthine (XVIII) in 78-80% yield in the same solvents in the presence of hydrogen chloride.

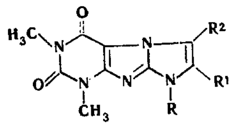
In analogy with the mechanism for closing of the thiazole ring [6-8], it is extremely likely that the closing of the imidazole ring during the cyclization of 7-acylalkyl-8-amino(alkylamino, arylamino)theophyllines to imidazo[1,2-f]xanthine derivatives also proceeds through an intermediate step involving the formation of 2-hydroxy derivatives of imidazolino[1,2-f]xanthine.

Zaporozhe Medicinal Institute. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 682-685, May, 1971. Original article submitted November 3, 1969.

TABLE 1. 7-Acylalkyl-8-amino(alkylamino, arylamino)theophyllines (VII-XIII) and Imidazo[1,2-f]xanthine Derivatives (XIV-XXIV)



XII XIII



XIV-XXIV

Comp.	R	R¹	R²	mp (dec.)[a]	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
VII	H	C_6H_5	H	248—250[b]	$C_{15}H_{15}N_5O_3$	—	—	—	—	—	—	82
VIII	H	p-BrC_6H_4	H	270—275[c]	$C_{15}H_{14}BrN_5O_3$	—	—	—	—	—	—	79
IX	CH_3	C_6H_5	H	220—222	$C_{17}H_{17}N_5O_3$	58,88	5,71	21,64	58,70	5,23	21,40	56
X	n-C_4H_9	C_6H_5	H	186—190[d]	$C_{19}H_{23}N_5O_3$	62,03	6,30	18,91	61,77	6,27	18,95	82
XI	n-C_4H_9	p-BrC_6H_4	H	188—190[e]	$C_{19}H_{22}BrN_5O_3$	50,69	5,16	15,32	50,90	4,95	15,62	80
XII	C_6H_5	C_6H_5	H	227—230[f]	$C_{21}H_{19}N_5O_3$	64,60	5,18	17,71	64,76	4,92	17,98	61
XIII	C_6H_5	p-BrC_6H_4	H	255—257[g]	$C_{21}H_{18}BrN_5O_3$	54,00	4,00	14,87	53,86	3,18	14,95	77
XIV	H	CH_3	CH_3	325—327	$C_{11}H_{13}N_5O_2$	53,62	5,34	28,58	53,43	5,30	28,33	39
XV	H	CH_3	C_6H_5	340	$C_{16}H_{15}N_5O_2$	62,21	4,99	22,64	62,12	4,88	22,64	78
XVI	H	C_6H_5	CH_3	330—331	$C_{16}H_{15}N_5O_2$	62,38	4,95	22,41	62,12	4,88	22,64	73
XVII	H	C_6H_5	C_6H_5	308—309	$C_{21}H_{17}N_5O_2$	68,43	4,50	18,55	67,92	4,61	18,85	77
XVIII	H	C_6H_5	H	340—345[h]	$C_{15}H_{13}N_5O_2$	—	—	—	—	—	—	48—89
XIX	H	p-BrC_6H_4	H	325[i]	$C_{15}H_{12}BrN_5O_2$	—	—	—	—	—	—	88
XX	CH_3	C_6H_5	H	235—236	$C_{16}H_{15}N_5O_2$	62,13	4,98	22,38	62,12	4,88	22,64	91
XXI	n-C_4H_9	C_6H_5	H	172—173	$C_{19}H_{21}N_5O_2$	64,91	6,31	19,72	64,93	6,02	19,93	85—90
XXII	n-C_4H_9	p-BrC_6H_4	H	186—187[j]	$C_{19}H_{20}BrN_5O_2$	53,21	4,80	16,25	53,03	4,68	16,27	87
XXIII	C_6H_5	C_6H_5	H	259—260	$C_{21}H_{17}N_5O_2$	67,66	4,63	18,32	67,91	4,61	18,85	87—92
XXIV	C_6H_5	p-BrC_6H_4	H	295—300[k]	$C_{21}H_{16}BrN_5O_2$	55,82	3,66	15,62	56,01	3,58	15,55	86—87

---

[a] The compounds were purified for analysis by crystallization: VII-IX, XIV, XVI, XVII, and XX from ethanol; X from 70% methanol; XI from toluene; XII and XXIII from dioxane; XIII from butanol; XV, XVIII, and XIX from glacial acetic acid; XXII from 50% ethanol; XXIV from 80% formic acid.

[b] mp 248-250° [1]. R_f values: 0.88 [butanol–acetic acid–water (4 : 1 : 5)], 0.80 [butanol–pyridine–acetic acid (6 : 4 : 3)], 0.79 [ethanol–acetic acid–water (17 : 2 : 1)].

[c] mp 270-275° [1].

[d] mp 285-287° [4,5].

[e] Found %: Br 18.02. Calculated %: Br 17.82.

[f] mp 246-248° [4,5].

[g] Found %: Br 17.19. Calculated %: Br 17.06.

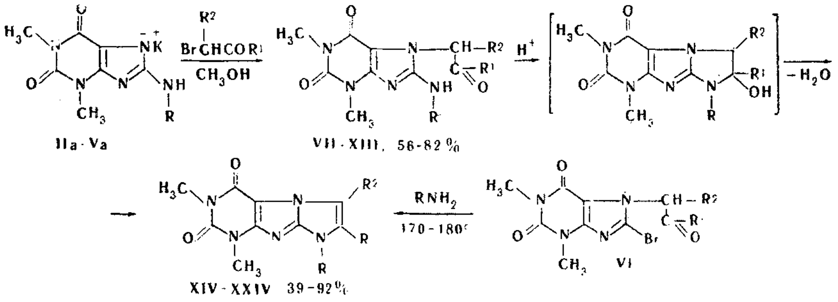
[h] mp > 320° (decomp.) [1]. R_f values: 0.62 [butanol–acetic acid–water (4 : 1 : 5)], 0.78 [butanol–pyridine–acetic acid (6 : 4 : 3)], 0.44 [ethanol–acetic acid–water (17 : 2 : 1)].

[i] Decomposes above 325° [1].

[j] Found %: Br 18.56. Calculated %: Br 18.57.

[k] Found %: Br 17.80. Calculated %: Br 17.75. IR spectra, cm^{-1}: XI 1632, 1670, 1715 (CO), 3345 (NH), XIII 1638, 1666, 1700 (CO), 3340 (NH); XIV 1678, 1720 (CO); XVI 1648, 1710 (CO); XVIII 1663, 1695 (CO); XX 1645, 1707 (CO); XXI 1665, 1707 (CO); XXIII 1645, 1709 (CO).

The purity of the 7-acylmethyl-8-amino(alkylamino, arylamino)theophyllines and imidazoxanthines that we obtained was confirmed by two-dimensional paper chromatography, while the structures were confirmed by the IR spectra and alternative synthesis of XVIII, XX, XXI, and XXIII by heating 7-phenacyl-8-bromotheophylline (VI) with ammonia and the appropriate amines [9]. Thus, it was simultaneously established that the three-ring compounds (XIV-XXIV) are 1H-imidazo[1,2-f]xanthine derivatives, while the intermediates (VII-XIII) are 7-acylalkyl-8-amino(alkylamino, arylamino)theophyllines.



EXPERIMENTAL*

Known methods were used to prepare 8-aminocaffeine (I) [10], 8-aminotheophylline (II) [11], 8-methylaminotheophylline (III) [12], 8-butylaminotheophylline (IV) [12], 8-phenylaminotheophylline (V) [11], and 7-phenacyl-8-bromotheophylline (VI) [13].

Potassium Salts of 8-Amino(methylamino, butylamino, phenylamino)theophyllines (IIa-Va). A mixture of 0.05 mole of amine (II-V) and 0,075 mole of KOH in 150 ml of water was heated to 95-100°, the resulting solution was cooled to 35-40°, 350 ml of acetone was added, and the resulting precipitate was filtered and washed with ethanol and acetone to give 77-97% of products with mp 330-332°, 275-277°, 252-255°, and 92-93° (decomp.), respectively.

7-Acylmethyl-8-amino(alkylamino, arylamino)theophyllines (VII-XIII, Table 1). The α-bromoketone (0.03 mole) was added to a suspension of 0.03 mole of IIa-Va in 100-150 ml of hot methanol, the mixture was refluxed with stirring for 10-30 min and cooled. The precipitate was filtered, washed with water, ethanol, and chloroform. Compounds X and XI were also obtained when the reaction was carried out in 50% aqueous methanol in the presence of an equimolecular amount of KOH or NaOH. The colorless or pale-yellow (VIII) crystalline substances were slightly soluble in most organic solvents and insoluble in water.

Imidazo[1,2-f]xanthine Derivatives (XIV-XXIV, Table 1). A. The α-bromo ketone (0.03 mole) was added to a suspension of 0.02 mole of IIa and 150 ml of hot methanol, and the mixture was refluxed with stirring for 2 h and cooled. The precipitate was filtered and washed with water, ethanol, and chloroform to give 73-78% of XV and XVI. Compounds XIV and XVII (39 and 77%, respectively) were similarly obtained, with the difference that the reaction was carried out in 50% aqueous ethanol for 24 h in the presence of an equimolecular amount of KOH or NaOH.

B. A solution of 3 mmole of VII, XII, or XIII in 10 ml of 85% formic acid was refluxed for 2 h and cooled. The precipitate was filtered and washed with ether to give 83-87% of XVIII, XXIII, and XXIV.

C. A solution of 3 mmole of VII, VIII, or X in 15 ml of acetic acid was refluxed for 2 h and worked up as in experiment B to give 85-90% of XVIII, XIX, and XXI.

D. A solution of 3 mmole of VII in 10 ml of 36% HCl was refluxed for 1 h and cooled, and the precipitate of XVIII was filtered and washed with water and acetone. The reaction was similarly carried out in 25% HCl in ethanol or butanol to give 77-80% of XVIII.

E. A solution of 3 mmole of VII or IX-XIII in 10-15 ml of 40-48% HBr was refluxed for 5-10 min and cooled, and the precipitate was filtered and washed with water and acetone to give 84-92% yield of XVIII and XX-XXIV.

---

*We thank V. V. Kolpakova and Yu. N. Sheinker and their co-workers for performing the microanalyses and obtaining the IR spectra of the compounds.

F. A solution of 3 mmole of VII in 15 ml of 85% H_3PO_4 was refluxed for 5 h and worked up as in experiment E to give 69% of XVIII.

G. A solution of 3 mmole of VII in 10 ml of 96% H_2SO_4 was allowed to stand for 12 h at 18-20° and then poured into 50 ml of water. The precipitate was filtered and washed with water and acetone to give 48% of XVIII.

H. A solution of 3 mmole of VII in 10 ml of $POCl_3$ was refluxed for 30 min and cooled, and the precipitate of XVIII was filtered and washed with water, ethanol, and ether to give 66% of XVIII.

I. A mixture of 0.02 mole of VI and 0.05 mole of butylamine or aniline in 60 ml of methanol or ethanol was heated in an autoclave at 170-175° for 7 h and cooled, and the precipitate of XXI or XXIII was filtered and washed with water and acetone. Compounds XVIII and XX were similarly obtained, with the difference that ammonia and methylamine were used in the form of 25% alcohol solutions (60 ml). The yields of XVIII, XX, XXI, and XXIII were 70, 78, 68, and 85%, respectively.

Compounds XIV-XXIV were colorless, crystalline substances which were slightly soluble in most organic solvents, insoluble in water and aqueous solutions of mineral acids, and did not form picrates and salts with mineral acids.

LITERATURE CITED

1. P. M. Kochergin and A. A. Tkachenko, Khim. Geterotsikl. Soedin., 475 (1965).
2. A. E. Chichibabin, Zh. Russk. Fiz. Khim. Obshchestva, 57, 421 (1925); 58, 1159 (1926); Ber., 58, 1704 (1925); 59, 2048 (1926).
3. W. L. Mosby, Heterocyclic Systems with Bridgehead Nitrogen Atoms, Vol. 1, New York (1961), p. 2.
4. J. Klosa, German Patent No. 1,024,968; Chem. Abstr., 54, 7748 (1960).
5. J. Klosa, J. Prakt. Chem., 6, 182 (1958).
6. P. M. Kochergin and M. N. Shchukina, Zh. Obshch. Khim., 26, 2905 (1956).
7. A. N. Krasovskii and P. M. Kochergin, Khim. Geterotsikl. Soedin., 321 (1969).
8. E. Ochiai, Ber., 69, 1959 (1936).
9. P. M. Kochergin, A. A. Tkachenko, and M. V. Povstyanoi, USSR Author's Certificate No. 213,881; Byull. Izobr., No. 11, 34 (1968).
10. E. Fischer, Ann., 215, 253 (1882).
11. German Patent No. 156,900; Frdl., 7, 677.
12. F. Cacace and R. Masironi, Ann. Chim. (Rome), 47, 362 (1957).
13. R. Zelnic, M. Pesson, and M. Polonovski, Bull. Soc. Chim. France, 888 (1956).