STUDIES IN THE IMIDAZOLE SERIES.

LII. SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF IMIDAZOLINO(1,2-*f*)XANTHINE DERIVATIVES*

P. M. Kochergin, I. V. Komissarov,
A. A. Tkachenko, and V. V. Vlasov

UDC 615.31:547.781.1].012.1

The preparation of 1-phenyl-6,8-dimethyl- and 1-cyclohexyl-6,8-dimethylimidazolino(1,2-*f*)xanthines by heating 7-(β-bromoethyl)-8-bromotheophyllin (IV) with aniline or cyclohexylamine without a solvent has been described in the literature [1]; however, nothing has been reported about the biological action of these compounds. By a similar scheme involving heating IV or 7-(β-chloroethyl)-bromotheophyllin (III) with ammonia or primary amines of the aliphatic or aliphatic-aromatic series in methanol at 155-160°, or by boiling in a high-boiling organic solvent (dimethylformamide or xylene), we have synthesized a series of new derivatives of imidazo(1,2-*f*)xanthine (IX-XXIII, see Table 1).

It must be noted that heating IV with amines at high temperature (about 190°), as has also been noted in the case of 7-acylalkyl-8-bromotheophyllins, leads to cleavage of the imidazoline ring in the imidazolino-(1,2-*f*)xanthines formed to the related 8-alkylaminoxanthines (XXIV-XXVI).

6,8-Dimethylimidazolino(1,2-*f*)xanthine (IX) and 1-m-tolyl-6,8-dimethylimidazolino(1,2-*f*)xanthine (XVIII) were also prepared, starting from 8-aminotheophyllin (V) and 8-methylmercaptotheophylline (VII), respectively (see scheme).

The structure of the compounds prepared was confirmed by elemental analyses and IR spectra.

The pharmacological properties of the imidazolinoxanthines were studied at the Department of Pharmacology of the Donets Medicinal Institute. Compounds XI, XII, XIV, XVI, XVIII, XX, XXI, and XXIII were subjected to detailed study. It was established that all the compounds studied, especially the N_1-substituted alkyl derivatives, possess a positive inotropic action on frog heart, comparable with the effect of theophyllin, and reduce arterial pressure by exerting a direct effect on the smooth muscles of the chambers. The preparations reduce the tone of isolated guinea pig iliac gut.

The compounds studied shorten the latent period of conventional reflexes and retard their damping; they increase "spontaneous" motor activity, but eliminate the stimulating effect of theophyllin on animal motor activity. The preparations do not change the convulsive activity of pentamethylenetetrazole or the effects of hexobarbital or chloral hydrate.

In acute experiments on cats, it was shown that compounds XI, XII, XIV, and XVI stimulate respiration, but do not eliminate breathing depression caused by morphine or hexobarbital.

Compounds XI, XII, XIV, XXI, and XXIII intensify diuresis and sodium diuresis in rats, but do not change the excretion of potassium with urine; the activity of XII is equal to that of theophyllin. The toxicity of the N_1-alkyl derivatives for mice when introduced into the stomach is 684-1958 mg/kg; the aryl-substituted derivatives do not exert a toxic action in doses up to 4000 mg/kg.

* For communication LI, see [6].

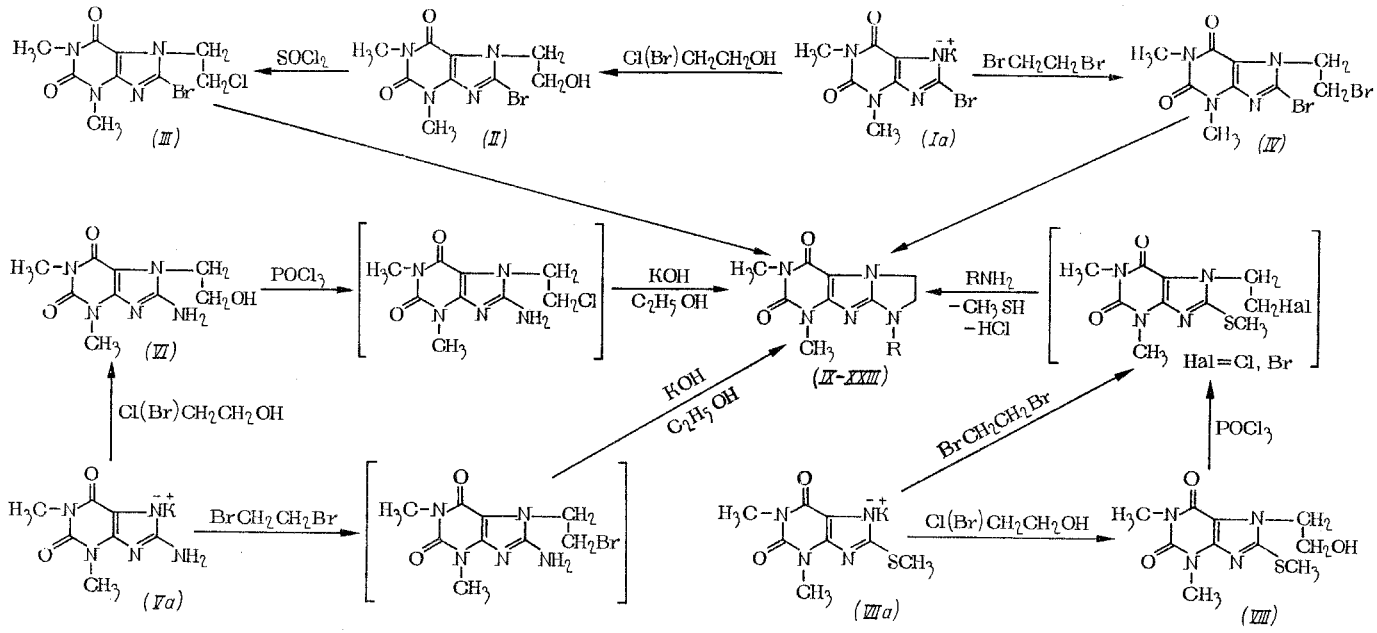
S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Zaporozhskii Medicinal Institute. Donets Medicinal Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 4, No. 12, pp. 14-18, December, 1970. Original article submitted February 5, 1970.

© 1971 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for $15.00.

TABLE 1. Imidazolino(1,2-*f*)xanthine Derivatives

Compound	R	Yield (in %) [a,b]	Mp (in deg), with dec.	Found (in %)			Empirical formula	Calculated (in %)		
				C	H	N		C	H	N
IX, Picrate[c]	H	57—61	263—5	38,43	3,76	23,50	$C_9H_{11}N_5O_2 \cdot C_6H_3N_3O_7$	38,47	3,44	23,93
X	CH_3	47—51	320—3	50,74	5,61	29,59	$C_{10}H_{13}N_5O_2$	51,05	5,57	29,77
XI	C_2H_5	67—70	297—8	52,72	5,62	28,15	$C_{11}H_{15}N_5O_2$	52,99	6,06	28,09
XII	CH_2CH_2OH	45—50	241—2	50,13	5,48	26,14	$C_{11}H_{15}N_5O_3$	49,80	5,70	26,40
XIII	n-C_3H_7	51—56	280—6	54,41	6,10	26,92	$C_{12}H_{17}N_5O_2$	54,73	6,50	26,60
XIV	$CH_2CH{=}CH_2$	54—60	289—91	54,99	5,56	27,02	$C_{12}H_{15}N_5O_2$	55,15	5,78	26,81
XV	n-C_4H_9	57—61	281—2	56,19	6,76	25,20	$C_{13}H_{19}N_5O_2$	56,30	6,90	25,25
XVI	iso-C_4H_9	53—58	250—2	56,62	7,24	25,22	$C_{13}H_{19}N_5O_2$	56,30	6,90	25,25
XII	$CH_2C_6H_5$	51—55	189—91	61,30	5,72	22,26	$C_{16}H_{17}N_5O_2$	61,72	5,50	22,49
XVIII	m-$CH_3C_6H_4$	90—95	245—6	61,45	5,43	22,26	$C_{16}H_{17}N_5O_2$	61,72	5,50	22,49
XIX	p-$CH_3C_6H_4$	74—78	285—7	62,07	5,80	22,70	$C_{16}H_{17}N_5O_2$	61,72	5,50	22,49
XX[d]	m-ClC_6H_4	71—75	253—5	54,03	4,47	21,06	$C_{15}H_{14}ClN_5O_2$	54,30	4,25	21,11
XXI	p-$CH_3OC_6H_4$	72—76	269—71	59,10	5,36	21,24	$C_{16}H_{17}N_5O_3$	58,71	5,23	21,39
XXII	$C_6H_4COOC_2H_5$-n	62—64	305—7	58,19	5,18	19,06	$C_{18}H_{19}N_5O_4$	58,52	5,18	18,96
XXIII	α-Naphthyl	72—75	260—1	65,41	4,78	19,19	$C_{19}H_{17}N_5O_2$	65,69	4,93	20,16

Notes: a) The compounds were purified for analysis by recrystallization as follows: IX, from dilute formic acid; X-XVII, XIX, XX, and XXIII, from methanol; XVIII and XXII, from ethanol; XXI, from glacial acetic acid; b) characteristic IR absorptions, in cm^{-1}: X, 1663, 1710 (CO); XI, 1668, 1698 (CO); XIII, 1645, 1713 (CO); XIV, 1650, 1710 (CO); XV, 1640, 1699 (CO); XVIII, 1660, 1707 (CO); XIX, 1670, 1712 (CO); XX, 1662, 1705 (CO); XXI, 1665, 1708 (CO); XXII, 1600, 1700 (CO); XXIII, 1662, 1710 (CO). The spectra were taken in the solid state (suspension in vaseline oil) on a UR-10 instrument. c) R_f values: 0.70 (butanol-acetic acid-water, 4 : 1 : 5); 0.83 (butanol-pyridine-acetic acid, 6 : 4 : 3); 0.73 (ethanol-acetic acid-water, 17 : 2 : 1); 0.65 (acetic acid-water, 1 : 49). Base IX, mp 318-320°, was not subjected to analysis. d) Found %: Cl 10.70; Calculated %: Cl 10.68.


SOCl2
Cl(Br)CH2CH2OH
BrCH2CH2Br
(III)
(II)
(Ia)
(IV)
POCl3
KOH
C2H5OH
RNH2
-CH3SH
-HCl
(V)
(IX-XXIII)
Hal=Cl, Br
Cl(Br)CH2CH2OH
BrCH2CH2Br
POCl3
(Va)
(VIIa)
(VIII)

EXPERIMENTAL*

7-(β-Hydroxyethyl)-8-bromotheophyllin (II). The potassium salt of 8-bromotheophyllin (Ia) (0.01 mole) and 0.0125 mole of ethylene bromohydrin or ethylene chlorohydrin in 20 ml of dimethylformamide were boiled together for 10 min; the solution was filtered and evaporated to a small volume under vacuum, cooled, and the solid washed with ether. The yield of II was 78-82%, mp 168-170° (from water). The IR spectrum had characteristic frequencies at 1660 and 1705 cm^{-1} (CO) and 3450 cm^{-1} (OH). Lit. [2]: mp 167-170°.

(7-(β-Chloroethyl)-8-bromotheophyllin, III. A solution of 0.01 mole of II in 25 ml of thionyl chloride was boiled for 3 h, the excess thionyl chloride was stripped off under vacuum, water was added to the residue, the residue was neutralized with aqueous ammonia, and the precipitate was filtered off, and washed with water and acetone. Yield, 67%; mp 163° (from methanol). Lit. [3]: mp 163°.

7-(β-Bromoethyl)-8-bromotheophyllin (IV). This was prepared by the known method of [4], with the difference that Ia was used, and the reaction was carried out in dimethylformamide for 10 min; the solution was filtered from the precipitate of potassium bromide, evaporated to a low volume under vacuum, cooled, and the precipitate filtered off and washed with water and acetone. Yield, 81%; mp 172° (from dimethylformamide). Prominent IR absorptions: 1705, 1670 cm^{-1} (CO). Lit. [4]: mp 168-172°.

8-Aminotheophyllin (V). This was prepared by a known method. Its potassium salt (Va) was prepared by heating 0.05 mole of V and 0.075 mole of KOH in 150 ml of water, pouring the solution into 350 ml of acetone, filtering off the precipitate and washing it with alcohol and acetone. Yield, 97%; mp 330-332° (dec).

7-(β-Hydroxyethyl)-8-aminotheophyllin (VI). A mixture of 0.03 mole of Va and 0.06 mole of ethylene bromohydrin or ethylene chlorohydrin in 85 ml of dimethylformamide was boiled for 2 h, filtered, and the filtrate evaporated under vacuum to a low volume; it was cooled, and the precipitate was filtered off and washed with acetone. Yield, 83-86%; mp 273-274° (dec., from water). The IR spectrum had the following major frequencies: 1650, 1690 cm^{-1} (CO); and 3155, 3340, and 3410 cm^{-1} (NH and OH). Found %: C 45.03; H 5.45; N 29.35. $C_9H_{13}N_5O_3$. Calculated %: C 45.18; H 5.47; N 29.27.

8-Methylmercaptotheophyllin (VII). This was prepared by a known method. Its potassium salt (VIIa) was prepared by heating 0.02 mole of VII with 0.03 mole of KOH in 35 ml of methanol; the solution was cooled, and the precipitate was filtered off and washed with methanol. Yield, 76%; mp 277-280° (dec).

9-(β-Hydroxyethyl)-8-methylmercaptotheophyllin (VIII). A mixture of 0.02 mole of VIIa and 0.03 mole of ethylene bromohydrin or ethylene chlorohydrin in 30 ml of dimethylformamide was boiled for 1 h, filtered, the filtrate evaporated under vacuum to a small volume, cooled, and the precipitate filtered off and washed with water and acetone. Yield, 80-83%; mp 181-183° (from water). IR spectrum: frequencies at 1655 and 1700 cm^{-1} (CO), and 3460 cm^{-1} (OH). Found %: C 44.30; H 5.46; N 20.83; S 12.03. $C_{10}H_{14}N_4O_3S$. Calculated %: C 44.43; H 5.22; N 20.73; S 11.86.

Imidazolino(1,2-*f*)xanthine Derivatives (IX-XXIII). A. A mixture of 0.025 mole of IV, 0.075 mole of amine (ammonia, methylamine, and ethylamine were used in large excess) was heated for 7 h at 155-160° (in an autoclave), the mixture was cooled, filtered, and the precipitate washed with water and acetone. Compounds XV and XXIII were also prepared from III; yield, 52% and 64% respectively.

B. A solution of 0.025 mole of IV and 0.075 mole of amine in 85 ml of dimethylformamide was boiled for 7 h, the solvent stripped off under vacuum to half its volume, the mixture cooled, and the precipitate filtered off and was washed with water and ether. Compounds XII, XVI, XVII, and XIX were so prepared. Yield were 50, 51, 56, and 91%, respectively. Compound XVIII was prepared similarly, but with the exception that the reaction was carried out in xylene.

C. A mixture of 0.03 moles of Va and 0.06 mole of 1,2-dibromoethane in 85 ml of dimethylformamide was boiled for 2 h, filtered, and the filtrate evaporated to a small volume under vacuum; the solution was cooled, and the precipitate of 7-(β-bromoethyl)-8-aminotheophyllin was filtered off, washed with acetone, and boiled for 8 h in 100 ml of ethanol containing 4.2 g of KOH. The reaction mixture was evaporated to dryness, the residue was dissolved in 30 ml of water, the solution was neutralized with acetic acid, and the precipitate of IX was filtered off and washed with water and acetone. Yield, 78%.

*We express thanks to V. V. Kolpakova, Yu. N. Sheinker, and their coworkers for performing microanalyses and taking IR spectra.

D. A solution of 0.01 mole of VI in 15 ml phosphorus oxychloride was boiled for 3 h; the excess $POCl_3$ was stripped off under vacuum and the residue decomposed with water and neutralized with aqueous ammonia to a weakly alkaline reaction; the precipitate of 7-(β-chloroethyl)-8-aminotheophyllin was filtered off and washed with water and acetone; it was then heated in an alcoholic KOH solution as described in experiment C. Yield of IX, 69%.

E. A mixture of 0.02 mole of VIIa and 0.04 mole of 1,2-dibromoethane in 30 ml of dimethylformamide was boiled for 2 h, the solution was filtered, the filtrate was concentrated and cooled, and the precipitate of 7-(β-bromoethyl)-8-methylmercaptotheophyllin was filtered off and washed with acetone. Yield, 71%; mp 258-260° (from dimethylformamide). This compound (0.0125 mole) and m-toluidine (0.03 mole) in 50 ml of methanol were heated for 7 h at 170°; the mixture was cooled and precipitate filtered off and washed with water and ether. Yield of XVIII, 63%.

F. A solution of 0.01 mole of VIII in 25 ml of phosphorus oxychloride was boiled for 3 h; the excess $POCl_3$ was stripped off under vacuum, the residue was decomposed with water, the solution was neutralized with ammonia to a weakly alkaline reaction, and the precipitate of 7-(β-chloroethyl)-8-methylmercaptotheophyllin was filtered off and washed with water and acetone. Yield, 72%; mp 170-171° (from methanol). This compound (2 g) and m-toluidine (3 g) in 50 ml of methanol was heated and worked up as described in experiment E. The yield of XVIII was 68%.

8-Alkylaminotheophyllins (XXIV-XXVI). A. A mixture of 9.12 g of IV, 20 ml of a 25% aqueous methylamine solution, and 50 ml of methanol was heated at 190° for 8 h; the mixture was cooled, and the precipitate was filtered off and washed with water and acetone. 8-Methylaminotheophyllin (XXIV) was isolated. Yield, 54%; decomposition temperature, 360-365° (from methanol). Lit. [5]; mp 364-366°. Under analogous temperature conditions, upon heating IV with aminoethanol or isobutylamine in methanol, there were isolated 8-(β-hydroxyethyl)aminotheophyllin (XXV, yield 61%, mp 294-295° from butanol, [7]: mp 294-295°) and the previously undescribed 8-isobutylaminotheophyllin (XXVI, yield 72%, mp 235-238° from acetic acid), identical with a sample obtained by heating I with isobutylamine in methanol at 160° (for 6 h). Found %: C 52.76; H 6.47; N 27.98. $C_{11}H_{17}N_5O_2$. Calculated %: C 52.57; H 6.81; N 27.87.

B. A solution of 0.01 mole of X, XII, or XVI in 50 ml of methanol was heated for 8 h at 190° and the mixture was worked up as described in A. Compounds XXIV-XXVI were isolated in yields of 57, 59, and 63%, respectively.

LITERATURE CITED

1. M. Eckstein, Diss. Pharm. (Cracow), 14, 435 (1962); Ref. Zh. Khim., No. 1329 (1964).
2. L. Fabbrini and L. Cencioni, Farmaco Ed. Sci., 17, 660 (1962); Chem. Abstracts, 58, 2452 (1963).
3. R. Weiss, Chem. Abstracts, 55, 17376 (1961).
4. F. Cacace and R. Masironi, Ann. Chim. (Rome), 46, 806 (1956); Chem. Abstracts, 51, 6655 (1957).
5. F. Cacace and F. Masironi, Ann. Chim. (Rome), 47, 362 (1957); Chem. Abstracts, 51, 15530 (1957).
6. I. A. Mazur, P. M. Kochergin, and V. I. Fomenko, Khim.-Farm. Zh., No. 8, 11 (1969).