STUDIES IN THE IMIDAZOLE FIELD

LIII. SYNTHESIS AND PHARMACOLOGICAL STUDY OF DERIVATIVES OF IMIDAZO[1,2-*f*]XANTHINE*

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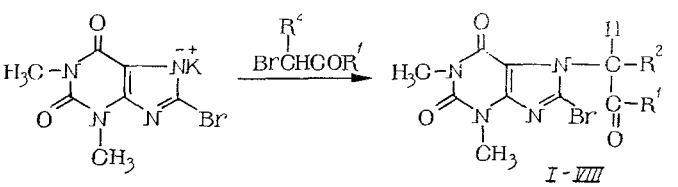
The preparation of some 7-acylmethyl-8-chlorotheophyllines and the analogous bromo derivatives has been described in the literature [2-5]. By the reaction of these compounds with primary and secondary amines we have synthesized 7-acylmethyl-8-alkylamino(arylamino, dialkylamino)-theophyllines, and from the latter the corresponding hydrazones, which are of interest for a study of their tuberculostatic properties.

By the reaction of the potassium salt of 8-bromotheophylline with α-bromoketones in methanol we have obtained a number of 7-acylalkyl-8-bromotheophyllines (I-VIII, see Table 1), the majority of which have not been described in the literature.

When (I-VIII) are heated with ammonia, primary amines, amino alcohols and amino acids in ethanolic or aqueous ethanolic solutions at 140-190°C, not only is the bromine atom replaced, but the cyclization of the intermediate 7-acylalkyl-8-amino(alkylamino, arylamino)-theophyllines to the corresponding derivatives of 1H-imidazo[1,2-*f*]xanthine (IX-LV, see Table 1) takes place. In the case of the high-boiling amines, this reaction can be carried out in an excess of the amine itself or in a high-boiling organic solvent (xylene, dimethylformamide, etc.).

It must be mentioned that the heating of the 7-acylalkyl-8-bromotheophyllines having a branched ketone chain (IV-VIII) with amines must be carried out at a temperature not higher than 160°C, since at a higher temperature (180-190°C) in place of the expected tricyclic compounds the 8-alkylaminotheophyllines (LVII, LVIII) are formed. It has been established that (LVII) and (LVIII) are obtained as a result of the cleavage of the imidazole ring of the imidazoxanthines (XLII, XLIX, LIV).

When 7-(α-benzoylethyl)-8-bromotheophylline (VI) was heated with ethylamine in ethanolic solution at 110-120°C, 7-(α-benzoylethyl)-8-ethylaminotheophylline (LVI) was isolated, and at 140-150°C in ethanol this was converted into 1-ethyl-3,6,8-trimethyl-2-phenylimidazo[1,2-*f*]xanthine (LIV), identical with the substance obtained in one stage by heating (VI) with an ethanolic solution of ethylamine at 150-160°C:



* For Communication LII, see [1].

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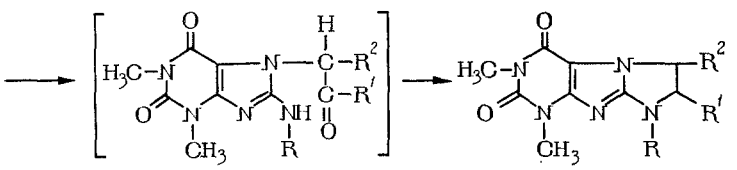
TABLE 1. 7-Acylalkyl-8-bromotheophyllines (I-VIII) and Imidazo[1,2-*f*]xanthine Derivatives (IX-LV)[a]

Compound	R	R¹	R²	Reaction (in hours)	Autoclave temperature (in °C)[b]	Yield (in %)	Melting point (°C)[b]	Found (%)			Empirical formula	Calculated (%)		
								C	H	N		C	H	N
I	—	CH_3	H	5	—	58—75	203—4	—	—	—	$C_{10}H_{11}BrN_4O_3$ [c]	—	—	—
II	—	C_6H_5	H	2—4	—	68—85	283—4	—	—	—	$C_{15}H_{13}BrN_4O_3$ [d]	—	—	—
III	—	p-BrC_6H_4	H	2—3	—	92—95	241—2	39.52	2.63	12.46	$C_{15}H_{12}Br_2N_4O_3$ [e]	39.49	2.65	12.28
IV	—	CH_3	CH_3	5	—	83—85	156—7	39.66	3.90	17.03	$C_{11}H_{13}BrN_4O_3$ [f]	40.13	3.98	17.02
V	—	C_2H_5	CH_3	5	—	90—92	137—8	41.68	4.19	16.48	$C_{12}H_{15}BrN_4O_3$ [g]	41.99	4.14	16.32
VI	—	C_6H_5	CH_3	5	—	70—79	142—3	49.05	4.06	13.67	$C_{16}H_{15}BrN_4O_3$ [h]	49.10	3.87	14.33
VII	—	n-C_3H_7	C_2H_5	5	—	63—70	126—7	45.38	4.83	15.03	$C_{14}H_{19}BrN_4O_3$ [i]	45.29	5.15	15.09
VIII	—	CH_3	C_6H_5	5	—	67	169—71	49.18	4.14	14.60	$C_{16}H_{15}BrN_4O_3$ [j]	49.12	3.87	14.32
IX	H	CH_3	H	5	160	74	360	51.26	4.78	29.80	$C_{10}H_{11}N_5O_2$	51.49	4.75	30.03
X	H	C_2H_5	CH_3	7	140	60	310	55.58	6.11	27.22	$C_{12}H_{15}N_5O_2$	55.15	5.79	26.80
XI	H	n-C_3H_7	C_2H_5	7	140	62	246—7	58.02	6.53	24.45	$C_{14}H_{19}N_5O_2$	58.11	6.61	24.20
XII	H	C_6H_5	H	5	190	70	325	61.24	4.45	23.70	$C_{15}H_{13}N_5O_2$ [k]	61.01	4.43	23.72
XIII	H	p-BrC_6H_4	H	7	190	71	325	47.97	3.11	18.58	$C_{15}H_{12}BrN_5O_2$ [l]	48.14	3.23	18.71
XIV	CH_3	CH_3	H	5	160	61	249—50	53.63	5.23	27.98	$C_{11}H_{13}N_5O_2$	53.43	5.29	28.32
XV	C_2H_5	CH_3	H	5	160	63	237—8	55.26	5.87	26.87	$C_{12}H_{15}N_5O_2$	55.15	5.78	26.81
XVI	n-C_4H_9	CH_3	H	7	160	50	187—9	58.35	6.43	24.40	$C_{14}H_{19}N_5O_2$	58.11	6.62	24.21
XVII	iso-C_4H_9	CH_3	H	7	160	52	169—71	58.27	6.41	24.20	$C_{14}H_{19}N_5O_2$	58.11	6.62	24.21
XVIII	iso-C_5H_{11}	CH_3	H	7	170	50	168—70	59.10	6.71	23.27	$C_{15}H_{21}N_5O_2$	59.38	6.97	23.09
XIX	n-C_5H_{13}	CH_3	H	7	170	60	173—5	60.49	7.06	21.79	$C_{16}H_{23}N_5O_2$	60.54	7.30	22.07
XX	C_6H_{11}	CH_3	H	8	175	63	248—49	61.03	6.45	22.22	$C_{16}H_{21}N_5O_2$	60.93	6.71	22.21
XXI	C_6H_5	CH_3	H	7	170	54	264—6	62.46	4.70	22.23	$C_{16}H_{15}N_5O_2$	62.12	4.88	22.64
XXII	$CH_2C_6H_5$	CH_3	H	7	160	51	226—8	62.90	5.15	21.32	$C_{17}H_{17}N_5O_2$	63.14	5.29	21.66
XXIII	m-$CH_3C_6H_4$	CH_3	H	7	170	58	239—40	62.77	5.23	21.61	$C_{17}H_{17}N_5O_2$	63.14	5.29	21.66
XXIV	p-$CH_3C_6H_4$	CH_3	H	7	160	51	275—7	63.22	5.32	21.66	$C_{17}H_{17}N_5O_2$	63.14	5.29	21.66
XXV	p-HOC_6H_4	CH_3	H	8	165	63	283—4	59.38	4.90	21.35	$C_{16}H_{15}N_5O_3$	59.07	4.65	21.53
XXVI	p-$CH_3OC_6H_4$	CH_3	H	7	170	87	285—6	60.60	5.04	20.30	$C_{17}H_{17}N_5O_3$	60.17	5.05	20.64
XXVII	$C_6H_4COOC_2H_5$-p	CH_3	H	8	160	83	290—2	59.63	5.11	18.09	$C_{19}H_{19}N_5O_4$	59.83	5.02	18.36
XXVIII	CH_3	C_6H_5	H	7	190	78	235—6	62.13	4.98	22.77	$C_{16}H_{15}N_5O_2$	62.12	4.88	22.64
XXIX	C_2H_5	C_6H_5	H	8	170	87	175—7	63.31	5.56	21.54	$C_{17}H_{17}N_5O_2$	63.14	5.30	21.66
XXX	n-C_4H_9	C_6H_5	H	6	190	69	172—3	64.91	6.31	19.72	$C_{19}H_{21}N_5O_2$	64.93	6.02	19.93
XXXI	iso-C_4H_9	C_6H_5	H	6	190	68	193	64.81	6.08	20.03	$C_{19}H_{21}N_5O_2$	64.93	6.02	19.93
XXXII	n-C_5H_{11}	C_6H_5	H	6	190	86	155—6	65.45	6.27	18.94	$C_{20}H_{23}N_5O_2$	65.73	6.34	19.16
XXXIII	iso-C_5H_{11}	C_6H_5	H	6	190	87	169—70	65.69	6.29	19.10	$C_{20}H_{23}N_5O_2$	65.73	6.34	19.16
XXXIV	n-C_6H_{13}	C_6H_5	H	6	190	85	113—4	66.12	6.47	18.78	$C_{21}H_{25}N_5O_2$	66.46	6.64	18.46
XXXV	$CH_3C_6H_5$	C_6H_5	H	6	190	93	201—2	68.80	4.85	18.13	$C_{22}H_{19}N_5O_2$	68.56	4.96	18.17
XXXVI	p-$CH_3C_6H_4$	C_6H_5	H	8	190	86	279—81	68.16	5.20	18.11	$C_{22}H_{19}N_5O_2$	68.56	4.96	18.17
XXXVII	p-$CH_3OC_6H_4$	C_6H_5	H	8	190	90	282—3	65.72	4.88	17.62	$C_{22}H_{19}N_5O_3$	65.82	4.77	17.44
XXXVIII	p-$C_2H_5OC_6H_4$	C_6H_5	H	6	170	80	263—4	66.33	4.90	16.98	$C_{23}H_{21}N_5O_3$	66.49	5.09	16.86
XXXIX	CH_2COOH	C_6H_5	H	8	160	72	275—7	58.10	4.44	19.91	$C_{17}H_{15}N_5O_4$	57.78	4.28	19.82
XL	CH_2CH_2N-$(C_2H_5)_2$	C_6H_5	H	8	160	63	151—2	63.95	6.95	21.57	$C_{21}H_{26}N_6O_2$	63.94	6.64	21.31
XLI	CH_3	p-BrC_6H_4	H	7	190	77	245—6	49.79	3.44	18.34	$C_{16}H_{14}BrN_5O_2$ [n]	49.49	3.63	18.04
XLII	CH_3	CH_3	CH_3	5	150	70	325	55.00	5.60	26.65	$C_{12}H_{15}N_5O_2$	55.16	5.78	26.80
XLIII	CH_3	CH_3	C_6H_5	8	140	80	194—6	63.27	5.12	21.57	$C_{17}H_{17}N_5O_2$	63.14	5.30	21.66
XLIV	C_2H_5	CH_3	CH_3	6	140	51	179—80	56.85	6.43	25.29	$C_{13}H_{17}N_5O_2$	56.71	6.22	25.44

XLV	CH_2CH_2OH	CH_3	CH_3	6	140	74	203—6	53.47	5.88	24.30	$C_{13}H_{17}N_5O_3$	53.59	5.88	24.04
XLVI	C_6H_5	CH_3	CH_3	8	160	70	232—3	63.21	5.16	21.69	$C_{17}H_{17}N_5O_2$	63.14	5.29	21.66
XLVII	$CH_2CH_2N\text{-}(C_2H_5)_2$	CH_3	CH_3	8	160	57	259—61	50.66	6.92	20.74	$C_{17}H_{26}N_6O_2 \cdot HCl \cdot H_2O$	50.92	7.29	20.96
XLVIII	CH_2CH_2OH	CH_3	C_6H_5	8	140	50	219—21	61.23	5.25	19.96	$C_{18}H_{19}N_5O_3$	61.18	5.42	19.82
XLIX	CH_3	C_2H_5	CH_3	7	140	74	256—7	56.83	6.57	25.31	$C_{13}H_{17}N_5O_2$	56.71	6.22	25.44
L	C_2H_5	C_2H_5	CH_3	7	160	72	174—5	58.15	6.46	23.97	$C_{14}H_{19}N_5O_2$	58.11	6.61	24.20
LI	C_6H_5	C_2H_5	CH_3	8	160	60	241—2	63.85	5.70	20.66	$C_{18}H_{19}N_5O_2$	64.07	5.67	20.76
LII	CH_3	$n\text{-}C_3H_7$	C_2H_5	7	140	52	131—2	58.99	6.88	22.40	$C_{15}H_{21}N_5O_2$	59.38	6.97	23.08
LIII	CH_3	C_6H_5	CH_3	8	140	71	233—4	63.27	5.22	21.51	$C_{17}H_{17}N_5O_2$	63.14	5.29	21.66
LIV	C_2H_5	C_6H_5	CH_3	8	140	69—87	187—8	64.14	5.42	20.36	$C_{18}H_{19}N_5O_2$	64.07	5.67	20.76
LV	$n\text{-}C_4H_9$	C_6H_5	CH_3	8	165	52	144—6	65.44	6.29	19.22	$C_{20}H_{23}N_5O_2$	65.73	6.34	19.16

Notes. a) For analysis, the compounds were purified by crystallization: (I-IV), (VI), (VIII-XI), (XIV), (XV), (XX), (XXVII), (XXVIII), (XXXIV), (XLI-XLV), (XLVII), (XLIX), (L), and (LII-LIV) – from ethanol; (V), (XVI), (XVIII), (XIX), (XXI-XXIV), (XXX), (XXXI), (XXXIII), (XXXIV), (XXXIX), and (XLVIII) – from methanol; (VII), (XVII), (XXXII), (XLIV), and (LV) – from 70% methanol; (XII), (XIII), (XXVI), (XXXVII), and (XXXVII) – from glacial acetic acid; (XXXI) – from dioxane; (XXXIV) – from dimethylformamide; and (XL) and (LI) – from dichloroethane. b) All the substances decomposed at the melting point; c) according to the literature [2], mp 203°C; d) according to the literature [2], mp 284°C. R_f: 0.83 [acetic acid–water (3 : 2)], 0.79 [acetic acid–formic acid–water (2 : 2 : 1)]; 0.92 [ethanol–acetic acid–water (17 : 2 : 1)]; e) found, %: Br 35.09, calculated, %: Br 35.04; f) found, %: Br 24.55, calculated, %: Br 24.27; g) found, %: Br 24.18, calculated, %: Br 24.28; h) found, %: Br 20.57, calculated, %: Br 20.43; i) found, %: Br 21.66, calculated, %: Br 21.52; j) found, %: Br 20.61, calculated, %: Br 20.43; k) R_f: 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)]; l) found, %: Br 21.55, calculated, %: Br 21.36; m) R_f value: 0.75 [butanol–acetic acid–water (4 : 1 : 5)], 0.77 [butanol–pyridine–acetic acid (6 : 4 : 3)], 0.73 [ethanol–acetic acid–water (17 : 2 : 1)]; n) found, %: Br 20.56, calculated, %: Br 20.58. IR spectra (in cm^{-1}): III) 1660, 1693 (CO); IV) 1660, 1708 (CO); V) 1670, 1710, 1738 (CO); VI) 1660, 1708 (CO); VII) 1660, 1708 (CO); IX) 1664, 1708 (CO); X) 1668, 1705 (CO); XII) 1663, 1695 (CO), 3150 (NH); XIII) 1650, 1715 (CO), 3210 (NH); XIV) 1668, 1700 (CO); XV) 1665, 1706 (CO); XVI) 1663, 1707 (CO); XVII) 1665, 1708 (CO); XIX) 1670, 1710 (CO); XX) 1665, 1718 (CO); XXI) 1674, 1721 (CO); XXII) 1680, 1712 (CO); XXIII) 1670, 1720 (CO); XXV) 1658, 1702 (CO); XXVI) 1667, 1715 (CO); XXVII) 1672, 1725 (CO); XXVIII) 1645, 1707 (CO); XXIX) 1680, 1710 (CO); XXX) 1665, 1708 (CO); XXXI) 1670, 1710 (CO); XXXII) 1665, 1705 (CO); XXXIII) 1660, 1703 (CO); XXXIV) 1672, 1705 (CO); XXXV) 1665, 1701 (CO); XXXVI) 1653, 1708 (CO); XXXVII) 1660, 1710 (CO); XXXVIII) 1658, 1708 (CO); XL) 1670, 1708 (CO); XLI) 1670, 1715 (CO); XLIV) 1665, 1704 (CO); XLV) 1670, 1711 (CO); XLVI) 1666, 1707 (CO); XLIX) 1665, 1700 (CO); L) 1665, 1705 (CO); LI) 1659, 1700 (CO); LII) 1665, 1700 (CO); LIII) 1670, 1717 (CO); LIV) 1663, 1715 (CO); LV) 1657, 1713 (CO). The spectra were taken in the solid state (mulls in paraffin oil) on a UR-10 instrument.



IX-LV

The structures of compounds (I-VIII) and (IX-LV) were confirmed by their IR spectra, and their individuality by two-dimensional paper chromatography.

The method of obtaining imidazo[1,2-*f*]xanthines [6, 7] described above from 8-bromotheophylline is simpler than the synthesis of the imidazoxanthines from 8-aminotheophylline [8] or from 8-methylthiotheophylline [9].

Some of the imidazo[1,2-*f*]xanthine derivatives have been subjected to a pharmacological study in the Department of Pharmacology of the Zaporozhe Medical Institute. Thus, compound (XIV) (preparation No. 1), (XV) (preparation No. 2), and (XLVII) (preparation No. 3) proved to be active with respect to the cardiovascular system. Preparation No. 3 has a pronounced depressive effect on cardiac activity in experiments on frogs, rabbits, and cats. Preparations Nos. 1 and 2 proved to have a low toxicity and were investigated in more detail. Preparation No. 1 in concentrations from $1 \cdot 10^{-3}$ to $1 \cdot 10^{-4}$ and preparation No. 2 in concentrations from $2 \cdot 10^{-2}$ to $1 \cdot 10^{-4}$ increase the amplitude of the contractions of the isolated frog heart. In experiments on previously fatigued hearts, this stimulating action appears more strongly.

In experiments on the vessels of isolated frog tails and isolated rabbit ears, preparation No. 1 in a concentration of from $2 \cdot 10^{-3}$ to $1 \cdot 10^{-4}$ causes contraction of the blood vessels.

Preparation No. 1 in doses of 5-30 mg/kg and preparation No. 2 in doses of 10-20 mg/kg cause an increase in the arterial pressure of rabbits by 10-20 mm, a retardation of the rate of cardiac contractions by 22 ± 1.4%, and an increase in the voltage of the R wave on the electrocardiogram. The bradycardia accompanied by an increase in the voltage of the waves of the gastric complex is more pronounced on the administration of preparation No. 1 than on the action of preparation No. 2. The same preparations cause an increase in the amplitude and rhythm of respiratory excursions in experiments on rabbits and cats.

EXPERIMENTAL*

8-Bromotheophylline was prepared by a known method [10]. Its potassium salt was obtained by heating 0.1 mole of 8-bromotheophylline with 0.1 mole of caustic potash in 75 ml of water, cooling the solution, filtering off the precipitate, and washing it with methanol. Yield 92%, mp < 330°C (decomp., from methanol).

7-Acylalkyl-8-bromotheophyllines (I-VIII). To a solution of 0.1 mole of the potassium salt of 8-bromotheophylline in 250 ml of methanol was added 0.12-0.15 mole of an α-bromoketone, the mixture was boiled with stirring for 2-5 h and filtered, the filtrate was evaporated in vacuum to half-volume and cooled, and the precipitate was filtered off and was washed with water and with acetone. Compounds (II) and (III) were isolated by the cooling of the reaction mixture. Compound (II) was also obtained by performing the reaction in 50% ethanolic solution in the presence of an equimolecular amount of caustic potash or caustic soda. They are colorless crystalline substance soluble in the majority of organic solvents and insoluble in H_2O.

Imidazo[1,2-*f*]xanthine derivatives (IX-LV). A. A mixture of 0.02 mole of one of compounds (I-VIII) and 0.05 mole of primary amine in 60 ml of methanol or ethanol was heated in an autoclave (capacity 0.15 liter) at 140-190°C (mainly at 160-175°C) for 5-8 h and cooled, and the precipitate was filtered off and was washed with water and with acetone. The ammonia, methylamine, and ethylamine were used in a large excess in the form of 15-25% ethanolic solutions (50-60 ml).

B. A mixture of 0.01 mole of (I), (II), or (IV) and 0.02 mole mole of amine in 30-75 ml of xylene or dimethylformamide was boiled for 3-5 h, the solvent was distilled off to half volume, the residue was cooled, and the precipitate was filtered off and washed with water and with acetone. This gave (XXI), (XXXV), and (XLVI).

C. A mixture of 0.01 mole of (I) or (II) and 0.02 mole of amine was heated for 8-12 min at the boiling point of the amine, whereupon the mass rapidly solidified. It was cooled, ground, and washed with water and with acetone. This gave (XXI) and (XXXV).

* For the performance of the microanalyses and the recording of the IR spectra of the compounds obtained, we express our thanks to V. V. Kolpakova, Yu. N. Sheinker, and their colleagues.

D. A solution of 0.01 mole of (LVI) in 50 ml of ethanol was heated in an autoclave at 150-160°C for 7 h and was cooled, and the precipitate of (LIV) was filtered off and washed with methanol. Yield 87%.

7-(α-Benzoylethyl)-8-ethylaminotheophylline (LVI). A mixture of 5.8 g of VI and 50 ml of 50% ethanolic ethylamine was heated in an autoclave at 110-120°C for 8 h and cooled, and the precipitate was filtered off and was washed with water. The evaporation of the alcoholic mother liquor gave an additional amount of the product. Yield 3.5 g (69%), mp 172-173°C (from ethanol). Found, %: C 60.62; H 6.20; N 19.69. $C_{18}H_{21}N_5O_3$. Calculated, %: C 60.83; H 5.96; N 19.71.

8-Alkylaminotheophyllines (LVII, LVIII). A. A mixture of 4.11 g of IV and 20 ml of 13% ethanolic methylamine was heated at 185-190°C for 8 h and cooled, and the precipitate was filtered off and was washed with water and with acetone. This gave 1.4 g (54%) of 8-methylaminotheophylline (LVII), mp 360-365°C (decomp., from isoamyl alcohol). According to the literature [11], mp 364-366°C (decomp.). Found, %: C 45.83; H 5.12; N 33.32. $C_8H_{11}N_5O_2$. Calculated, %: C 45.92; H 5.30; N 33.48.

Under similar conditions, when (V) was heated with 13% ethanolic methylamine compound (LVII) was obtained with a yield of 68%, and when (VI) was heated with 50% ethylamine 8-ethylaminotheophylline compound (LVIII) was obtained with mp 318-319°C (decomp., from propanol). According to the literature [11], mp 318-319°C (decomp.). Found, %: C 48.36; H 5.58; N 31.29. $C_9H_{13}N_5O_2$. Calculated %: C 48.42; H 5.87; N 31.38.

B. A solution of 2.61 g of XLII in 50 ml of ethanol was heated and treated as described in Experiment A. This gave a 67% yield of (LVII), mp 360-365°C (decomp.). Under similar conditions, when (XLIX) was heated with ethanol, (LVIII) was obtained with a yield of 62%, and (LIV) gave compound (LVIII) with a yield of 77%.

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