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A Search for New Drugs in the Group of Xanthine Derivatives. XXII. Chemical Properties of 1,3-Dimethyl-6H,7H-ozazolo-[2,3-*f*]xanthine System[1]

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By the action of alkali, 7-β-hydroxy-γ-chloropropyl derivatives of 8-chloro- and 8-bromotheophylline cyclized to 1,3-dimethyl-7-chloromethyl-6H,7H-oxazolo-[2,3-*f*]xanthine.[2] We have found that the 7-β-hydroxy-γ-bromo- and -γ-iodo-8-halotheophyllines (I, III and II, IV) undergo cyclization with alkali to give the 8-bromomethyl- and 8-iodomethyl-6H,7H-oxazolo[2,3-*f*]-xanthines (V and VI) in high yield; no oxazirane products were obtained. The reaction of these oxazolidine derivatives with acids was then examined.

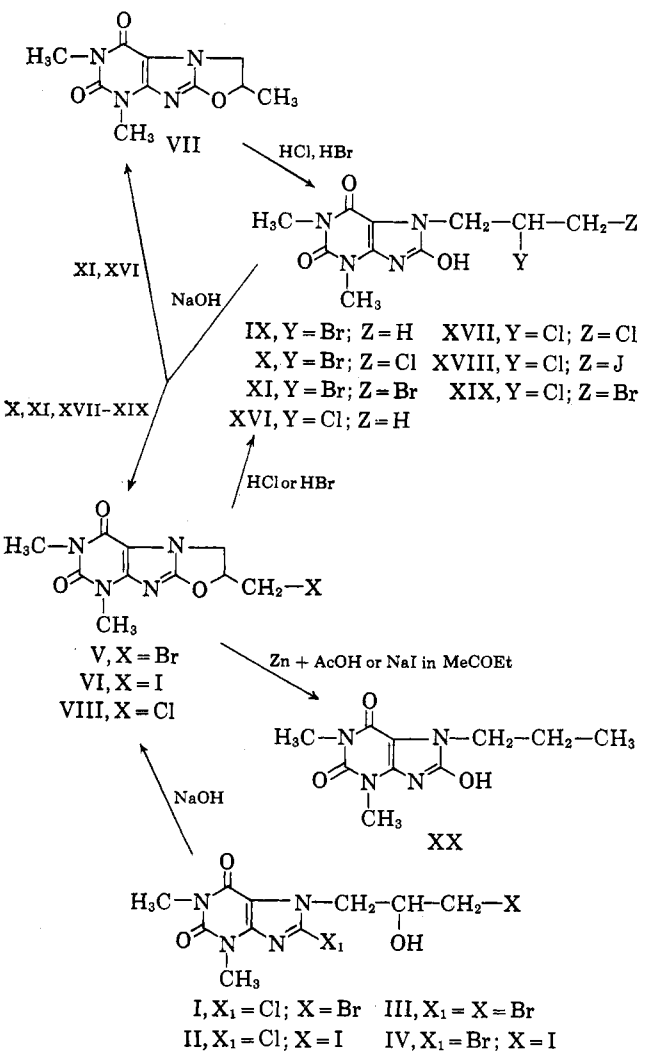
Compounds V–VIII dissolved readily in concentrated hydrobromic acid at room temperature and, after brief boiling, acidic products separated from the hot solution. The acid obtained from VII was transformed back to VII on heating with base and is assigned the uric acid structure IX. Similarly VIII gave the 7-(β-bromo-γ-chloropropyl)-1,3-dimethyluric acid (X), which was not identical with the isomeric 7-(β-hydroxy-γ-chloropropyl)-8-bromotheophylline obtained from 8-bromotheophylline and epichlorohydrin.[2] The same product XI was obtained from both the bromo compound V and iodo compound VI (Scheme I); in the latter case iodine was liberated.

Like compounds IX and X, compound XI is soluble in cold alkali and is precipitated unchanged on acidification. Recyclization by heating with sodium hydroxide solution gave 1,3-dimethyl-7-bromomethyl-6H,7H-oxazolo[2,3-*f*]xanthine (V). The dibromopropyluric acid structure XI was confirmed by an alternative synthesis shown in Scheme II.

By analogy to the work of Fischer[3] on 8-chlorocaffeine, the 7-allyl derivative XII[4] gave XIII which was readily hydrolyzed to 1,3-dimethyl-7-allyluric acid (XIV). Addition of bromine gave XI. In contrast to the uric acid derivatives IX and X, compound XI is readily methylated by dimethyl sulfate in the presence of sodium hydroxide, giving 1,3,9-trimethyl-7-(β,γ-dibromopropyl)uric acid (XV).

The cleavage of the oxazolidines V–VIII with hydrochloric acid was analogous to that observed with hydrobromic acid, giving the chloro-substituted uric acids XVI, XVII, and XIX (Scheme I). The acid XVI was converted back to VII with alkali, but much less readily than bromide IX. Halogen exchange did not occur with VI in this case, and the β-chloro-γ-iodo derivative was obtained. Attempts to reduce the halogen in position 7 of compounds V and VI by means of zinc and acetic or hydrochloric acid to obtain VII, gave only product XX, containing no halogen. The crystalline form, melting point, and analysis of compound XX (see Table I) conformed to those of VII, but the mixture melting point of the two substances was depressed. Moreover compound XX, in contrast to VII, was readily soluble in alkali and separated unchanged after acidification, indicating that it is a uric acid derivative. The structure of compound XX as 1,3-dimethyl-7-*n*-propyluric acid was confirmed by conversion with phosphorus oxychloride and dimethylaniline to 7-*n*-propyl-8-chlorotheophylline (XXI), identical with a sample prepared by alkylation of 8-chlorotheophylline with *n*-propyl bromide. On heating with sodium ethoxide solution compound XXI was converted to 1,3-dimethyl-7-*n*-propyl-8-ethyluric acid (XXII) which with hydrochloric acid gave XX. 1,3,7-Trimethyl-6H,7H-oxazolo[2,3-*f*]xanthine (VII) is not altered by heating with zinc and acetic acid, indicating that reductions of V and VI with zinc and acetic acid described above involve

SCHEME I



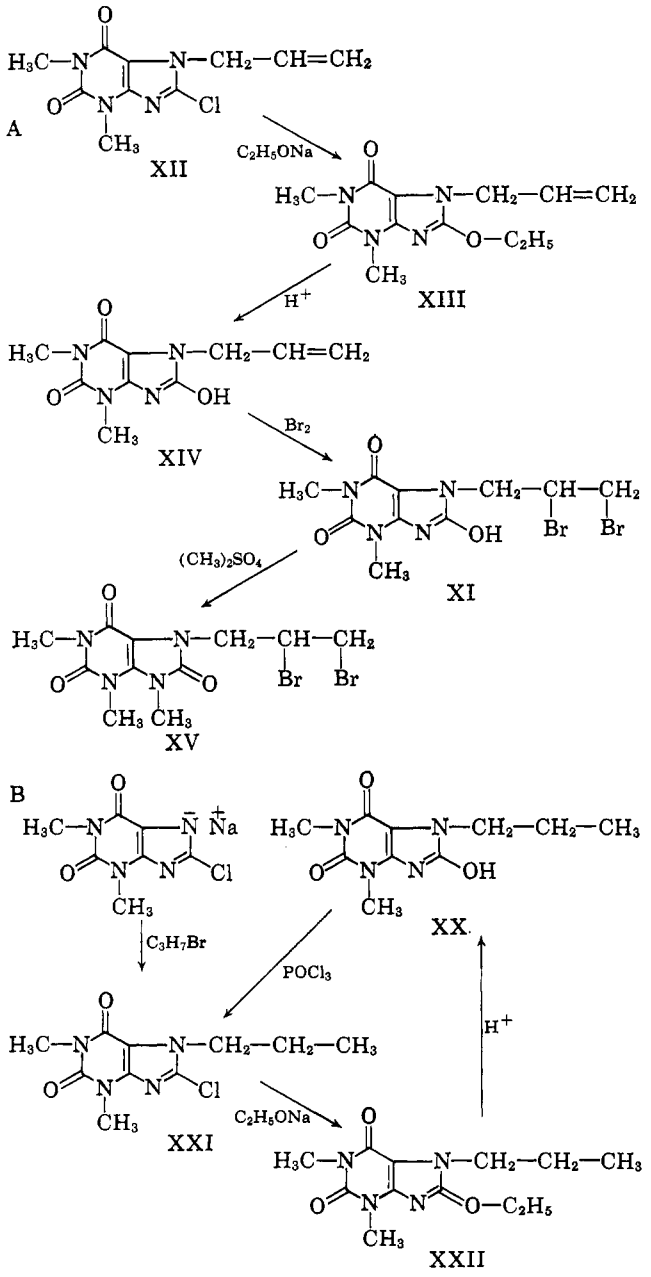
(1) This work was partially supported by Polish Academy of Science-Committee of Pharmaceutical Sciences.

(2) M. Eckstein, *Dissertationes pharm.*, **14**, 425 (1962).

(3) E. Fischer and F. Ach, *Ber.*, **39**, 430 (1906).

(4) M. Eckstein and M. Gorczyca, A. Zejc, *Dissertationes pharm.*, **16**, 61 (1964).

SCHEME II



initial loss of hydrogen halide which then cleaves the oxazolidine. The reaction of VIII with sodium iodide in methyl ethyl ketone also gave XX rather than the expected product VI.[5]

The transformations produced by hydrochloric and hydrobromic acid on the 7-substituted 1,3-dimethyl-6H,7H-oxazolo[2,3-*f*]xanthines (V–VIII) are in agreement with previous observations on the instability of oxazolidines[6] and oxazolines[7] in acid media. These ring-opening reactions of the theophylline–oxazolidines give good yields and represent a convenient method for obtaining 7-substituted derivatives of uric acid. The above-described reaction of 7-β-chloroalkyl derivatives of uric acid with alkali furnishes new possibilities of obtaining 7-substituted derivatives of 1,3-dimethyl-6H,7H-oxazolo[2,3-*f*]xanthine.

Studies on the chemical properties of oxazoloxanthines and related imidazolidinexanthines[8] and hexahydropyrimidinexanthines[8] are under way.

(5) Examples of reduction by heating with sodium iodide are known in the literature; *e.g.*, sulfonyl chlorides are reduced to the sodium salts of sulfinic acids, with collateral formation of certain amount of sulfoxide and sulfone [R. Otto and J. Troeger, *Ber.*, **24**, 482, 486, 488, 494 (1891); S. Gebauer-Fülnegg and E. Riesz, *Monatsh.*, **49**, 41 (1928)].

(6) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).

(7) J. D. Loudon in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1957, pp. 353, 357, 376.

Experimental

The starting products, 7-(β-hydroxy-p-bromopropyl)-8-chlorotheophylline (I), 7-(β-hydroxy-p-iodopropyl)-8-chlorotheophylline (II), 7-(β-hydroxy-p-bromopropyl)-8-bromotheophylline (III), 7-(β-hydroxy-p-iodopropyl)-8-bromotheophylline (IV), and 7-allyl-8-chlorotheophylline (XII), were obtained according to methods described previously.[4]

1,3-Dimethyl-7-bromomethyl-6H,7H-oxazolo[2,3-*f*]xanthine (V). Method A.—To a solution of 3.51 g. (0.01 mole) of I or 3.96 g. (0.01 mole) of III in 20 ml. of 60% ethanol (or 50 ml. of water), a solution of 0.4 g. (0.01 mole) of sodium hydroxide in 10 ml. of water was added, and the mixture was heated in the water bath for 0.5–1 hr. (until neutral reaction was reached). The product separated on cooling and crystallized from 96% ethanol, m.p. 254–256° dec. The product was slightly soluble in water, benzene, and chloroform, and somewhat more soluble in ethanol and acetone; yield 88%.

Method B.—From the cooled reaction mixture obtained by hydroxybromination of 0.01 mole of 7-allyl-8-chloro- or -8-bromotheophylline,[4] after making basic with sodium hydroxide at room temperature, a product was obtained in 85% yield, m.p. 254–256°. It was not depressed on admixture with the compound prepared by method A.

Method C.—A solution of 0.39 g. (0.001 mole) of XI in 5 ml. of 50% ethanol containing 0.04 g. (0.001 mole) of sodium hydroxide was heated for 10 min. on the water bath. A product separated from the hot solution, which after crystallization from ethanol had m.p. 254–256° which was not depressed on admixture with the compound, obtained by method A or B.

Anal. Calcd. for $C_{10}H_{11}BrN_4O_3$: C, 38.13; H, 3.55; N, 17.79. Found: C, 38.48; H, 3.77; N, 18.10.

1,3-Dimethyl-7-iodomethyl-6H,7H-oxazolo[2,3-*f*]xanthine (VI). Method A.—Under conditions analogous with those described by method A to obtain V, 3.98 g. (0.01 mole) of II or 4.43 g. (0.01 mole) of IV gave a product in 85% yield which, when crystallized from 70% ethanol, melted at 214–215° dec. The compound was slightly soluble in water, ethanol, benzene, acetone, and chloroform.

Method B.—From the reaction mixture after hydroxyiodination of 7-allyl-8-chloro- or -8-bromotheophylline,[4] described by method B for compound V, a substance was obtained in 80% yield, m.p. 214–215° dec., which did not depress the mixture melting point with the product that was obtained by method A above.

Anal. Calcd. for $C_{10}H_{11}IN_4O_3$: C, 33.18; H, 3.06; N, 15.48. Found: C, 33.19; H, 3.11; N, 15.78.

1,3,7-Trimethyl-6H,7H-oxazolo[2,3-*f*]xanthine (VII).—A solution of 0.32 g. (0.001 mole) of IX or 0.27 g. (0.001 mole) of XVI in 5 ml. of 50% ethanol containing 0.04 g. (0.001 mole) of sodium hydroxide was heated on a water bath until the alkaline disappeared. The product separated after cooling and, after recrystallization from 20% ethanol, melted at 243.5–244.5°. A mixture melting point with the compound obtained by another method[2] showed no depression.

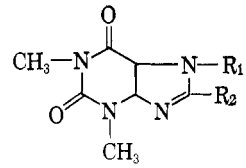
Reaction Products of 7-Substituted 1,3-Dimethyl-6H,7H-oxazolo[2,3-f]xanthine with Hydrobromic Acid. 1,3-Dimethyl-7-(β-bromopropyl)uric Acid (IX).—After dissolving 2.36 g. (0.01 mole) of VII in 25 ml. of hydrobromic acid (*d* 1.48), the solution was refluxed for 6 hr. On cooling, diluting with water, and crystallizing from 50% ethanol, a product with m.p. 250–251° was obtained which was moderately soluble in water and ethanol and readily soluble in solutions of alkali, from which the unaltered product was separated (yield 70%) after acidification.

1,3-Dimethyl-7-(β-bromo-γ-chloropropyl)uric Acid (X). Method A.—A solution of 2.7 g. (0.01 mole) of VIII[2] in 25 ml. of hydrobromic acid (*d* 1.48) was refluxed for 1 hr. Recrystallization from 80% acetic acid gave the product, m.p. 272–272.5°, which was insoluble in water and ethanol and readily soluble in

(8) M. Eckstein, *Dissertationes pharm.*, **14**, 435 (1962).

TABLE I

7,8-DISUBSTITUTED 1,3-DIMETHYLXANTHINES



Compd.	R_1	R_2	M.p., °C.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found % C	Found % H	Found % N
IX	$CH_2CH(Br)CH_3$	OH	250–251	$C_{10}H_{13}BrN_4O_3$	37.79	4.13	17.68	37.50	4.14	17.41
X	$CH_2CH(Br)CH_2Cl$	OH	272–272.5	$C_{10}H_{12}BrClN_4O_3$	34.12	3.44	15.92	33.91	3.44	15.66
XI	$CH_2CH(Br)CH_2Br$	OH	265–266	$C_{10}H_{12}Br_2N_4O_3$	30.33	3.05	14.15	30.50	3.13	14.55
XIII	$CH_2CH=CH_2$	OC_2H_5	93–94	$C_{12}H_{16}N_4O_3$	54.59	6.11	21.22	54.54	6.03	21.15
XIV	$CH_2CH=CH_2$	OH	257–259	$C_{10}H_{12}N_4O_3$	50.90	5.13	23.74	51.07	5.03	24.04
XVI	$CH_2CH(Cl)CH_3$	OH	255–256	$C_{10}H_{13}ClN_4O_3$	43.99	4.80	20.56	44.15	4.78	20.20
XVII	$CH_2CH(Cl)CH_2Cl$	OH	253–254	$C_{10}H_{12}Cl_2N_4O_3$	39.12	3.94	18.25	39.44	3.92	18.01
XVIII	$CH_2CH(Cl)CH_2I$	OH	231–231.5	$C_{10}H_{12}ClIN_4O_3$	30.10	3.03	14.04	30.30	2.98	13.92
XIX	$CH_2CH(Cl)CH_2Br$	OH	255–256	$C_{10}H_{12}BrClN_4O_3$	34.18	3.44	15.92	34.48	3.55	16.21
XX	$CH_2CH_2CH_3$	OH	255–256	$C_{10}H_{14}N_4O_3$	50.46	5.93	23.54	50.21	5.59	23.18
XXI	$CH_2CH_2CH_3$	Cl	123.5–124	$C_{10}H_{13}ClN_4O_2$	46.79	5.10	21.80	47.45	5.25	21.84
XXII	$CH_2CH_2CH_3$	OC_2H_5	80.5–81	$C_{12}H_{18}N_4O_3$	54.18	6.82	21.06	54.50	7.02	21.15

[a] All melting points are corrected; for recrystallization solvents and yields, see Experimental.

alkali, from which the unaltered product was separated on acidification.

Method B.—To a solution of 2.7 g. (0.01 mole) of VIII[2] in 50 ml. of chloroform cooled to 5°, 1.75 ml. of hydrobromic acid (*d* 1.48) was gradually dropped in 30 min. The reaction mixture was allowed to stand for 12 hr. at approximately 0°. Removal of the solvent and purification as described above gave a product with m.p. 272° and m.m.p. (with compound obtained in A) 272°.

1,3-Dimethyl-7-(β,γ-dibromopropyl)uric Acid (XI). Method A.—A solution of 3.1 g. (0.01 mole) of V in 25 ml. of hydrobromic acid (*d* 1.41) was refluxed for 1 hr. A product, which separated from the hot solution and crystallized from 80% acetic acid, melted at 265–266°; yield 83%. The compound was very slightly soluble in water and ethanol, slightly in acetic acid, and readily in alkali.

Method B.—A solution of 3.62 g. (0.01 mole) of VI in 25 ml. of hydrobromic acid (*d* 1.41) was refluxed for 4 hr. (the sublimation of iodine occurred). The product, which separated from the hot solution and crystallized from 80% acetic acid, melted at 265–266° and did not depress the melting point on admixture with compound obtained in A.

Method C.—To a solution of 2.36 g. (0.01 mole) of XIV in 100 ml. of chloroform was slowly dropped 2.4 g. of bromine in 10 ml. of chloroform at room temperature, and the mixture was allowed to stand for 24 hr. The solvent was removed and the residue was crystallized from 80% acetic acid yielding 70% of X, m.p. 265°. The melting point was not depressed on admixture with samples obtained in A and B.

1,3-Dimethyl-7-allyl-8-ethyluric Acid (XIII).—To a solution of 0.46 g. (0.02 g.-atom) of metallic sodium in 100 ml. of absolute ethanol was added 5.08 g. (0.02 mole) of 7-allyl-8-chlorotheophylline (XII) and the mixture was refluxed for 1 hr. (until appearance of neutral reaction). The solution was then evaporated under reduced pressure; the residue crystallized from water had m.p. 93–94°; yield 90%.

1,3-Dimethyl-7-allyluric Acid (XIV).—A solution of 5.2 g. (0.02 mole) of XIII in 15 ml. of concentrated hydrochloric acid was heated for 3 min., then cooled, diluted with water, filtered, and washed several times with water. Recrystallization from water and then from absolute ethanol gave the sample, m.p. 257–259°, yield 91%.

1,3,9-Trimethyl-7-(β,γ-dibromopropyl)uric Acid (XV).—Into a solution of 0.4 g. (0.001 mole) of XI in 5 ml. of water and 0.04 g. of sodium hydroxide was dropped 0.1 ml. of dimethyl sulfate (about 10°), and the mixture was then heated on the water bath for 0.5 hr. The product, separated while hot, was washed with dilute sodium hydroxide and crystallized from ethanol, yielding 70% of a compound of m.p. 210–211.5° dec.

Anal. Calcd. for $C_{11}H_{14}Br_2N_4O_3$: C, 32.22; H, 3.44. Found: C, 32.16; H, 3.65.

Reaction Products of 7-Substituted 1,3-Dimethyl-6H,7H-oxazolo[2,3-*f*]xanthine with Hydrochloric Acid. 1,3-Dimethyl-7-(β-chloropropyl)uric Acid (XVI).—A solution of 2.36 g. (0.01 mole) of VII in 20 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The product, separated while hot, was washed several times with water, and after crystallization from ethanol melted at 255–256°. It was very slightly soluble in water and readily soluble in alkali, from which the unaltered product was separated on acidification; yield 65%.

1,3-Dimethyl-7-(β-chloro-γ-chloro-, -γ-bromo-, or -γ-iodopropyl-) uric Acids (XVII, XVIII, and XIX).—From the compounds VIII, VI, and V in a manner described for compound XVI, but with prolongation of the reaction time to 4 hr., were obtained XVII, m.p. 253–254° (from 50% ethanol); XVIII, m.p. 231–231.5° (from aceic acid); and XIX, m.p. 255–256° (from 70% ethanol).

1,3-Dimethyl-7-propyluric Acid (XX). Method A.—A mixture of 0.002 mole of V or XI, 2 g. of zinc dust, 1 ml. of glacial acetic acid, and 60 ml. of ethanol was refluxed for 4 hr. From the filtrate a product, m.p. 255–256° (from water or ethanol), was obtained; yield 60–65%.

Method B.—A solution of 0.27 g. (0.001 mole) of VIII and 0.9 g. (0.006 mole) of sodum iodide in 20 ml. of methyl ethyl ketone was refluxed for 30 hr. The solvent was removed under reduced pressure. The residue was crystallized from water and ethanol and gave XX, m.p. 255–256°, yield 58%, which did not depress the melting point on admixture with compound obtained in A.

Method C.—A solution of 0.52 g. (0.002 mole) of XXII in 2 ml. of concentrated hydrochloric acid was boiled for 3 min. After cooling, diluting with water, and recrystallizing, a product, m.p. and m.m.p. 255–256°, was obtained.

7-Propyl-8-chlorotheophylline (XXI). Method A.—A mixture of 2.36 g. (0.01 mole) of XX, 1.2 ml. of dimethylaniline, and 5.6 ml. of phosphorous oxychloride was refluxed for 20 hr. The solution was poured into ice and the product, after crystallization from water, melted at 123.5–124°; yield 49%.

Method B.—To a solution of 2.14 g. (0.01 mole) of 8-chlorotheophylline and 0.4 g. (0.01 mole) of sodium hydroxide in 15 ml. of 60% ethanol was added 1 ml. of *n*-propyl bromide and heated until disappearance of the alkaline reaction (approximately 3 hr.). After partial evaporation of the solvent under reduced pressure, the solid was filtered, washed with water, and crystallized from anhydrous ethanol to yield 85% of XXI, m.p. 123.5–124°. A mixture melting point with compound obtained in A showed no depression.

1,3-Dimethyl-7-propyl-8-ethyluric Acid (XXII).—A solution of 2.57 g. (0.01 mole) of XXI in 100 ml. of absolute ethanol containing 0.23 g. (0.01 g.-atom) of metallic sodium was refluxed for 1 hr. The solvent was evaporated under reduced pressure, and the residue crystallized from anhydrous ethanol had m.p. 80.5–81°; yield 85%.

The properties of compounds IX–XI, XIII, XIV, and XVI–XXII and elemental analyses are shown in Table I.