stability between amylose and the commercial control.

The results of accelerated aging on amylose-based tablets are shown in Table IV. It can be seen that physical stability was relatively good, even in cases where chemical decomposition was marked. Although changes in hardness, disintegration, and friability occurred, they were still well within the limits for acceptable tablets. Data on sodium *p*-aminosalicylate tablets are not included since this compound degraded to such an extent that the tablets were destroyed under the conditions of this test.

Drug Availability.—The results of the availability experiments are shown graphically in Figs. 1 and 2, where the mean and range of cumulative urinary excretion are plotted for each time period. It can be seen that even for the sodium *p*-aminosalicylate tablets showing poor *in vitro* disintegration the availability is essentially the same as for the control. Apparently the viscous surface film which retarded *in vitro* disintegration was mechanically eroded in the gastrointestinal tract.

CONCLUSIONS

It appears, from the results of this investigation, that amylose merits serious consideration for use as a direct compression tablet binder. In the form used in this study it can effect compression of problem drugs at relatively low concentration and yields tablets possessing the characteristics desired for pharmaceutical use. Although each drug formulation is unique and must be thoroughly tested, there is every indication from these results that successful application can be obtained. It should be pointed out that these results relate only to this particular amylose and may not extrapolate to other amyloses or amylose derivatives.

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Notes

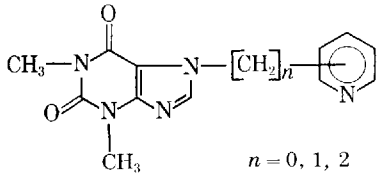
New Drugs in Xanthine Derivatives XXVI. Pyridylthioethyl Derivatives of Theobromine and Theophylline, and Products of Their Oxidation

By M. ECKSTEIN and J. SULKO

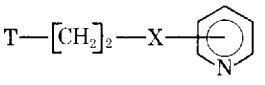
The synthesis of new 1- or 7-pyridylthioethyldimethylxanthines and their oxidation products (sulfoxides, *N*-oxides, and sulfones) are described.

SEVERAL, among previously synthesized theophylline (1) and theobromine (2) derivatives containing in the side-chain —S, —SO, —SO_2 groups, displayed interesting pharmacodynamic properties (3, 4). Compounds of the alkylthioether type are more hypotensive and less toxic than aminophylline. Water-soluble arylalkylsulfoxide derivatives appear to be active diuretics and their therapeutic index more favorable than aminophylline. The authors were interested in the synthesis of new sulfur derivatives of dimethylxanthines containing pyridyl rest in the side-chain. Among 7-substituted theophyllines, only a few compounds with a pyridine ring of type A are known.

Jucker *et al.* (5) patented 7-(pyridyl-4′)-theophylline (A, $n = 0$), and 7-(picolyl-3′ and 4′)-theophylline



A



B

T = 7-Theophyllinyl, resp. 1-theobrominyl rest.
X = —S, —SO, —SO_2

(A, $n = 1$) as the reaction products of sodium theophylline with 4-chloropyridine or picolyl chlorides, respectively. 7-β-(2′ and 4′-Pyridylethyl)-theophyllines were obtained in the reactions of pyridylethylation.

In this paper the synthesis of compounds of type B is described in which pyridine is coupled with the

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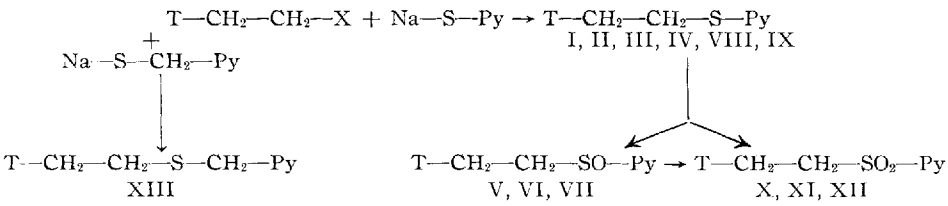

T = the 7-Theophyllinyl; resp. 1-theobrominyl rest.
X = Cl, Br

I, V, X, T = Tb, Py = 2-pyridyl
II, T = Tb, Py = 4-pyridyl
III, VI, XI, T = Th, Py = 2-pyridyl
IV, VII, XII, T = Th, Py = 4-pyridyl
VIII, T = Tb, Py = 2-pyridyl *N*-oxide
IX, T = Th, Py = 4-pyridyl *N*-oxide
XIII, T = Tb, Py = 3-pyridyl

Scheme I

xanthine system through an aliphatic chain containing sulfur as the thioether, sulfoxy, or sulfonyl group. The presence of a pyridyl group in these compounds intensifies their basic character in comparison with previously described sulfur-containing xanthine derivatives (1, 2).

The authors obtained 2- and 4-pyridylthioethyl derivatives of theobromine, and theophylline (I–IV) through condensation of 1-β-chloroethyltheobromine or 7-β-bromoethyltheophylline with sodium salts of 2- or 4-mercaptopyridines in anhydrous ethanol solution. Compounds I–IV are colorless, crystalline, easily soluble in alcohols, well soluble in dilute mineral acid solutions, and less soluble in water. They give stable picrates. By oxidation of I, III, and IV with an equimolar quantity of hydrogen peroxide in glacial acetic acid at room temperature, V, VI, and VII were formed. From comparison of physicochemical properties of V, VI, and VII with those of isomeric *N*-oxides (VIII and IX), it can be concluded that the former have a sulfoxide grouping. VIII and IX were prepared in an unambiguous way, in the reaction of halogentoethyl derivatives of theobromine resp. theophylline with the well-known 2-mercapto (6) or 4-mercapto-pyridine *N*-oxides (7). It is also in accordance with observations of other authors that in the oxidation conditions used, the pyridine *N*-oxides are formed only on heat (8–10) whereas the *S*-oxides are formed readily at room temperature. Alkyl-pyridyl sulfides give, by oxidation with hydrogen peroxide in acetic acid or with perbenzoic acid, the respective sulfoxides (6, 11). Taking into account the fact that purines are either degradated or unaffected by hydrogen peroxide (12), it may be assumed that purine *N*-oxides are not formed in the applied conditions of oxidation. Compound VI ($\lambda_{max.}$ 272 mμ, log ε 5.04) and IX ($\lambda_{max.}$ 291 mμ, log ε 5.71) showed no absorption band at ~230 mμ, which is characteristic for purine *N*-oxides (in neutral or alkaline solution) (13, 14). Similar results were obtained by U.V. examination of hydrogen peroxide oxidation products of sulfides I and IV. This supports the presence of a sulfoxide group in compounds V, VI, and VII. When, for the oxidation of I, III, and IV, an excess of hydrogen peroxide was used under analogous conditions the sulfonyl compounds (X, XI, XII) were obtained. The latter can be prepared also by oxidation of the corresponding sulfoxides. Sulfones (X, XI, XII) in the series of sulfide-sulfoxide-sulfone, have the highest melting points. X, XI, and XII, are readily soluble in ethanol and insoluble in water. Moreover, the condensation of pyridine-3-methanthiol (15) with 1-β-chloroethyltheobromine carried out in a manner analogous to compounds I–IV gives 1-β-(pyridyl-3′-methyl)-thioethyltheobromine (XIII), with a relatively low melting point.[1]

Analyses are reported in Table I.

EXPERIMENTAL[2]

1-β-(2′-Pyridyl)-thioethyltheobromine (I).—To a solution of 0.23 Gm. (0.001 mole) of sodium in 20 ml. of absolute ethanol, 1.11 Gm. (0.01 mole) of 2-mercaptopyridine (16) and 2.42 Gm. (0.01 mole) of 1-β-chloroethyltheobromine (17) were added, and the mixture was refluxed for 10 hr. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to obtain colorless needles, m.p. 197°. Picrate, m.p. 185° (from ethanol).

1-β-(4′-Pyridyl)-thioethyltheobromine (II), 7-β-(2′-pyridyl)-thioethyltheophylline (III), and 7-β-(4′-pyridyl)-thioethyltheophylline (IV) were obtained similarly.

1-β-(2′-Pyridyl)-sulfoxyethyltheobromine (V).—To a solution of 0.95 Gm. (0.003 mole) of 1-β-(2′-pyridyl)-thioethyltheobromine (I) in 10 ml. of glacial acetic acid, 1 drop of sulfuric acid solution and 0.34 ml. (0.003 mole) of 30% hydrogen peroxide were added. The mixture was allowed to stand for 3 days at room temperature. Acetic acid then was evaporated *in vacuo*, and the residue was crystallized from 70% ethanol to obtain colorless needles, m.p. 181°.

Similarly, the sulfoxides (VI and VII) were obtained from II and III, correspondingly.

1-β-(2′-Pyridyl)-sulfonylethyltheobromine (X).—*Method A.*—To a solution of 1.19 Gm. (0.006 mole) of 1-β-(2′-pyridyl)-thioethyltheobromine (I) in 20 ml. of glacial acetic acid, 1 drop of sulfuric acid in acetic acid solution (10 ml. of acetic acid + 2 drops of concentrated sulfuric acid), and 1.4 ml. (0.012 mole) of 30% hydrogen peroxide were added. The mixture was kept at room temperature for 3 days. After vacuum evaporation of the acetic acid, the residue was crystallized from 50% ethanol, and a colorless product, m.p. 216°, was obtained.

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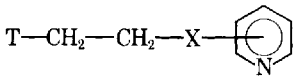
[1] It is probably due to the presence of a methylene bridge between the pyridine ring and sulfur. Similarly, 7-γ-picolyltheophylline has a lower melting point than 7-γ-pyridinetheophylline (5).

[2] Melting points were determined by the open capillary tube method and are not corrected. The analyses were done by T. Kulawik and Z. Pasternak from this laboratory.

TABLE I.—PYRIDYLTHIOETHYL DERIVATIVES OF THEOBROMINE AND THEOPHYLLINE



No.	T[a]	X	4-Pyridyl	M.p., °C., Solv. for Recrystn.	Formula, Mol. Wt.		Anal. C	H	N
I	Tb	S	2-Pyridyl[b]	195–197°	$C_{14}H_{15}N_5O_2S$	Calcd.	53.04	4.77	22.09
				Ethanol	317.36	Found	53.64	5.03	22.30
II	Tb	S	4-Pyridyl	174–175°	$C_{14}H_{15}N_5O_2S$	Calcd.	53.04	4.77	22.09
				Ethanol	317.36	Found	53.13	5.00	22.53
III	Th	S	2-Pyridyl	170–171°	$C_{14}H_{15}N_5O_2S$	Calcd.	53.04	4.77	22.09
				Ethanol	317.36	Found	52.86	4.90	22.26
IV	Th	S	4-Pyridyl	183–185°	$C_{14}H_{15}N_5O_2S$	Calcd.	53.04	4.77	22.09
				Ethanol	317.36	Found	53.15	5.21	22.40
V	Tb	SO	2-Pyridyl	181°	$C_{14}H_{15}N_5O_3S$	Calcd.	50.49	4.54	21.03
				Ethanol	333.36	Found	49.96	4.45	20.78
VI	Th	SO	2-Pyridyl	165–167°	$C_{14}H_{15}N_5O_3S$	Calcd.	50.49	4.54	21.03
				Ethanol	333.36	Found	50.31	4.73	20.91
VII	Th	SO	4-Pyridyl	204–206°	$C_{14}H_{15}N_5O_3S$	Calcd.	50.49	4.54	21.03
				80% Ethanol	333.36	Found	50.20	4.93	21.15
VIII	Tb	S	2-Pyridyl	200–201°	$C_{14}H_{15}N_5O_3S$	Calcd.	50.49	4.54	21.03
			N-oxide	Ethanol	333.36	Found	50.17	4.49	20.72
IX	Th	S	4-Pyridyl	220–221°	$C_{14}H_{15}N_5O_3S$	Calcd.	50.49	4.54	21.03
			N-oxide	Ethanol	333.36	Found	50.56	4.32	20.72
X	Tb	SO_2	2-Pyridyl	214–216°	$C_{14}H_{15}N_5O_4S$	Calcd.	48.18	4.33	20.07
				Ethanol	349.36	Found	48.18	4.52	20.15
XI	Th	SO_2	2-Pyridyl	193–194°	$C_{14}H_{15}N_5O_4S$	Calcd.	48.18	4.33	20.07
				50% Ethanol	349.36	Found	47.62	4.08	20.33
XII	Th	SO_2	4-Pyridyl	205–208°	$C_{14}H_{15}N_5O_4S$	Calcd.	48.18	4.33	20.07
				80% Ethanol	349.36	Found	48.63	4.01	20.53
XIII	Tb	S	3-Picolyl	123–124°	$C_{15}H_{17}N_5O_2S$	Calcd.			21.21
				Ethanol	331.38	Found			21.49

[a] T = the 7-theophyllinyl, resp. 1-theobrominyl rest. [b] Picrate m.p. 185° from ethanol. *Anal.*—Calcd. for $C_{20}H_{18}O_9N_8S$: C, 43.87; H, 3.33. Found: C, 43.97; H, 3.50.

The sulfones (XI and XII) were prepared similarly.

Method B.—To a solution of 0.5 Gm. (0.0015 mole) of 1-β-(2′-pyridyl)-sulfoxyethyltheobromine (V) in 20 ml. of glacial acetic acid with the catalytic amount of sulfuric acid, 0.2 ml. (0.0018 mole) of 30% hydrogen peroxide was added, and the mixture kept at room temperature for 2–3 days. After evaporation of acetic acid *in vacuo*, the residue crystallized from 50% ethanol yielded the product, m.p. 215°. No melting point depression was found for a mixture of the 2 products.

N-Oxide of 1-β-(2′-Pyridyl)-thioethyltheobromine (VIII).—A solution of 0.23 Gm. (0.01 mole) of sodium and 1.27 Gm. (0.01 mole) of 2-mercaptopyridine *N*-oxide (6) in 25 ml. of ethanol was added dropwise to a boiling solution of 2.42 Gm. (0.01 mole) of 1-β-chloroethyltheobromine in 25 ml. of ethanol. Heating was continued for 4 hr.; the hot solution was filtered and then cooled. The precipitate recrystallized from ethanol yielded the product, m.p. 201°. *N*-Oxide of 7-β-(4′-pyridyl)-thioethyltheophylline (IX) was obtained in the above manner by condensation of 7-β-bromoethyltheophylline (18) with 4-mercaptopyridine *N*-oxide (7) in ethanolic sodium ethoxide solution.

1 - β - (Pyridyl - 3′ - methyl) - thioethyltheobromine (XIII).—To the solution of 0.23 Gm. (0.01 mole) of sodium and 1.23 Gm. (0.01 mole) of 3-mercaptomethylpyridine (16) in 20 ml. of ethanol, 2.42 Gm. (0.01 mole) of 1-β-chloroethyltheobromine was added, and the mixture was heated under reflux for 8 hr. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to obtain a colorless product, m.p. 124°.

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