[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Potential Antivirals. II. Simple Analogs of Chloramphenicol (Chloromycetin). Assorted 2,5-Dimethoxyphenethylamides

BY ARTHUR P. PHILLIPS

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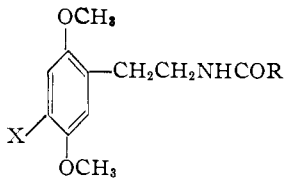
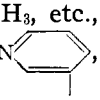
A series of substituted 2,5-dimethoxyphenethylamides has been prepared for examination as potential antiviral agents related to chloramphenicol. These compounds have been varied by changing both the substituent in the 4-position of the benzene ring and the acyl of the amide group.

In an earlier paper several groups of modified phenethylamine derivatives, analogous to chloramphenicol,[1] were presented as potential antivirals.[2] Of these the most promising compounds were derived from 2,5-dimethoxyphenethylamine. This paper presents several related series all made from 2,5-dimethoxyphenethylamine. These are represented in I



I

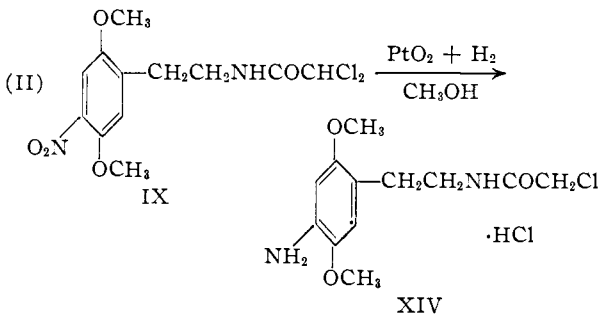
where X = H, NO_2, NH_2·HCl, $NHCOCH_3$, etc., and R = CH_3, CH_2Cl, $CHCl_2$, CCl_3,  , $-(CH_2)_4-$, etc.

The compounds were made by reaction of 2,5-dimethoxyphenethylamine with the appropriate acid anhydride, chloride or ester. The amides were then nitrated to give the 4-nitro derivatives and the latter on catalytic hydrogenation gave the 4-amino products. These 4-amino compounds were subsequently further acylated in some instances and in two cases were combined with chloropyrimidines to give 4-substituted pyrimidino compounds. Table I lists all the compounds with pertinent data including melting points and analyses.

The simple amides, I–VI of Table I, were made by reaction of 2,5-dimethoxyphenethylamine with acetic anhydride (I), chloroacetic anhydride (II), methyl dichloroacetate (III),[2] methyl trichloroacetate (IV), ethyl nicotinate (V) and methyl adipate (VI).

The nitro derivatives, VII–XII, were obtained from the amides, I–VI, by reaction with concentrated nitric acid in glacial acetic acid solution.

Catalytic hydrogenation of the nitro compounds gave the 4-amino derivatives XIII–XV. The nitro groups were reduced using Adams catalyst in alcohol solution. An interesting transformation was observed in certain of these cases. When the nitrodichloroacetyl derivative, IX, was hydrogenated in alcohol solution the product was not the expected XV, but XIV, the hydrochloride of the 4-amino-monochloroacetylamide. This results (see II) from the catalytic hydrogenolysis of one of the chlorines from the dichloroacetyl group, presumably following the conversion of nitro to amino. Similarly the 4-amino-dichloroacetyl derivative XV resulted not from reduction IX, but from the nitrotrichloroacetyl compound X, again with the reductive cleavage of one of the chlorines from the trichloroacetyl group, probably after reduction of the nitro. These transformations were not entirely unprecedented, for earlier studies on catalytic hydrogenolysis[3] had shown that under similar conditions one or more chlorines were removed from dichloro- or trichloroacetic acid, or their ethyl esters. It had also been observed[3] that catalytic hydrogenolysis of aromatic halogen compounds was greatly facilitated by the presence on the aromatic ring of an amino group.



XIV

Compounds XVI–XX were made from the corresponding amino compounds by reaction with acetic anhydride, phenyl isocyanate, or ethyl chlorocarbonate as required.

Reaction of XIII and XV with 2-amino-4-chloro-6-methylpyrimidine according to the method of Banks[4] gave the 4-substituted pyrimidino amides XXI and XXII, respectively.

Bromination of III in glacial acetic acid gave XXIII.

Most of the compounds shown in Table I were examined for antiviral activity by Dr. D. J. Bauer of The Wellcome Laboratories of Tropical Medicine, 183 Euston Road, London, England. None of the variations showed any better activity than IX, the most active compound found in the earlier series.[2]

Experimental

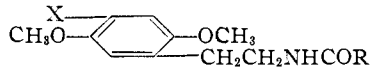
A number of typical preparative procedures are outlined below.

N-(2,5-Dimethoxyphenethyl)-trichloroacetamide (IV).—A mixture of 18 g. (0.1 mole) of 2,5-dimethoxyphenethylamine, 30 cc. of methanol and 20 g. (0.11 mole) of methyl trichloroacetate was heated for two hours on the steam-bath, letting methanol evaporate freely. The reaction is exothermic. The residue, after completion of the reaction, was purified by several crystallizations from ethyl acetate–Skellysolve B mixtures. The yield of pure, white, crystalline product melting at 75–76° was 95%.

(1) M. C. Rebstock, *et al.*, THIS JOURNAL, **71**, 2458 (1949).
(2) A. P. Phillips, *ibid.*, **74**, 6125 (1952).
(3) R. Baltzly and A. P. Phillips, *ibid.*, **68**, 261 (1946).
(4) C. K. Banks, *ibid.*, **66**, 1127 (1944).

TABLE I

ASSORTED 2,5-DIMETHOXYPHENETHYL AMIDES AS CHLORAMPHENICOL ANALOGS



Compound no.	X	R	M.p., °C.[a]	Crystn.[b] solv.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I[c]	H	CH_3	95–96	M.Aq.					
II	H	CH_2Cl	91–92	Ea.H.	$C_{12}H_{16}ClNO_3$	55.9	56.1	6.3	6.2
III[d]	H	$CHCl_2$	83–84	B.H.	$C_{12}H_{15}Cl_2NO_3$	49.3	49.2	5.2	5.2
IV	H	CCl_3	75–76	Ea.H.	$C_{12}H_{14}Cl_3NO_3$	44.1	44.1	4.3	4.3
V	H	3-Pyridyl	84–85	Ea.H.	$C_{16}H_{18}N_2O_3$	67.1	66.6	6.3	6.2
VI[e]	H	$-(CH_2)_4-$	125–126	M	$C_{26}H_{36}N_2O_6$	66.0	66.0	7.7	7.4
VII	NO_2	CH_3	142–143	M	$C_{12}H_{16}N_2O_5$	53.7	53.4	6.0	6.0
VIII	NO_2	CH_2Cl	118–119	M.Ea.H	$C_{12}H_{15}ClN_2O_5$	47.6	47.3	5.0	4.8
IX[d]	NO_2	$CHCl_2$	155–156	M	$C_{12}H_{14}Cl_2N_2O_5$	42.7	43.0	4.2	4.2
X	NO_2	CCl_3	146–147	M	$C_{12}H_{13}Cl_3N_2O_5$	38.7	38.6	3.5	3.8
XI	NO_2	3-Pyridyl	154–155	M.Ea.H	$C_{16}H_{17}N_3O_5$	58.0	58.2	5.2	5.2
XII[e]	NO_2	$-(CH_2)_4-$	206–207	HOAc.M	$C_{26}H_{34}N_4O_{10}$	55.5	56.0	6.1	6.1
XIII	$NH_2 \cdot HCl$	CH_3	211–212	M.Ea	$C_{12}H_{19}ClN_2O_3$	52.4	52.6	7.0	7.0
						N 10.0	N 9.7		
XIV	$NH_2 \cdot HCl$	CH_2Cl	205–207	M.Ea	$C_{12}H_{18}Cl_2N_2O_3$	46.6	46.9	5.8	5.8
XV	$NH_2 \cdot HCl$	$CHCl_2$	214–216	M.Ea	$C_{12}H_{17}Cl_3N_2O_3$	N 8.1	N 7.9		
XV(a)[f]	NH_2	$CHCl_2$	142–143	M	$C_{12}H_{16}Cl_2N_2O_3$	46.9	47.2	5.2	5.5
XVI	CH_3CONH	CH_3	180–181	M.E	$C_{14}H_{20}N_2O_4$	59.9	59.9	7.2	6.9
XVII	$C_6H_5NHCONH$	CH_3	200–201	M.Ea.H	$C_{19}H_{23}N_3O_4$	63.9	64.1	6.5	6.4
						N 11.7	N 11.4		
XVIII	CH_3CONH	CH_2Cl	191–192	M	$C_{14}H_{19}ClN_2O_4$	53.4	53.9	6.1	5.7
XIX	CH_3CONH	$CHCl_2$	159–160	M.Ea.H	$C_{14}H_{18}Cl_2N_2O_4$	48.1	48.2	5.2	5.4
						N 8.0	N 7.8		
XX	C_2H_5OCONH	$CHCl_2$	172–173	Ea	$C_{15}H_{20}Cl_2N_2O_5$	47.5	47.7	5.3	5.4
						N 7.4	N 7.2		
XXI	2-Amino-6-methyl-4-pyrimidylamino	CH_3	218–219	M	$C_{17}H_{23}N_5O_3$	59.1	59.2	6.7	7.0
XXII	2-Amino-6-methyl-4-pyrimidylamino·HCl	$CHCl_2$	184–185	M.Ea.E	$C_{17}H_{22}Cl_3N_5O_3$	45.2	45.4	4.9	5.0
XXIII	Br	$CHCl_2$	141–142	M	$C_{12}H_{14}BrCl_2NO_3$	38.8	38.6	3.8	3.7

[a] All melting points are uncorrected. All yields were greater than 80%. [b] Aq = water; B = benzene; E = ethyl ether; Ea = ethyl acetate; H = Skellysolve B; HOAc = acetic acid; M = methanol. [c] S. Sugasawa and H. Shigehara, *Ber.*, **74**, 459 (1941). [d] Reference (2). [e] The bis amide from adipic acid. [f] The free base from the hydrochloride XV.

N-(2,5-Dimethoxy-4-nitrophenethyl)-trichloroacetamide (X).—To a solution of 16 g. (0.05 mole) of IV (see above) in 100 cc. of glacial acetic acid was added 10 cc. (0.15 mole) of concentrated nitric acid (sp. gr. 1.42) dropwise with stirring and cooling in a cold water-bath. The nitric acid addition required 10 to 15 minutes. A yellow crystalline solid began to precipitate during the process. The reaction mixture was allowed to stand for two hours at room temperature and was then diluted with 400 cc. of cold water. The yellow product was collected by filtration and after recrystallization from methanol, 18 g. (95%) of yellow crystals melting at 146–147° were obtained.

N-(2,5-Dimethoxy-4-aminophenethyl)-dichloroacetamide Hydrochloride (XV).—A solution of 11 g. (0.03 mole) of X (above) in 100 cc. of methanol was hydrogenated in a Burgess–Parr type apparatus, using about 0.1 g. of Adams catalyst, two to three atmospheres overpressure of hydrogen, and shaking. Hydrogen uptake was rapid and the calculated amount (0.12 mole) was absorbed in about three hours before coming to a complete stop. After removing the platinum, addition of excess ethyl acetate to the reaction solution precipitated 9 g. (90%) of white crystals, m.p. 214–216°.

This product proved to be XV. An aqueous solution gave a white precipitate of silver chloride with aqueous silver nitrate.

Liberation of the free base, XV (a), gave fluffy white needles which were recrystallized from methanol and melted at 142–143°,

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included.

TUCKAHOE 7, N. Y.