SYNTHESIS OF 1-ARYL-2,6-BIS(CHLOROMETHYL)PIPERIDINES

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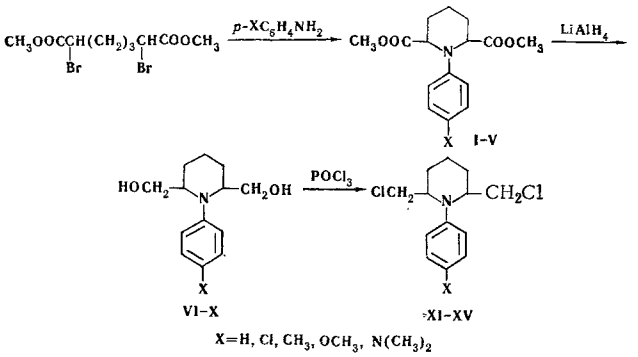
Several derivatives of 2,6-bis(chloromethyl)piperidine have been synthesized as model compounds with "rigid" bis(β-chloroethyl)amino groups. They have aryl substituents on the nitrogen atom.

We have previously described 2,5-bis(chloromethyl)pyrrolidines, which are compounds possessing the rigid form of the cytotoxic bis(β-chloroethyl)amine group [1]. In order to examine the comparative chemical and biological activities of a number of cyclic analogs of bis(β-chloroethyl)amine, we have prepared compounds in which the α,α'-carbon atoms of the cytotoxic group are locked into a piperidine ring by means of a trimethylene bridge. The synthesis of these compounds was effected as follows:



The starting esters of 2,6-piperidinedicarboxylic acid (I-V) (see table 1) were prepared by condensation of dimethyl meso-α,ε-dibromopimelate with primary aromatic amines.

2,6-Bismethoxycarbonylpiperidines are reduced smoothly by $LiAlH_4$ in good yields to the corresponding bis(hydroxymethyl) derivatives VI-X.

Attempts to prepare 1-aryl-2,6-bis(chloromethyl)piperidines by heating the bis(hydroxymethyl) derivatives VI-X with thionyl chloride, as described for 2,6-bischloromethylpiperidines with aliphatic substituents [2, 3], resulted in considerable resinification. We have previously described similar difficulties in the attempted preparation of 1-piperidino-2,5-bis(chloromethyl)pyrrolidine using thionyl chloride [4]. 1-Aryl-2,6-bis(chloromethyl)piperidines (XI-XV) and 1-piperidino-2,5-bis(chloromethyl)pyrrolidine (XVI) were obtained by reaction of the diols with phosphoryl chloride.

1-Phenyl-2,6-bis-substituted piperidines readily undergo reactions characteristic of tertiary aromatic amines. Thus, reaction of the diester I with nitrous acid gives the nitroso derivative XVII. The 1-phenyl derivatives I and XI undergo the azo coupling reaction with p-nitrophenyldiazonium chloride to give the azo dyes XVIII and XXVIII. 1-(p-Nitroazobenzene)-2,6-bis(chloromethyl)piperidine is a latent form of

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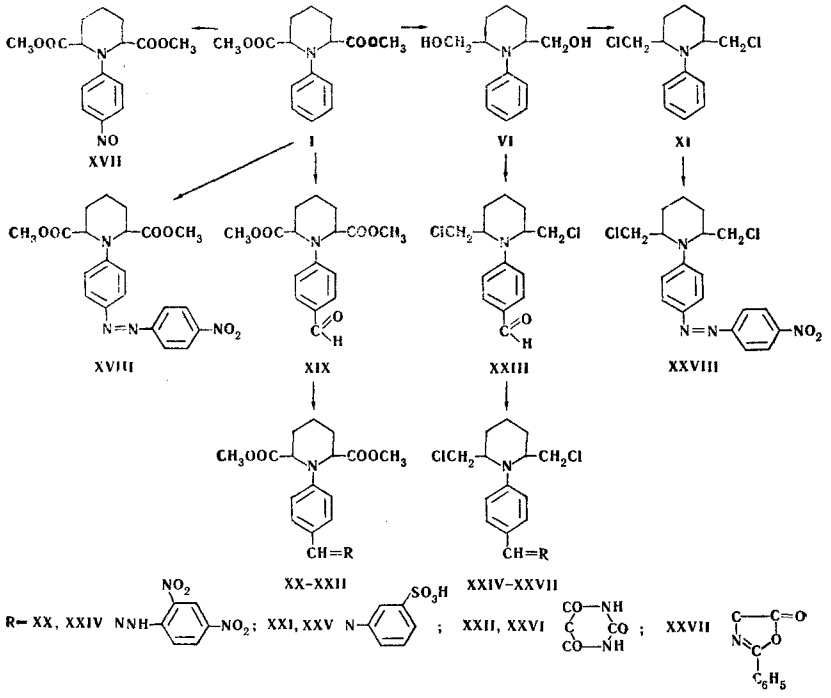
1-phenyl-2,6-bis(chloromethyl)piperidine. It is known that a similar compound with the p-bis (β-chloroethyl)amino group has a significant suppressive effect on the growth of the Walker carcinoma [5].



Reaction of the diester I with dimethylformamide in the presence of phosphoryl chloride gives the aldehyde XIX. The diol VI under the conditions of the Vilsmeier reaction gives p-[2,6-bis(chloromethyl)-piperidino] benzaldehyde (XXIII), which is the cyclic analog of p-[bis(β-chloroethyl)amino]benzaldehyde, which finds wide application in the synthesis of antitumor compounds.

In a manner similar to other aromatic aldehydes, the aldehydes XIX and XXIII readily form 2,4-dinitrophenylhydrazones XX and XXIV, and azomethines XXI and XXV with metanilic acid.

It is known that p-[bis(β-chloroethyl)amino]benzylidene derivatives of barbituric acid possess high antitumor activity [6]. The benzylidene derivative XXVI is readily formed on heating the aldehyde XXIII with barbituric acid. The aldehyde XIX also reacts with barbituric acid.

The aldehyde XXIII reacts with hippuric acid in acetic anhydride to give the azolactone XXVII.

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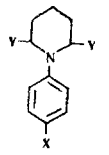
EXPERIMENTAL

1-Aryl-2,6-bis(methoxycarbonyl)piperidines (I-V). Dimethyl meso-α,ε-dibromopimelate (0.1 mole), bp 186-191° (12 mm) [7], 0.3 mole of the amine, and 0.5 g of KI in 50 ml of benzene were boiled for 30 hr (for IV and V) and 70 hr (for I-III). The reaction mixture was diluted with water until the precipitate dissolved completely, then extracted with ether. The ether extract was washed with small portions of 6-N HCl. The acid extract was neutralized with conc. NaOH and extracted with ether. After drying over $MgSO_4$, the ether was distilled off, and the residue distilled in vacuo to give a slightly yellow viscous oil, which crystallized on prolonged cooling, except compounds III and IV (see Table 1).

1-Aryl-2,6-bis(hydroxymethyl)piperidines (VI-X). The diester I-V (0.3 mole) in 25 ml of dry ether was added dropwise to 0.75 mole of $LiAlH_4$ in 350 ml of dry ether. The mixture was boiled for 4 hr; then 50 ml of water was added with care. The ether layer was separated, and the residue extracted carefully with small portions of ether. The extract was dried over $MgSO_4$, and the ether removed. The residue was distilled in vacuo to give a Vaseline-like oil (see Table 1).

1-Aryl-2,6-bis(chloromethyl)piperidines (XI-XV). The diol VI-X (0.7 mole) in 40 ml of dry benzene was boiled with 1.6 ml of freshly distilled phosphoryl chloride for 4 hr. The reaction mixture was cooled,

TABLE 1



Compound	X	Y	bp, °C (pressure, nm)	mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
I	H	$COOCH_3$	182—185 (3)	45—46	$C_{15}H_{19}NO_4$	65.08	6.80	—	64.98	6.90	—	65
II	Cl	$COOCH_3$	207—210 (4)	80—81	$C_{15}H_{18}ClNO_4$ *	58.12	6.10	—	57.81	5.81	—	35
III	CH_3	$COOCH_3$	190—195 (4)	—	$C_{16}H_{21}NO_4$	66.41	7.34	4.91	65.98	7.27	4.81	45
IV	OCH_3	$COOCH_3$	207—210 (4)	—	$C_{16}H_{21}NO_5$	62.49	7.11	—	62.55	6.89	—	55
V	$(CH_3)_2N$	$COOCH_3$	220—225 (6)	89—90	$C_{17}H_{24}N_2O_4$	64.17	7.68	8.96	63.75	7.73	8.75	40
VI	H	OH	207 (5)	—	$C_{13}H_{19}NO_2$	—	—	6.13	—	—	6.33	90
VII	Cl	OH	217—220 (6)	45—47	$C_{13}H_{18}ClNO_2$	—	—	5.33	—	—	5.49	70
VIII	CH_3	OH	195—198 (2)	—	$C_{14}H_{21}NO_2$	71.47	9.06	6.20	71.47	8.95	5.95	80
IX	OCH_3	OH	225—227 (5)	—	$C_{14}H_{21}NO_3$	66.40	8.72	—	66.89	8.43	—	70
X	$(CH_3)_2N$	OH	215—220 (2)	—	$C_{15}H_{24}N_2O_2$	—	—	11.01	—	—	10.59	50
XI	H	Cl	—	79—80	$C_{13}H_{17}Cl_2N$ †	60.94	6.94	5.52	60.47	6.64	5.42	85
XII	Cl	Cl	—	192—193	$C_{13}H_{16}Cl_3N \cdot HCl$	46.93	5.15	4.19	47.44	5.20	4.26	35
XIII	CH_3	Cl	—	207—208	$C_{14}H_{19}Cl_2N \cdot HCl$ ‡	54.84	6.27	4.82	54.50	6.51	4.55	80
XIV	OCH_3	Cl	—	229—230	$C_{17}H_{19}Cl_2NO \cdot HCl$	51.38	6.57	4.11	51.79	6.20	4.31	60
XV	$(CH_3)_2N$	Cl	—	215—216	$C_{15}H_{22}Cl_2N_2 \cdot 2HCl$	48.63	6.45	7.56	48.71	6.46	7 48	60

*Found, %: Cl 11.32. Calculated, %: Cl 11.38. †Found, %: Cl 26.98. Calculated, %: Cl 27.47. ‡Found, %: Cl 34.74. Calculated, %: Cl 34.44.

poured onto ice, and neutralized with conc ammonia. The benzene layer was separated, and the residue further extracted with small portions of benzene. The combined benzene extracts were dried over $MgSO_4$, and the benzene removed in vacuo at a bath temperature not exceeding 40°C. The residual oil failed to crystallize on prolonged cooling except for XI and XIII. The hydrochlorides were obtained by treatment of the ether solutions of the dichloro compounds with alcoholic HCl, and were purified by recrystallization from absolute ethanol (see Table 1).

1-Piperidino-2,5-bis(chloromethyl)pyrrolidine (XVI). To a solution of 1.3 g (0.006 mole) of 1-piperidino-2,5-bis(hydroxymethyl)pyrrolidine [4] in 25 ml of dry benzene was added 1.3 ml of $POCl_3$, and the mixture boiled for 5 hr. The mixture was worked up as above. The free base, a slightly yellow oil, was dissolved in ether and treated with alcoholic HCl to give the hydrochloride, mp 185°C (from absolute alcohol). Found, %: C 45.92; H 7.46; N 9.66. Calculated for $C_{11}H_{26}Cl_2N_2 \cdot HCl$, %: C 45.91; H 7.36; N 9.74.

1-p-Nitrosophenyl-2,6-bis(methoxycarbonyl)piperidine (XVII). 3.05 g (0.01 mole) of the diester I was dissolved with heating in 7.5 ml of conc HCl, the solution cooled, and a solution of 1.26 g (0.018 mole) of sodium nitrite in 4 ml of water was added at 0-5°C. After standing for one hr, the mixture was diluted with twice its volume of water, and extracted with chloroform. The reaction product was precipitated with petroleum ether, and crystallized from ether to give 2 g of bright-green needles, mp 136°C. Found, %: C 58.87; H 5.95; N 9.10. Calculated for $C_{15}H_{18}N_2O_5$, %: C 58.80; H 5.88; N 9.14.

1-(p-Nitroazobenzene)-2,6-bis(methoxycarbonyl)piperidine (XVIII). A solution of 1.5 g (0.005 mole) of the diester I in 10 ml of acetone was added at 0-5°C to p-nitrophenyldiazonium chloride (from 0.7 g of p-nitroaniline and 0.8 g of $NaNO_2$ in 3 ml of HCl). The mixture was kept in the refrigerator for two days, the precipitate was filtered off and recrystallized from aqueous acetone giving a bright-red product, mp 154-154.5°C. Found, %: N 13.10. Calculated for $C_{21}H_{22}N_4O_6$, %: N 13.14.

p-[2,6-Bis(methoxycarbonyl)piperidino]benzaldehyde (XIX). To 15.2 ml of dimethylformamide was added at 0-5°C 1.86 ml of phosphoryl chloride. After 15 min at this temperature, 5.54 g (0.018 mole) of the diester I in 15.2 ml of dimethylformamide was gradually added, and the mixture was stirred for 15 min. It was then warmed to 40°C, kept at this temperature for 2 hr, cooled, poured onto ice, and neutralized with conc ammonia. The precipitate was filtered off on a cooled funnel, and washed with ice water. The crude product was an oil at room temperature, weight 4 g. Purification was effected via the m-sulfoanil derivative. This (0.2 g) was recrystallized from aqueous methanol and triturated with 4 ml of 5% sodium carbonate with gentle warming on a water bath. The aldehyde which separated was filtered off and crystallized

from water, giving a finely crystalline, colorless compound, mp 87-89°C. Found, %: N 4.62. Calculated for $C_{16}H_{19}NO_5$, %: N 4.58. 2,4-Dinitrophenylhydrazone (XX). Dark-red, finely crystalline compound, mp 207-209°C (from benzene). Found, %: N 14.62. Calculated from $C_{22}H_{23}N_5O_8$, %: N 14.44. m-Sulfoanil (XXI). Bright-yellow crystalline compound, mp > 350°C (prisms, from aqueous methanol). Found, %: N 6.14. Calculated from $C_{22}H_{24}N_2O_7S$, %: N 6.08.

5-[p-2,6-Bis(methoxycarbonyl)piperidinobenzylidene]barbituric acid (XXII). Hot solutions of 1.5 g (0.005 mole) of the aldehyde XIX in 30 ml of ethanol, and 0.68 g (0.005 mole) of barbituric acid in 6 ml of water, were mixed and heated to boiling for 2 min. The precipitate was filtered off and recrystallized from a dimethylformamide–butanol mixture (1:25) to give a bright-orange finely crystalline product, mp 288-289°C. Yield 1.6 g (80%). Found, %: C 58.42; H 5.13; N 10.10. Calculated for $C_{20}H_{21}N_3O_7$, %: C 58.33; H 5.10; N 10.12.

p-[2,6-Bis(chloromethyl)piperidino]benzaldehyde (XXIII). To 7 ml of dimethylformamide was added at 0-5°C 4.6 ml of phosphoryl chloride, and after 15 min, 3.2 (0.015 mole) of the diol VI in 7 ml of dimethylformamide was added dropwise. The mixture was stirred at 0-5°C for 15 min, then heated at 85-90°C for 4 hr 30 min. Conc ammonia was then added with cooling, to pH 8, and the precipitate was filtered off and recrystallized from ethanol to give colorless prisms, mp 83-85°C. Yield 75%. Found, %: C 60.65; H 6.55; N 5.15. Calculated for $C_{14}H_{17}Cl_2NO$, %: C 60.88; H 6.20; N 5.07.

2,4-Dinitrophenylhydrazone (XXIV). Dark-red finely crystalline solid, mp 175-176°C (from butanol). Found, %: N 14.91. Calculated for $C_{20}H_{21}Cl_2N_5O_4$, %: N 15.02.

m-Sulfoanil (XXV). Bright-yellow finely crystalline solid, mp > 350°C (from 50% ethanol). Found, %: N 6.64. Calculated for $C_{20}H_{22}Cl_2N_2O_3S$, %: N 6.34.

5-[p-2,6-Bis(chloromethylpiperidino)benzylidene]barbituric acid (XXVI). This was obtained in a similar manner to XXII, in 60% yield. The deep-orange crystalline solid had mp 237°C (decomp, from butanol). Found, %: C 54.95; H 5.12; Cl 17.39. Calculated for $C_{18}H_{19}Cl_2N_3O_3$, %: C 54.53; H 4.83; Cl 17.80.

4-[p-(2,6-Bischloromethylpiperidino)benzylidene]phenyl-5-oxazolone (XXVII). 5.72 g (0.02 mole) quantity of the aldehyde XXIII, 3.6 g (0.02 mole) of hippuric acid, and 2.8 g of anhydrous potassium carbonate in 20 ml of acetic anhydride were heated gradually to 100°C (15 min), and stirred for an additional 15 min. On the following day, the reaction mixture was poured into a mixture of ice and water. The aqueous layer was decanted off, and the residual oil was triturated with ether and crystallized from glacial acetic acid. The bright-orange needles had mp 154-156°C, yield 3.5 g (25%). Found, %: N 6.82. Calculated for $C_{23}H_{22}Cl_2N_2O_2$, %: N 6.52.

1-(p-Nitroazobenzene)-2,6-bis(chloromethyl)piperidine (XXVIII). This was obtained in 45% yield by the method given above for XVIII, as a bright-red, finely crystalline solid, mp 113-114°C (from isopropanol). Found, %: Cl 14.91; N 14.76. Calculated for $C_{20}H_{21}Cl_2N_5O_4$, %: Cl 15.27; N 15.02.

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