# 1,4-BIS(AMINOMETHYL)-2,3,5,6-TETRACHLOROBENZENES*

Z. J. VEJDĚLEK and M. PROTIVA

*Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3*

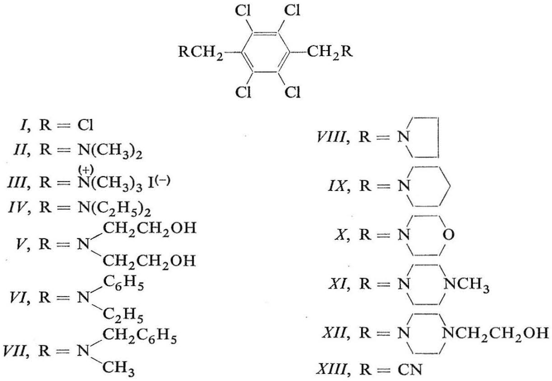
Received July 10th, 1973

---

Chloromethylation of 1,2,4,5-tetrachlorobenzene yielded 1,4-bis(chloromethyl)-2,3,5,6-tetrachlorobenzene (*I*) which underwent substitution reactions with a series of aliphatic, aromatic and heterocyclic amines giving rise to amines *II* and *IV*—*XII*. Reaction of dichloride *I* with potassium cyanide produced the nitriles *XIII* and *XIV* in a low yield. Compounds *II*—*XII* showed some neurotropic activity and some signs of antibacterial and anthelminthic activity.

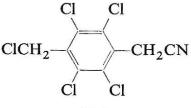
---

Chloromethylation of 1,2,4,5-tetrachlorobenzene[1] with bis(chloromethyl) ether[2] in the presence of fuming sulfuric acid gives rise to 2,3,5,6-tetrachlorobenzyl chloride according to a patent[3]. This is further chloromethylated to 1,4-bis(chloromethyl)-2,3,5,6-tetrachlorobenzene (*I*). In an attempt to repeat the first chloromethylation step we obtained directly the bis(chloromethyl) derivative *I* as the sole crystalline



---

* Part LXXII in the series Neurotropic and Psychotropic Agents; Part LXXI: This Journal *39*, 1366 (1974).



*XIV*

product which became the starting compound for preparation of a series of amines described in this communication. Heating with excess dimethylamine, diethylamine, diethanolamine, N-ethylaniline, benzylmethylamine[4], pyrrolidine, piperidine, morpholine, 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine yielded the corresponding substitution products *II* and *IV–XII*. In the case of dimethylamine the reaction was carried out in an autoclave in the presence of dimethylformamide. With other amines there was no solvent present, working either at the boiling temperature of the given amine or, if the b.p. was too high, at 160–190°C. In the experimental section the preparation of amines *II* and *XI* is described. The other compounds prepared similarly, are summarized with the usual experimental data in Table I.

Attempts at a reaction of *I* with potassium cyanide yielded no preparatively useful results. After a reaction in boiling ethanol 92% of the starting compound was recovered and only a small amount of impure dinitrile *XIII* was isolated. When working at a higher temperature in dimethylformamide, a mixture of products was formed, partly of polymeric nature, from which only chromatography permitted to isolate a small amount of a crystalline compound which appears to be the mononitrile *XIV* according to its chlorine content and IR spectrum.

Hydrochlorides of *II*, *IV* and *IX–XI*, as well as the quaternary salt *III*, were tested pharmacologically by the general screening methods at the unit of this institute at Rosice n/L under the direction of Dr J. Němec. The hydrochlorides were applied intravenously; the values of acute toxicity for mice $LD_{50}$ are shown: *II*, 125 mg/kg; *IV*, 75 mg/kg; *IX*, 50 mg/kg, *X*, 75 mg/kg; *XI*, 30 mg/kg. The quaternary salt *III* was applied *per os*; $LD_{50} = 1$ g/kg. In most *in vivo* tests the compounds were applied in a dose D equal to 20% $LD_{50}$. While the dimethylamine derivative *II* at a dose D showed signs of central stimulation for mice, compounds *IX* and *X* at doses exceeding D showed some central depressant effect. Compounds *II* and *XI* applied to normotensive rats bring about brief blood pressure drops; with *XI*, in addition, a brief peripheral vasodilating effect was observed. The quaternary salt *III*, at an oral dose of 200 mg/kg, causes a disturbance of motor coordination in the rotating-rod test in mice which is apparently caused by its central depressant activity as indicated by the slight potentiation of thiopental sleep in mice by this compound. Only 3 h after an oral application of 200 mg/kg did the compound bring about a drop of blood pressure in normotensive rats. In contrast with the hydrochlorides of tertiary amines which were found to be inactive toward a whole spectrum of typical microorganisms *in vitro*, the quaternary salt *III* inhibits growth of *Streptococcus β-haemolyticus* and *Staphylococcus pyogenes aureus* at a concentration of 50–100 μg/ml (determined by Dr A. Šimek and Dr J. Turinová at the bacteriological department of this institute). Amines *V–VIII* and *XII* were screened for coccidiostatic and anthelminthic activities at the Research Centre of Spofa for veterinary drugs at Chotouň under the direction of Dr B. Ševčík. While no coccidiostatic activity was found, the aniline derivative VI was remarkably effective against the tapeworm *Hymenolepis nana*.

TABLE I

Amines and Derived Salts *II*–*XII*

| Compound (bath temperature, °C) | M.p., °C (solvent) | Formula (m.w.) | Calculated/Found | | | |
|---|---|---|---|---|---|---|
| | | | % C | % H | % N | % Cl |
| *II* | 146–147 | $C_{12}H_{16}Cl_4N_2$ | 43·67 | 4·89 | 8·49 | 42·95 |
| [a] | (heptane) | (330·1) | 43·49 | 4·87 | 8·56 | 42·97 |
| *II*-2HCl | 272–273 | $C_{12}H_{18}Cl_6N_2$ | 35·77 | 4·50 | 6·95 | 52·78 |
| | (ethanol–ether) | (403·0) | 35·78 | 4·59 | 6·69 | 52·80 |
| *III* | 213–215 | $C_{14}H_{22}Cl_4I_2N_2$ | 27·35 | 3·61 | 4·56 | 23·08 |
| [a] | (benzene–ethanol) | (614·0) | 27·59 | 3·62 | 4·53 | 23·43 |
| *IV* | 75–76 | $C_{16}H_{24}Cl_4N_2$ | 49·75 | 6·27 | 7·26 | 36·72 |
| (90) | (hexane) | (386·2) | 49·73 | 6·19 | 7·34 | 37·51 |
| *IV*-2HCl | 219–220 | $C_{16}H_{26}Cl_6N_2$ | 41·86 | 5·71 | 6·10 | 46·33 |
| | (ethanol) | (459·1) | 41·71 | 5·71 | 5·91 | 46·66 |
| *V* | 156–157 | $C_{16}H_{24}Cl_4N_2O_4$ | 42·67 | 5·38 | 6·23 | 31·50 |
| (160) | (ethanol) | (450·2) | 42·88 | 5·53 | 5·90 | 31·59 |
| *V*-2HCl | 248–249 | $C_{16}H_{26}Cl_6N_2O_4$ | 36·72 | 5·01 | 5·36 | 40·67 |
| | (ethanol) | (523·1) | 36·93 | 5·07 | 5·37 | 40·58 |
| *VI* | 171–172[b] | $C_{24}H_{24}Cl_4N_2$ | 59·76 | 5·02 | 5·81 | 29·41 |
| (190) | (ethanol–benzene) | (482·3) | 59·67 | 5·01 | 5·86 | 29·82 |
| *VII* | 157–158[c] | $C_{24}H_{24}Cl_4N_2$ | 59·76 | 5·02 | 5·81 | 29·41 |
| (165) | (benzene–heptane) | (482·3) | 59·76 | 5·10 | 5·83 | 29·58 |
| *VII*-2HCl | 251–252 | $C_{24}H_{26}Cl_6N_2$ | 51·91 | 4·72 | 5·05 | 38·31 |
| | (aqueous ethanol) | (551·2) | 51·61 | 4·73 | 4·94 | 38·41 |
| *VIII* | 149–150 | $C_{16}H_{20}Cl_4N_2$ | 50·28 | 5·28 | 7·33 | 37·11 |
| (100) | (heptane) | (382·2) | 50·51 | 5·24 | 7·03 | 37·38 |
| *VIII*-2HCl[d] | 276–277 | $C_{16}H_{23}Cl_6N_2O_{0.5}$ | 41·41 | 5·00 | 6·04 | 45·80 |
| | (ethanol) | (464·1) | 41·36 | 5·10 | 6·09 | 45·30 |
| *IX* | 195–196 | $C_{18}H_{24}Cl_4N_2$ | 52·71 | 5·90 | 6·82 | 34·57 |
| (120) | (benzene) | (410·2) | 52·96 | 5·92 | 6·50 | 34·69 |
| *IX*-2HCl | 268–270 | $C_{18}H_{26}Cl_6N_2$ | 44·75 | 5·42 | 5·80 | 44·03 |
| | (2-propanol–ether) | (483·2) | 44·47 | 5·46 | 6·35 | 44·00 |
| *X* | 214–215 | $C_{16}H_{20}Cl_4N_2O_2$ | 46·40 | 4·87 | 6·76 | 34·24 |
| (150) | (benzene) | (414·2) | 46·69 | 4·91 | 6·47 | 34·45 |
| *X*-2HCl | 272–273 | $C_{16}H_{22}Cl_6N_2O_2$ | 39·45 | 4·55 | 5·76 | 43·67 |
| | (aqueous ethanol) | (487·1) | 39·58 | 4·74 | 5·72 | 43·45 |

TABLE I

*(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| *XI* | 189—190 | $C_{18}H_{26}Cl_4N_4$ | 49·11 | 5·95 | 12·73 | 32·21 |
| [a] | (ethanol) | (440·2) | 49·49 | 6·00 | 12·74 | 32·34 |
| *XI*-4 HCl[e] | 267—269 | $C_{18}H_{34}Cl_8N_4O_2$ | 34·75 | 5·51 | 9·01 | 45·59 |
| | (ethanol) | (622·1) | 35·28 | 5·51 | 9·18 | 45·72 |
| *XII* | 207—208 | $C_{20}H_{30}Cl_4N_4O_2$ | 48·01 | 6·05 | 11·20 | 28·34 |
| (170) | (benzene) | (500·3) | 47·84 | 6·02 | 11·06 | 28·66 |
| *XII*-4 HCl[f] | 219—220 | $C_{20}H_{36}Cl_8N_4O_3$ | 36·17 | 5·46 | 8·44 | 42·70 |
| | (aqueous ethanol) | (664·2) | 36·21 | 5·43 | 8·52 | 42·33 |

[a] See the Experimental; [b] NMR spectrum: $\delta$ 6·60—7·50 (m, 10 H, aromatic protons), 4·70 (s, 4 H, $NCH_2$—Ar—$CH_2N$), 3·17 (q, $J = 7·0$ Hz, 4 H, 2 $CH_2$ of ethyls), 0·98 (t, $J = 7·0$ Hz, 6 H, 2 $CH_3$ of ethyls); [c] NMR spectrum: $\delta$ 7·40 (s, 10 H, aromatic protons), 3·59 and 3·87 (2 s, 8 H, 4 $ArCH_2$), 2·10 (s, 6 H, 2N-$CH_3$); [d] hemihydrate; [e] dihydrate; [f] monohydrate.

## EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected. The samples were dried at c. 0·5 Torr over $P_2O_5$ at a temperature related to the melting point. The IR spectra (KBr) were recorded in the Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss-Jena) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on silica gel G (Merck).

### 1,4-Bis(chloromethyl)-2,3,5,6-tetrachlorobenzene (*I*)

Bis(chloromethyl) ether[2] (128 g) was added dropwise under stirring over a period of 20 min to a mixture of 280 ml 20% fuming sulfuric acid and 200 g 1,2,4,5-tetrachlorobenzene[1] and the mixture was stirred for 60 h at 50—60°C. After cooling, it was poured into 3 kg ice. The precipitated substance was filtered, washed with water and dried (215 g). Then it was extracted twice with hot 200 ml 1,2-dichloroethane. The insoluble fraction (140 g) was recrystallized three times from a large volume of n-heptane; 83 g homogeneous product, free of the starting compound which represented the major component of the crude product; m.p. 171°C. NMR spectrum: $\delta$ 4·91 (s, 4 H, $CH_2$—Ar—$CH_2$). For $C_8H_4Cl_6$ 312·9 calculated: 30·73% C, 1·26% H, 68·01% Cl; found: 30·77% C, 1·33% H, 67·78% Cl. Patent[3] describes the preparation of the compound by chloromethylation of 2,3,5,6-tetrachlorobenzyl chloride and reports a m.p. of 170—172°C.

### 1,4-Bis(dimethylaminomethyl)-2,3,5,6-tetrachlorobenzene (*II*)

A mixture of 12·5 g compound *I* and a solution of 9·0 g dimethylamine in 100 ml dimethylformamide was heated in a steel autoclave for 5 h in a 160°C bath and for 5 h to 120—130°C. After cooling, the precipitated compound was filtered and the filtrate evaporated *in vacuo* to dryness. The residue was combined with the filtered product, suspended in 300 ml warm water and, by adding 15 ml concentrated hydrochloric acid, a solution was formed. The solution of the hydrochloride was filtered with charcoal, the filtrate was evaporated to dryness and the crude dihydrochloride was recrystallized from aqueous ethanol; 8·20 g (52%), m.p. 272—273°C. The base was liberated from the sample by treatment with $NH_4OH$ and was recrystallized from heptane; m.p. 146—147°C.

Treatment with methyl iodide in a mixture of benzene and ethanol yielded the bis(methiodide) *III*, m.p. 213–215°C. The analytical data are shown in Table I.

### 1,4-Bis(4-methylpiperazinomethyl)-2,3,5,6-tetrachlorobenzene (*XI*)

A mixture of 8·0 g chloro derivative *I* and 25 ml 1-methylpiperazine was refluxed for 6 h in a 130°C bath. After cooling, it was diluted with 100 ml water, the precipitated base was filtered, washed with water and dried; 10·5 g (93%). Recrystallization from heptane resulted in an analytical sample melting at 189–190°C. MNR spectrum: $\delta$ 3·78 (s, 4 H, $CH_2$—Ar—$CH_2$), 2·52 and 2·40 (2 m, 16 H, $CH_2$ groups of piperazine), 2·22 (s, 6 H, 2N-$CH_3$). Neutralization of the base with aqueous hydrochloric acid, evaporation of the solution and recrystallization of the residue from ethanol yielded the tetrahydrochloride, crystallizing as dihydrate; m.p. 267–269°C. The analytical data are shown in Table I. Similarly, the other compounds shown in the table, with the exception of *II* and *III* were prepared (bath temperature given, the crude product yields were about 90%).

### 1,4-Bis(cyanomethyl)-2,3,5,6-tetrachlorobenzene (*XIII*)

A mixture of 6·3 g *I*, 3·25 g KCN and 35 ml ethanol was refluxed for 5 h. It was then diluted with water, the solid substance was filtered and, after drying, extracted with 50 ml benzene at room temperature. The insoluble residue (5·8 g, m.p. 168°C) was identified as unaltered compound *I*. Evaporation of the benzene solution yielded 0·60 g of a compound which was recrystallized from benzene and hexane to a m.p. 303–305°C. IR spectrum: 925, 1 140, 1 328 and 2 260 $cm^{-1}$ (R-CN). For $C_{10}H_4Cl_4N_2$ (294·0) calculated: 40·85% C, 1·38% H; found: 40·91% C, 1·47% H.

### 1-Chloromethyl-4-cyanomethyl-2,3,5,6-tetrachlorobenzene (*XIV*)

A solution of 6·5 g KCN in 15 ml water was added to a suspension of 12·6 g compound *I* in 100 ml dimethylformamide and the mixture was heated for 8 h in a 120–140°C bath. After cooling, it was diluted with 600 ml water, the solid was filtered, washed with water and dried in air. Extraction with benzene yielded 4·0 g fraction which was chromatographed on a column of 100 g alumina (activity II). Elution with benzene procuced in the first fractions 1·65 g not fully homogeneous compound which was repeatedly recrystallized from heptane, ethanol and a mixture of benzene and hexane; m.p. 178–180°C. According to chromatography it contains traces of a less polar admixture. IR spectrum: 666 (C-Cl), 691, 870, 920, 1 098, 1 139, 1 160, 1 309, 1 359, 1 372, 1 400, 1 419, 1 427 and 2255 $cm^{-1}$ (R-CN). For $C_9H_4Cl_5N$ (303·4) calculated: 58·42% Cl; found: 58·22% Cl.

*The spectra were recorded and interpreted by Drs B. Kakáč, J. Holubek and E. Svátek at the physico-chemical department of this institute. Analyses were carried out in the analytical laboratory of the institute by Mr M. Čech, Mrs J. Komancová, Mr K. Havel, Mrs V. Šmídová and Miss J. Hrdá. Mr L. Tůma cooperated in the preparative section.*

## REFERENCES

1. Mills L. E. (Dow Chemical Co.): US 1,934.675 (2. III. 1931); Chem. Zentr. *1934*, I, 1390.
2. Buc S. R.: Org. Syn., Coll. Vol. *4*, 101 (1963).
3. Boehringer C. H., Sohn: Fr. 1,447.375 (German Appl. 18. VI. 1964); Chem. Abstr. *66*, 94794 (1967).
4. Cromwell N. H., Babson R. D., Harris Ch. E.: J. Am. Chem. Soc. *65*, 312 (1943).

Translated by A. Kotyk.