

**PHYSICAL CHARACTERISATION OF THE NEW BIS
(N-PHENYLPIPERAZINES)†**

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ABSTRACT

1, 3-dichloromethylbenzene; 1, 4-dichloromethyl-2, 5-dimethylbenzene; 1, 3-dichloromethyl-4, 6-dimethylbenzene and 1, 4-dichloromethyl-2, 3, 5, 6-tetramethylbenzene were condensed with a saturated heterocyclic amine, N-phenylpiperazine in absolute alcohol. Following compounds were prepared:

- α, α' -Bis (N-phenylpiperazino)-p-xylene;
- α, α' -Bis (N-phenylpiperazino)-2, 5-dimethyl-p-xylene;
- α, α' -Bis (N-phenylpiperazino)-4, 6-dimethyl-m-xylene;
- α, α' -Bis (N-phenylpiperazino)-2, 3, 5, 6-tetramethyl-p-xylene.

An attempt has been made to assign the structure of these compounds through physico-chemical studies.

Introduction

The piperazine ring is found in the molecular structure of numerous synthetic compounds which are physiologically active e.g. butaperazine maleate, Hydroxyzine, Hexocycliam methyl sulphate (Tral, Abbot), Pipobroman. Therefore we were interested in synthesizing new heterocyclic diamines having phenylpiperazine nucleus, by condensing dichloromethylated compounds with N-phenylpiperazine (Baloch and Iovu 1981 in press). This was done also to compare the physiological properties of the compounds already synthesised (Baloch, Iovu, Dobrescu & Cristea 1980 and 1982).

Not only the physiological, but also this helped us to compare physical properties of these compounds with compounds already synthesised in terms of melting temperatures and U.V., I.R. spectra.

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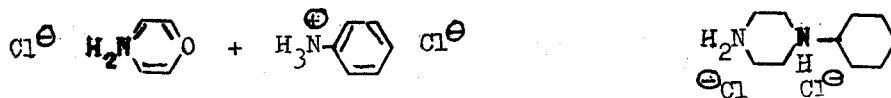
Experimental

One mole of bis-chloromethylated compound is condensed with two moles of heterocyclic amine, in absolute ethanol. The product is cooled, filtered and purified by recrystallization and is dried.

Free diamines were prepared by neutralising the hydrochlorides of the diamines with aqueous NaOH in isobutyl alcohol. Preparation of the intermediates, crystallisation of the hydrochlorides and their liberation to the free heterocyclic diamines is discussed in detail in our previous communication (Baloch & Iovu 1981 in press).

Reagents used:

Preparation of N-phenyl piperazine. M.F. $C_{10}H_{14}N_2$; M.W. 162 Amongst the known synthetic methods of the preparation of N-phenylpiperazine in the literature, we selected the one described by Popescu (1967), which consists of the condensation of morpholine with aniline:



A round bottomed flask (750 ml) fitted with an ascending condenser was taken. An attempt was made to connect the upper end of the condenser with vacuum pump. In the flask were added 87 g (1.1 mole) of morpholine, 102.4 g (1.1 mole) aniline and 230 g (1.1 mole) conc. HCl (35%). Reaction mixture was heated under vacuum, until the complete removal of water. After that the reaction mixture was heated for 8 hours on an oil bath at 235-240°C. After cooling, the reaction mixture was stirred mechanically and 50% aqueous NaOH was added in small portions, till an oily layer separated, which was extracted with benzene. This benzene solution was dried with sodium sulphite, solvent separated by distillation. Residue was again distilled under lower pressure. Fraction distilling at 135-137°C/4mm was collected. Yield 102 g. Percent yield 63%. $n_D^{20} = 1.59053$; $n_D^{20} = 1.59053$ (Heilbron 1965).

Apparatus and method used:

Elemental analysis of carbon, hydrogen and nitrogen was carried out by classical semi-micro method.

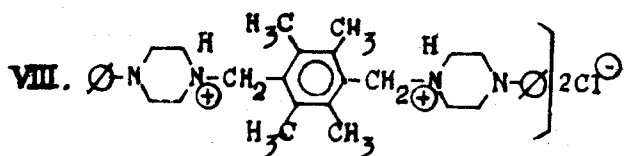
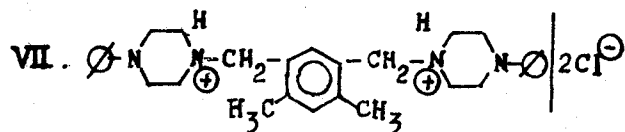
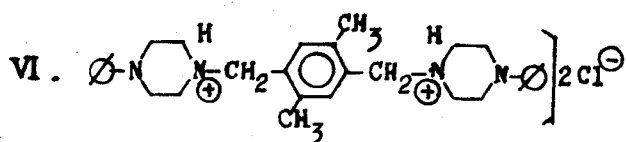
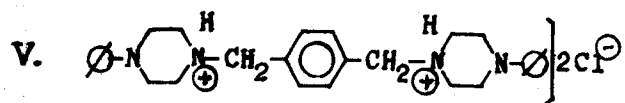
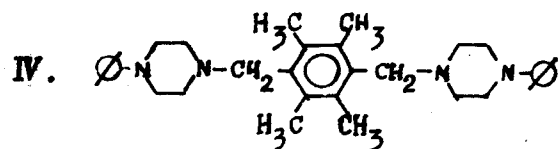
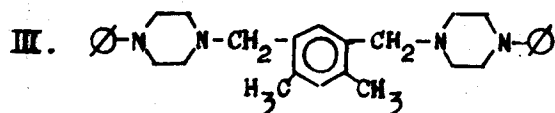
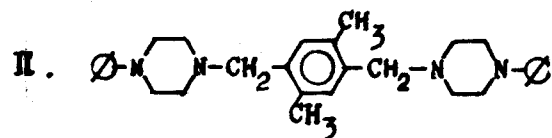
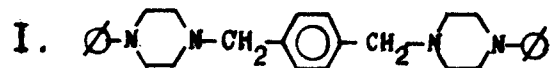
UV spectra were recorded on UV-VIS carl-Zeis-jenna. IR by the spectrograph IR-71 and 75-IR carl-zeis-jenna. Unless and otherwise stated, UV spectra of free diamines were recorded in absolute ethanol; of hydrochlorides in distilled water; I.R. spectra of both (free diamines and their hydrochlorides) were recorded in KBr discs. For free diamines $\sqrt{C-N}$ and for hydrochlorides $\overset{\oplus}{N}-H$.

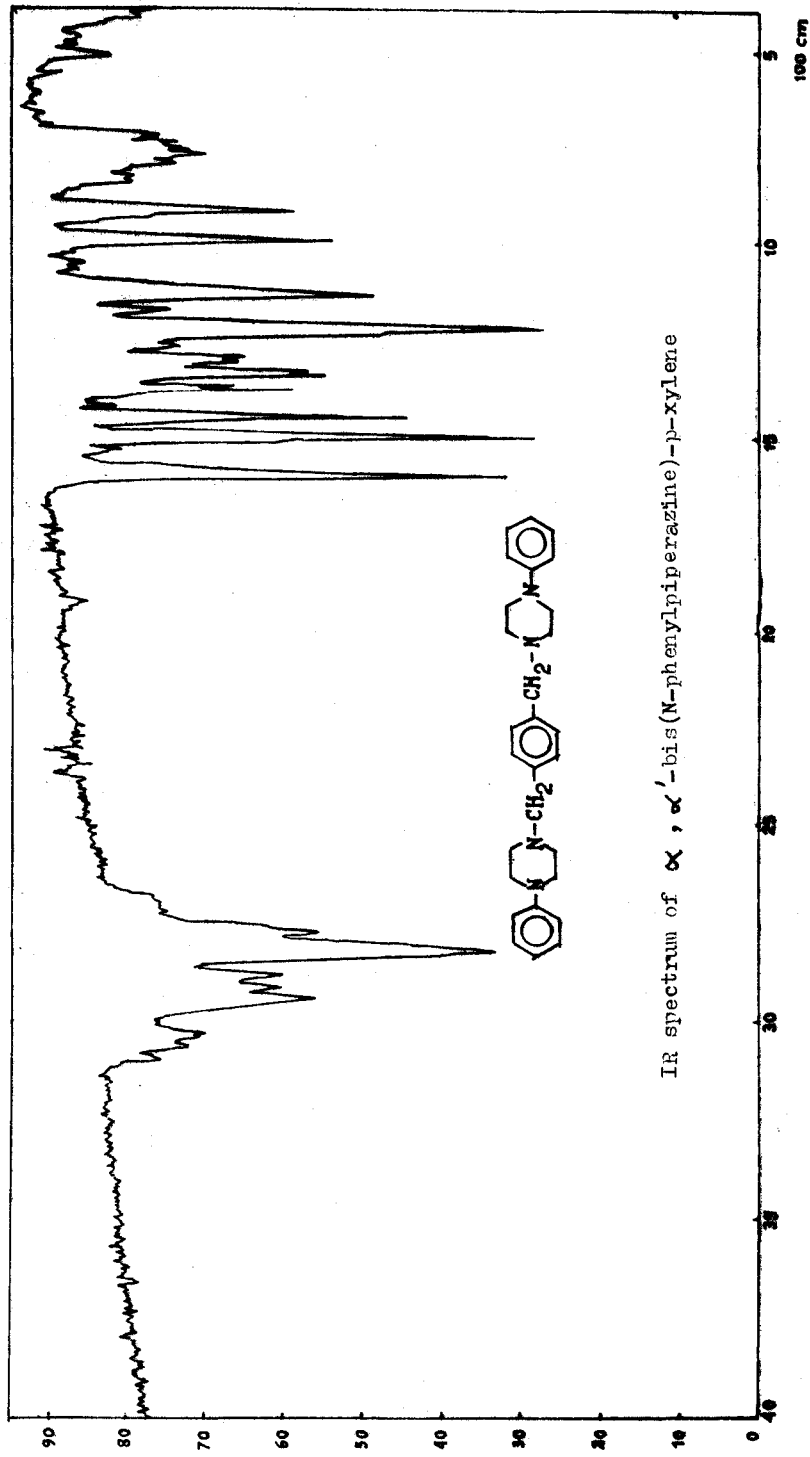
Results

- (I) α, α' -Bis (N-phenylpiperazine)-p-xylene. Colourless solid, m.p. 165-167°C (Found: C, 79.30; H, 8.40; N, 13.19. $C_{28}H_{34}N_4$, requires C, 78.83; H, 8.03; N, 13.13%). λ_{\max} 209.6, 250, 288.2 nm; ν_{\max} 1458, 1340, 1260, 1232, 1150, 1138, 1008 Cm^{-1} .
- (II) α, α' -Bis (N-phenylpiperazino)-2, 5-dimethyl-p-xylene. Colourless, solid, m.p. 196-198°C. (Found: C, 79.47; H, 8.68; N, 11.85. $C_{30}H_{38}N_4$, requires H, 79.25; H, 8.43; N, 12.32%). λ_{\max} 212.8, 250.5, 277.8, 287.4 nm. ν_{\max} 1460, 1350, 1253, 1238, 1149, 1133, 1013 Cm^{-1} .
- (III) α, α' -Bis (N-phenylpiperazino)-4, 6-dimethyl-m-xylene. Colourless, solid, m.p. 170°C. (Found: C, 79.75; H, 8.07; N, 12.80. $C_{30}H_{38}N_4$, requires C, 79.25; H, 8.43; N, 12.32%). λ_{\max} 212, 250, 285 nm. ν_{\max} 1460, 1352, 1340, 1250, 1233, 1155, 1140, 1008 Cm^{-1} .
- (IV) α, α' -Bis (N-phenylpiperazino)-2, 3, 5, 6-tetramethyl-p-xylene. Yellowish solid, m.p. 209-214°C. (Found: C, 80.02; H, 8.87; N, 11.96. $C_{32}H_{42}N_4$. Requires, C, 79.62; H, 8.77; N, 11.61%). λ_{\max} 208, 227 (sh), 252, 285 nm. ν_{\max} 1458, 1350, 1240, 1225, 1150, 1130, 1008 Cm^{-1} .
- (V) α, α' -Bis (N-phenylpiperazino)-p-xylene hydrochloride. Colourless, solid, m.p. 186°C, yield 57.58%. (Found: C, 66.85; H, 7.35; N, 10.77. $C_{28}H_{36}N_4Cl_2$. Requires, C, 67.32; H, 7.26; N, 11.21%). λ_{\max} 219, 223, 228, 271.7 nm. ν_{\max} 2790, 2300 Cm^{-1} .
- (VI) α, α' -Bis (N-phenylpiperazino)-2, 3-dimethyl-p-xylene hydrochloride. Colourless, solid, m.p. 208-212°C yield 55.79. (Found: C, 68.81; H, 8.03; N, 10.21. $C_{30}H_{40}N_4Cl_2$. Requires, C, 68.30; H, 7.64; N, 10.61%). λ_{\max} 237, 277 nm. ν_{\max} 2800, 2300 Cm^{-1} .
- (VII) α, α' -Bis (N-phenylpiperazino)-4, 6-dimethyl-m-xylene hydrochloride. Colourless, solid, m.p. 143-165°C, yield, 47.09%. (Found, C, 67.85; H, 7.63; N, 11.10. $C_{30}H_{40}N_4Cl_2$. Requires C, 68.30; H, 7.64; N, 10.61%). λ_{\max} 236, 277 nm. ν_{\max} 2780, 2380 Cm^{-1} .
- (VIII) α, α' -Bis (N-phenylpiperazino)-2, 3, 5, 6-tetramethyl-p-xylene hydrochloride. Colourless, solid, m.p. 231-234°C, yield, 50.84%. (Found; C, 69.17; H, 7.98; N, 10.09. $C_{32}H_{44}N_4Cl_2$. Requires; C, 69.02; H, 8.48; N, 10.19%). λ_{\max} 238.1, 277.8 nm. ν_{\max} 2800, 2300 Cm^{-1} .

Discussion

Increase in the molecular weight of the diamines and the polarity of the molecules results, in higher melting points, compounds I, II, III and IV, as compared to the diamines





IR spectrum of α, α' -bis(N-phenylpiperazine)-p-xylene

having other heterocyclic groups, e.g. pyrrolidine (Baloch & Iovu 1981 in press), morpholine (Baloch & Iovu 1982), dimethylmorpholine (Baloch & Iovu 1983 in press) and piperidine (Baloch & Iovu 1981).

The melting points of the hydrochlorides of the diamines containing heterocyclic rings N-phenylpiperazine are much higher (compounds V, VI, VII and VIII), than the compounds having pyrrolidine (Baloch & Iovu 1981 in press), morpholine (Baloch & Iovu 1982) and dimethylmorpholine rings (Baloch & Iovu 1983 in press).

Attempts to obtain tetrahydrochlorides of the corresponding α , α' -bis (N-phenylpiperazino) xylenes did not succeed. This is probably because of the basicity of the corresponding nitrogen of the piperazine, attached to the phenyl group, is lower, due to the $n \rightarrow \pi$ conjugation. However tetrachloride of compound No. I (or compound No. V) was formed.

The UV spectra are characterised by the presence of the benzenoid bands situated approximately at 250 nm (compounds No. I, II, III and IV), corresponding to the phenyl rings (peripheral); bands which are absent in the other compounds having pyrrolidine, piperidine, morpholine and dimethyl-morpholine nuclei.

In the corresponding hydrochlorides, the benzenoid band is shifted towards the lower wave lengths values, approximately at 237 nm.

Many IR spectra are found in the region $1500 - 1000 \text{ Cm}^{-1}$, compared to the compounds containing the morpholine nucleus (Baloch & Iovu 1982), where it is at $1010 - 1458 \text{ Cm}^{-1}$.

Frequency values between $1300 - 1200 \text{ Cm}^{-1}$ and $1200 - 1100 \text{ Cm}^{-1}$, in fact correspond to the two broken flat bands. Formation of the tetrahydrochloride was indicated (after passing dry HCl in the dihydrochloride of the bis (N-phenylpiperazino)-p-xylene by comparing the IR spectrs (using the KBr tablets) of the dihydrochlorides and tetrahydrochlorides. Here in case of tetrahydrochloride, the intensity of the absorption is much more, in the region $2800 - 2300 \text{ Cm}^{-1}$. Tetrahydrochloride of only one diamine (compound No. I) could be prepared, therefore the values of that is given.

IR spectrum of α , α' -bis (N-Phenylpiperazino)-p-xylene is given here as an illustration.

References

- Baloch, A.W., (1981). Pak. J. Sc. Research (in press).
Baloch, A.W., Dobrescu, D., Cristea, E., and Iovu, M. (1980). Kexue Tongbao, China.
Baloch, A.W., Dobrescu, D., Cristea, E., and Iovu, M. (1982). *ibid*.
Baloch, A.W., Iovu, M. (1981). Sind Univ. Res. Jour. (Sci. Ser.) XIII: 21-28.
Baloch, A.W., Iovu, M. (1982). *ibid* XIV: 19-24.
Baloch, A.W., Iovu, M. (1982). *ibid* (In press).
Heilbron, J. (1965). Eyreand Spottiswoode publ. Ltd. London.
Popescu, M. (1967). Farmacia (Roamnia) 15, 4, 229.