Studies in Potential Filaricides: Part III—Synthesis of Homopiperazine Analogues of Antifilarial Piperazines

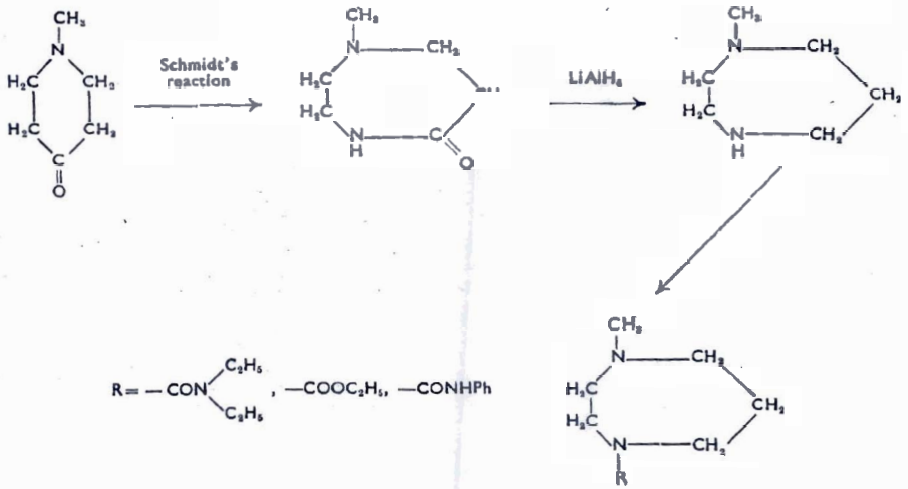
P. S. WADIA & NITYA ANAND
Central Drug Research Institute, Lucknow

(*Manuscript received* 30 *September* 1957)

1-Methyl-4-diethylcarbamyl phenylcarbamido and carbethoxyhomopiperazines have been synthesized starting from 1-methylhomopiperazine.

IN continuation of the synthesis of cyclic analogues of the antifilarial piperazine hetrazan, the synthesis of homopiperazine analogues is reported in this paper. These compounds were prepared from 1-methylhomopiperazine, which was obtained by the lithium aluminium hydride reduction of 1-methyl-5-homopiperazinone[1]. 1-Methyl-5-homopiperazine was synthesized earlier by Dickerman and Lindwall[2] from 1-methyl-4-piperidone by Schmidt reaction. During the present investigation no piperazinone could be obtained under the experimental conditions employed by these workers. They extracted the final product from the aqueous solution with chloroform. Our results were contrary in that the piperazinone had a tendency to stay preferentially in the aqueous phase and very little of it passed into chloroform. The aqueous solution was, therefore, evaporated to dryness and the piperazinone obtained by extracting the residue with chloroform in a yield of about 50 per cent. (Dickerman and Lindwall[2] reported a yield of 53 per cent.) As this was the starting material for the present investigation, a thorough study of this step was made, and by suitable modification of the conditions it has been possible to increase the yield to 90 per cent.

Treatment of 1-methylhomopiperazine with ethyl chloroformate, diethylcarbamyl chloride and phenyl-*iso*cyanate gave the respective homopiperazine analogues, 1-methyl-4-(carbethoxy, diethylcarbamyl and phenylcarbamido)-homopiperazines of the corresponding antifilarial piperazines. Since hetrazan has been found useful for the treatment of tropical eosinophilia, the homopiperazines reported in this paper would be of obvious interest in this condition.



Experimental procedure

1-Methyl-4-piperidone — The crude hydrochloride of 1-methyl-4-piperidone was prepared in 60 per cent yield from *bis*-(β-carbethoxyethyl)-methylamine[3] according to the procedure employed by Fuson *et al.*[4] for the preparation of 1-ethyl-4-piperidone hydrochloride. The hydrochloride was treated with 60 per cent potassium carbonate solution and the liberated base extracted with chloroform. The chloroform solution was dried over anhydrous potassium carbonate, the solvent removed and the residue distilled to give a colourless oily liquid which changed to pale yellow on standing, b.p. 69°/10 mm., yield 37 per cent on the basis of the quantity of *bis*-(β-carbethoxyethyl)-methylamine. (Prill and McElvain[5] reported b.p. 56°-58°/8 mm. and Howton[6], 43°-44°/6 mm.)

1-Methyl-5-homopiperazinone — 1-Methyl-4-piperidone (2·2 g.; 0·019 mole) was added dropwise, with vigorous stirring, to concentrated sulphuric acid (10 ml.) at 0°C. After the addition was complete, sodium azide (1·8 g.; 0·027 mole) was added in small portions during 1 hr., with continuous stirring at 0°C. Stirring was continued for another hour, and the mixture poured over crushed ice (about 50 g.). The aqueous solution was made alkaline with potassium carbonate and the water removed by distillation under reduced pressure. The solid residue was extracted with chloroform, the chloroform solution dried and the solvent removed to give a reddish yellow liquid which solidified readily on cooling. This was dried in a vacuum desiccator and crystallized from benzene-petroleum ether mixture; m.p. 83°-84°, b.p. 140°/2 mm., yield 2·2 g. (88 per cent).

1-Methylhomopiperazine was prepared by the method of Sommers *et al.*[1], except that the extraction of the lithium salt residue with ether helped to raise the yield to 55-58 per cent (Sommers *et al.*[1] reported a yield of 47-50 per cent); b.p. 76°/40 mm.

1-Methyl-4-diethylcarbamylhomopiperazine was prepared by the treatment of 1-methylhomopiperazine (3·3 g.) with diethylcarbamyl chloride (5·87 g.) and 10 per cent caustic soda solution (50 ml.), and was obtained as a colourless viscous liquid, b.p. 128°/4 mm., $n_D^{34°} = 1·4789$, yield 5·8 g., 76 per cent. (Found: C, 61·7; H, 10·8; N, 19·9. $C_{11}H_{23}N_3O$ requires C, 62·0; H, 10·8; N, 19·7 per cent.)

1-Methyl-4-carbethoxyhomopiperazine was prepared from 1-methylhomopiperazine (3·0 g.) and ethyl chloroformate (5·7 g.) in absolute alcohol (100 ml.) in the presence of anhydrous sodium carbonate (8·4 g.) according to the conditions described in an earlier communication[7], b.p. 107°/4 mm., $n_D^{32°} = 1·4615$, yield 4·0 g., 81 per cent. (Found: C, 58·6; H, 9·7; N, 15·4. $C_9H_{18}N_2O_2$ requires C, 58·1; H, 9·6; N, 15·1 per cent.)

1-Methyl-4-phenylcarbamidohomopiperazine was prepared by heating equimolar quantities of 1-methylhomopiperazine and phenyl-*iso*cyanate in benzene on the steam bath for 1 hr. The product was purified by sublimation at 140°-45° at 1 mm., m.p. 101°, yield 90 per cent. (Found: N, 17·5. $C_{13}H_{19}N_3O$ requires N, 18·0 per cent.)

Acknowledgement

Our thanks are due to Dr. B. Mukerji and Dr. M. L. Dhar for their interest in this work, to the National Institute of Sciences of India for the grant of a fellowship to one of us (P.S.W.) and to Shri J. Saran for microanalysis.

References

1. Sommers, A. H. *et al.*, *J. Amer. chem. Soc.*, **76** (1954), 5805.
2. Dickerman, S. C. & Lindwall, H. G., *J. org. Chem.*, **14** (1949), 530.
3. Mozingo, R. & McCkracken, J. H., *Organic Synthesis*, **20** (1940), 35.
4. Fuson, R. C. *et al.*, *J. Amer. chem. Soc.*, **68** (1946), 1239.
5. Prill, E. A. & McElvain, S. M., *J. Amer. chem. Soc.*, **55** (1933), 1233.
6. Howton, D. R., *J. org. Chem.*, **10** (1945), 279.
7. Wadia, P. S. *et al.*, *J. sci. industr. Res.*, **17B** (1958), 11, 24.