Search for Potential Filaricides. III

Synthesis of l-alkyl 4-dialkyl Aminoacetylpiperazines

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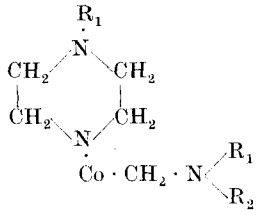
Abstract

A number of new 1:4 disubstituted piperazines (I) have been synthesised as potential filaricides.

Among the compounds tested for antifilarial activity the best balance between antifilarial activity and toxicity is found in piperazines especially in hetrazan (1 methyl-4-dimethyl carbamyl piperazine) which is considered in recent years as a drug of choice.

However, the major drawback of this drug is its rapid metabolism in the human body Hawking[1]) resulting in its rapid excretion.



Piperazines having an additional methylene group ($N \cdot Co \cdot CH_2N$) instead of ($NCO \cdot N$) have been synthesised. With the expectation that they may be more stable towards rapidly metabolising enzyme system and easily distributed throughout the body by way of their increased lipoid solubility.

Carboethoxy piperazine was prepared by the action of ethyl chloroformate on piperazine. The carboethoxy piperazine was refluxed with alkyl-p-toluene sulphonate in absolute alcohol. The resulting N-alkylated ester was hydrolysed with 20% hydrochloric acid to yield the monoalkyl piperazine HCl.

Dialkyl amino acetic acids were obtained by the condensation of dialkylamine with monochloro acetic acid. These acids were converted into chlorides HCl by refluxing them with thionyl chloride in chloroform.

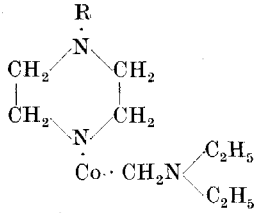
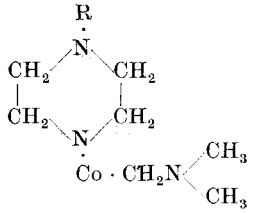
[1]) F. P. Hawkings, Pharmacol. Rev. I, **229**, 299 (1955).

Experimental

Carboethoxy piperazine: Was prepared according to the method of MOORE[2]).

Monoalkyl piperazines: Carboethoxy piperazine (1 M) and excess of appropriate alkyl p-toluene sulphonate (2.5 M) in absolute alcohol (50 cc) were refluxed for five hours. The alcohol was removed under reduced pressure and the redidue basified with NaOH (1 N) under cooling and then extracted with ether. The ether layer was dried over K_2, CO_3 (anhydrous) filtered and the solvent distilled off. The residual oil was refluxed with excess hydrochlorid acid (20%) for 48 hours and concentrated in vacuum. The resulting alkyl piperazine dihydrochloride was precipitated by the addition of absolute alcohol and filtered.

Table 1

R	B. P.	Yield %	% Nitrogen Calc.	% Nitrogen Found
				
$COOC_2H_5$	150°/5	35	15.49	15.12
C_2H_5	140°/8	40	18.50	18.20
CH_3	150°/5	50	19.74	19.22
n-C_3H_7	130°/5	60	17.42	17.12
iso-C_3H_7	160°/10	70	17.42	17.20
n-C_4H_9	152°/8	40	16.47	16.12
iso-C_4H_9	135°/5	30	16.47	16.21
C_6H_5	165°/15	70	15.27	15.00
				
$COOC_2H_5$	160°/10	55	17.25	17.10
CH_3	130°/4	50	22.70	22.42
C_2H_5	125°/5	45	21.10	21.00
n-C_3H_7	160°/15	40	19.74	19.23
iso-C_3H_7	120°/5	30	19.74	19.30
n-C_4H_9	130°/8	50	18.50	18.24
iso-C_4H_9	145°/10	45	18.50	18.12
C_6H_5	170°/10	60	17.00	16.96

[2]) J. MOORE, J. chem. Soc. London **1939**, 39.

The free base was obtained by dissolving the dihydrochloride in minimum quantity of water und neutralising with sodium hydroxide (50%) under cooling. The separated oil extracted with ether dried over K. O. H. solvent removed and the residue distilled. Thus were prepared 1-Ethyl (155—158 °C)[3], 1 Butyl[3] (186—192 °C) 1-carboethoxy[1]) (237 °C) n-propyl H · Br (223 °C). Isopropyl (194 °C) isobutyl (150 °C/1 mm). Phenyl piperazine[4]) and N-methyl piperazine[3]) were synthesised by reported methods.

Dialkylaminoacetyl chloride Hydrochloride: To monochloroacetic acid (1 M) and crushed ice (50 g.) was added Dimethylamine (2 M, 40%). The mixture was then set aside for 60 hours at room temperature. Sodium hydroxide (5 N, 2 M) was then added and the solution evaporated on a steam-bath until the smell of amine had disappeared. The residual solution was then made strongly acidic with HCl to Congo red and again evaporated to a viscous syrup. The syrup was taken up in absolute alcohol, filtered from sodium chloride, filtrate concentrated and the residue oartly crystallised on standing in a desiccator over sulphuric acid. It was purified by tituration with methanol, acetone (1:4) mixture (50 cc). The filtrate, on dilution with acetone gave a further crop of dimethylamino acetic acid (total yield 35 gr) as prisms, m. pt. 85 °C. Diethyl amino acetic m. pt. 135 °C, was obtained in the same way.

The acid (5 gm) was dissolved in chloroform (20 cc) and thionyl chloride (2 gm) was added, and the mixture was refluxed for one hour on the water bath, chloroform and excess of thionyl chloride were removed in vacuum and the residual light brown solid was kept in vacuum dessicator overnight. Diethylaminoacethyl chloride hydrochloride was also prepared by the same method and these were used without further purification.

Condensation of substituted piperazines with dialkyl amino acetyl chloride: To 1-alkyl substituted piperazine (0.13 M) in dry chloroform (50 cc), dialkylaminoacetyl chloride (0.08 M) in dry chloroform (20 cc) was added dropwise with stirring during four hours and the reaction mixture refluxed for one hour. It was then cooled, washed thrice with saturated potassium carbonate solution, dried over anhydrous magnessium sulphate and filtered. Chloroform was removed in vacuum and the reidual oil was distilled at reduced pressure. Their boiling point, yield, analysis, are given in table 1.

[3]) Stewart et al., J. Org. Chem. **1948**, 148.

[4]) Pollard, J. Amer. chem. Soc. **1934**, 2199.

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