Search for Potential Filaricides. II

Synthesis of Substituted l-alkyl Homopiperazines

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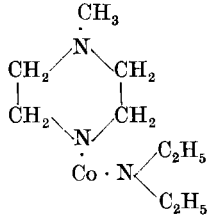
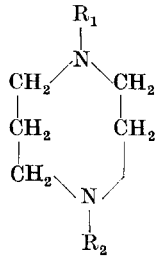
Abstract

A number of new 1:4-disubstituted-homopiperazines have been synthesised as potential filaricides.

In recent years, Hetrazan(1-methyl-4-diethylcarbamyl piperazine), has been widely used in the treatment of filariasis[1]). The pharmacological activity of this compound has been attributed to the interaction of its three nitrogen centres with appropriate bioceptors through hydrogen bonding[2]).



Hetrazan



(ii)

It was conceived worthwhile to incorporate the three nitrogen bridges into an isosteric non-planer hetero system.

In the present investigation therefore 1:4 disubstituted homopiperazines (I) with the substituents effecting varying water/lipoid solubility have been synthesised as potential filaricides.

For the synthesis of these homopiperazines at first alkyl piperidones were prepared by the condensation of ethyl acrylate with alkyl amine[3]) followed by Dieckmann condensation. The alkyl piperidones were then converted to homopiperazinones by the Schmidt reaction, which were then reduced with lithium aluminium hydride to yield the alkyl homopiperazines.

[1]) R. Hewitt et al., Amer. J. Trop. Med. **30**, 217, 237 (1950).

[2]) R. Oliver et al., Amer. J. Trop. Med. **139**, 308, 309 (1949).

[3]) R. Fuson et al., J. Amer. chem. Soc. **68**, 1239 (1946).

The alkyl homopiperazines were converted into phenylcarbamido and phenylthiocarbamido derivatives – by condensing them with phenylisocyanate and phenyl isothiocyanate respectively in order to introduce the chain N · CO · N responsible for antifilarial activity in hetrazan.

Experimental

Bis-(β-carbothoxyethyl)-alkylamines: These were obtained by reacting ethylacrylate (1 M) and appropriate alkylamine (1.4 M) in absolute alcohol[3]). Thus were prepared:

Ethyl (b. p. 110/1 M) n-propyl (b. p. 120/5 M), and Butyl (b. p. 130/5 M).

1-alkyl-4-piperidone: To a mixture of sodium sand (0.15 M) in boiling xylene (40 ml) and of absolute alcohol (0.2 ml), the appropriate bis-β-carbethoxyethyl alkylamine (0.18 M) was slowly added (44—50 mc) with stirring. The stirring was further montinued for another hour and then the mixture was cooled and poured over crushed ice. The aqueous layer was cooled and acidified with conc. HCl, saturated with potassium carbonate and extracted with ether. The residual liquid after the removal of ether was hydrolysed with HCl (20%, 53 ml) till a drop of the solution to give a red colour with 1% $FeCl_3$. The solution was then concentrated in vacuum and the resulting gummy solid recrystallised from acetone or absolute alcohol. 1-Ethyl piperidone[4]) hydrochloride (mpt. 104 °C; Yield (85%) 1-n-propyl piperidone[4]) hydrochloride (m. p. 116 °C) Yield (70%) 1-n-Butyl piperidene[4]) hydrochloride (m. p. 176 °C) yield (65%)[4]). The alkyl piperidone hydrochlorides were reacted with 60% potassium carbonate at −2 °C and the liberated base extracted with ether and dried over anhydrous K_2CO_3. On removal of the solvent under reduced pressure, the free base (crude) was obtained.

N-alkyl homopiperazinones. The crude 1-alkyl piperidone (0.018 M) was added dropwise (one hour) to cold sulphuric acid (conc., 10 cc) at 0 °C under stirring. Sodium azide (0.027 M) was then added in small portions (one hour) to this stirred solution at 0 °C and the stirring continued for another two hours and then the reaction mixture poured over crushed ice (50 gm.). The solution was saturated with K_2CO_3 and extrated repeatedly with ether. The etheral extract was dried over anhydrous K_2CO_3. The solvent removed and the redisual oil allowed to stand in cold till it solidified. It was recrystallised from benzene. The melting point, yield, analysis, etc. of these are given in table.

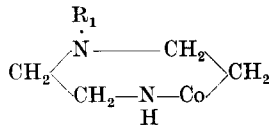
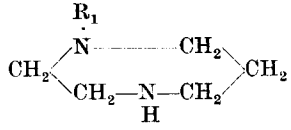
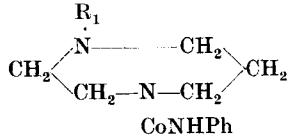
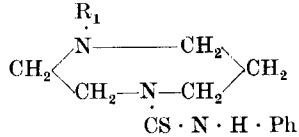
N-alkyl homopiperazines. Appropriate alkyl homopiperazinone (0.08 M) in dry ether (200 c.c.) was taken in a three necked flask fitted with a mechanical stirrer and the air displaced by nitrogen. Lithium aluminium hydride (0.2 M) suspended in dry ether (100 c.c.) was then added during two hours and the mixture stirred for further twelve hours under nitrogen atmosphere. After cooling the unreacted lithium aluminium hydride was decomposed by the cautions addition of moist ether and then water (6 c.c.). The reaction mixture was filtered and the residual Lithium salt was extracted repeatedly with ether. The combined ether extracts were dried over anhydrous K_2CO_3, filtered, ther removed and the residual oil distilled under reduced pressure. The boiling points, yield, analysis, etc. of these are reported in table 1.

1-Alkyl-4-phenylcarbamido homopiperazines: Appropriate 1-alkyl homopiperazine (0.1 M) and phenyl isocyanate (0.1 M) in dry thiophene free Benzene (50 c. c.) were refluxed for five hours. Benzene and excess of phenyl isocyanate were removed by distillation under reduced pressure. The solid residue thus obtained was recrystallised from benzene, petroleum ether (40—60) mixture.

Melting point, yield, analysis of these are reported in table No. 1.

[4]) N. W. BOLYARD et al., J. Amer. chem. Soc. **51**, 922 (1929).

Table 1

R 1	M. P. or B. P.	Yield %	Nitrogen Found	Nitrogen Calc.
				
C_2H_5	95°	50	19.42	19.71
C_3H_7	85°	55	17.52	17.94
C_4H_9	140°	40	16.12	16.47
				
C_2H_5	105°/10	40	21.34	21.86
C_3H_7	95°/5	35	19.23	19.71
C_4H_9	115°/8	38	17.55	17.95
				
C_2H_5	190°	50	16.96	17.00
C_3H_7	78°	45	15.96	16.09
C_4H_9	126°	50	15.02	15.27
				
C_2H_5	127°	55	15.54	15.96
C_3H_7	83°	50	14.93	15.16
C_4H_9	71°	45	14.13	14.43

1-Ethyl-4-phenylcarbomido homopiperazine: Ethyl homopiperazine (1 M) and phenyl isocyanate (1 M) were refluxed for three hours in dry acetone (50 c. c.). Acetone and unreacted phenyl isocyanate were removed by distillation under reduced pressure and the solid residue was crystallised from acetone petroleum ether mixture. The melting point, analysis, yield etc. of these are given in table.

1-Alkyl-4-phenyl thiocarbamido homopiperazines: Appropriate 1-Alkyl homopiperazine (1 M) and phenyl isothiocyanate (1 M) were refluxed in dry xylene for eight hours. Xylene and excess of phenyl isothiocyanate were removed by distillation under reduced pressure. The solid residue thus obtained was recrystallised from Acetone-petroleum ether mixture. The melting point, vield, analysis of these are given in table.

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