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Synthesis of Some N-[2-(2,4-Dialkoxy-5-Alkylphenyl) Ethyl]-2,4-Dialkoxy-5-Alkylbenzenepropanamine Hydrochlorides as Antiamoebic Agents

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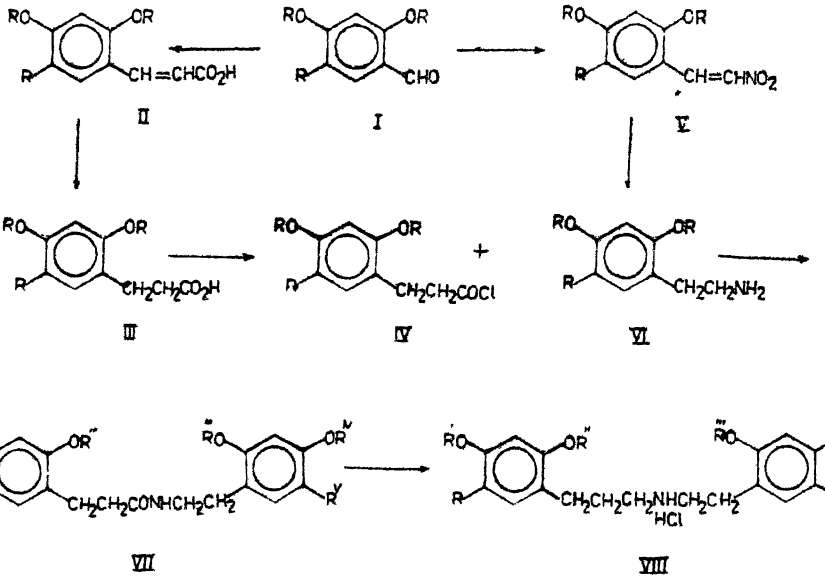
Sixteen N-[2-(2,4-dialkoxy-5-alkylphenyl) ethyl]-2,4-dialkoxy-5-alkylbenzenepropanamine hydrochlorides have been synthesised from 2,4-dialkoxy-5-alkylbenzenepropanoyl chlorides by condensation with 2,4-dialkoxy-5-alkylbenzeneethanamines followed by LAH reduction. These have been tested *in vitro* against *E. histolytica* for antiamoebic activity.

SYNTHESIS and pharmacological studies on non-nitro antiamoebic agents continue to attract attention owing to the reported carcinogenicity in test animals[1,2] and mutagenicity to bacteria[3,4] by the protracted use of metronidazole and related nitroheterocycles.



II I V

III IV VI

VII VIII

Emetine hydrochloride, the most potent amoebicide, still continues to be used as an amoebicide despite its cardiotoxicity. Many open models of emetine[5] based on hypothetical degradation products have been synthesised to arrive at structures free from the toxicity associated with emetine. Among the various substituted benzenealkanamines[6-9], benzeneethanamines and benzenepropanamines have shown appreciable *in vitro* antiamoebic activity against *E. histolytica*. As substitution at N-atom was found to enhance the activity of these amines, it was of interest to synthesise compounds possessing moieties derived from both benzeneethanamines and benzenepropanamines and study their antiamoebic activity.

N-[2-(2,4-dialkoxy-5-alkylphenyl) ethyl]-2,4-dialkoxy-5-alkylbenzenepropanamine hydrochlorides

TABLE 1—N-[2 (2,4-DIALKOXY-5-ALKYLPHENYL) ETHYL]-2,4-DIALKOXY-5-ALKYLBENZENEPROPANAMINE HYDROCHLORIDES* AND THEIR *in vitro* ANTIAMOEBIC ACTIVITY

	Compounds	m.p. °C	*In vitro* antiamoebic activity (μg/ml)		
			Compounds	Corresponding benzeneethanamine hydrochlorides	Corresponding benzenepropanamine hydrochlorides
VIIIa	R = R″ = R‴ = Rᵛ = Et, R′ = Rⁱᵛ = Me	136	15.6	250	500
VIIIb	R = R″ = Rⁱᵛ = Rᵛ = Et, R′ = R‴ = Me	141	7.8	250	500
VIIIc	R = R″ = R‴ = Rⁱᵛ = Et, Rⁱ = Me, Rᵛ = n-Pr	131	15.6	62.5	500
VIIId	R = R″ = R‴ = Rⁱᵛ = Et, R′ = Me, Rᵛ = n-Bu	119	31.25	62.5	500
VIIIe	R = R′ = R‴ = Rᵛ = Et, R″ = Rⁱᵛ = Me	142	15.6	250	62.5
VIIIf	R = R′ = Rⁱᵛ = Rᵛ = Et, R″ = R‴ = Me	131	7.8	250	62.5
VIIIg	R = R′ = R‴ = Rⁱᵛ = Et, R″ = Rᵛ = Me	148	15.6	62.5	62.5
VIIIh	R = R′ = R‴ = Rⁱᵛ = Et, R″ = Me, Rᵛ = n-Pr	134	15.6	62.5	62.5
VIIIi	R = R′ = R‴ = Rⁱᵛ = Et, R″ = Me, Rᵛ = n-Bu	121	31.25	62.5	62.5
VIIIj	R = R′ = R″ = Rⁱᵛ = Rᵛ = Et, R‴ = Me	134	15.6	250	250
VIIIk	R = R′ = R″ = R‴ = Rⁱᵛ = Et, Rᵛ = n-Bu	128	125	62.5	250
VIIIl	R = n-Pr, R′ = R″ = Rⁱᵛ = Rᵛ = Et, R‴ = Me	131	31.25	250	62.5
VIIIm	R = Rᵛ = n-Pr, R′ = R″ = R‴ = Et, Rⁱᵛ = Me	124	31.25	125	62.5
VIIIn	R = n-Pr, R′ = R″ = R‴ = Rⁱᵛ = Et, Rᵛ = Me	134	15.6	250	62.5
VIIIo	R = Rᵛ = n-Pr, R′ = R″ = R‴ = Rⁱᵛ = Et	120	31.25	62.5	62.5
VIIIp	R = n-Pr, R′ = R″ = R‴ = Rⁱᵛ = Et, Rᵛ = n-Bu	112	31.25	62.5	62.5

* All compounds gave satisfactory C, H and N analysis.

(VIII) were prepared by taking 2,4-dialkoxy-5-alkylbenzenepropanoic acids (III) [prepared from the corresponding 2,4-dialkoxy-5-alkylbenzaldehydes (I) via the cinnamic acids (II) by the standard procedure], converting them into the acid chlorides (IV) with $SOCl_2$ and condensing with 2,4-dialkoxy-5-alkylbenzeneethanamines (VI) [prepared from the corresponding 2,4-dialkoxy-5-alkylbenzaldehydes (I) via their nitrostyrenes (V)], followed by reduction of the amides (VII) with LAH and isolation of the amines as hydrochlorides. Their structures were established on the basis of elemental analysis and spectral data. Their ir spectra recorded in KBr gave the following absorption bands (νcm^{-1}) : 2840-2540 (b, N-H stretch), 1585-1575 and 1510-1500 (N-H bend). Their ^1H nmr spectra in TFA gave signals at : δ 0.96-1.5 (-CH_3 and saturated -CH_2- groups), 2.16 (m, Ar-CH_2-CH_2-CH_2-NH- and s, Ar-CH_3), 2.4-2.9 (m, 2 × Ar-CH_2- and Ar-CH_2-CH_2-CH_2-NH-), 2.9-3.5 (m, Ar-CH_2-CH_2-NH-CH_2-), 3.9 (s, -OCH_3), 4.13 (q, -OCH_2-), 6.7 (2H, s, Ar-*H*) and 7.0 (2H, s, Ar-*H*).

Antiamoebic activity :

Aqueous solutions of the amine hydrochlorides were tested *in vitro* against axenically grown *E. histolytica* by the cavity slide method[10]. The results are presented in Table 1 along with the results of similar studies on the corresponding benzeneethanamine and propanamine hydrochlorides.

It is obvious from the comparison of minimum inhibitory concentration values that the amoebicidal activity of the present secondary amine hydrochlorides is much greater than the two corresponding related primary amine hydrochlorides. The activity of these N-substituted amine hydrochlorides in certain compounds is about 32 times the activity of the corresponding benzeneethanamine hydrochlorides and about 64 times that of the corresponding propanaminehydrochlorides. However, the *in vivo* testing of VIIIb, VIIIc, VIIIf and VIIIj showed appreciable toxicity especially with regard to liver function.

Experimental

All melting points are uncorrected. ^1H NMR spectra were recorded with TMS as internal standard. Chemical shifts are recorded in δ(ppm) units.

N-[2-(2,4-dialkoxy-5-alkylphenyl ethyl]-2,4-dialkoxy-5-alkylbenzenepropanamine hydrochlorides : 2,4-Dialkoxy-5-alkylbenzenepropanoic acids (III) (0.15 mol) prepared from the corresponding 2,4-dialkoxy-5-alkylbenzaldehydes (I) by condensation with malonic acid followed by reduction of the cinnamic acids (II) with 3% Na/Hg, were dissolved in dry benzene (25 ml) and refluxed with distilled $SOCl_2$ (0.2 mol) under anhydrous conditions for 0.5 hr. Excess of $SOCl_2$ was distilled off under reduced pressure with 2-3 dilutions with dry benzene. The acid chlorides were cooled, diluted with dry benzene and treated with 2,4-dialkoxy-5-alkylbenzeneethanamines (VI) (0.1 mol) prepared from the corresponding 2,4-dialkoxy-5-alkylbenzaldehydes (I) by condensation with nitromethane followed by LAH reduction of nitrostyrenes (V), in dry benzene. The mixture was refluxed for 0.5 hr, cooled, washed first with $NaHCO_3$ solution, then with 6% HCl and dried over anhydrous $CaCl_2$. Benzene was distilled

off, the residue dried under vaccum and dissolved in dry ether (50 ml).

The ethereal solution was added to a slurry of LAH (4 mol) in dry ether, at such a rate that the ether refluxed gently. The addition was completed in 0.5 hr. The reaction mixture was refluxed for 3-4 hr and left overnight. Excess LAH was destroyed by dropwise addition of 15% NaOH solution. The ethereal layer was dried over anhydrous Na_2SO_4 and KOH. Dry HCl was passed and the solution allowed to stand when the amine hydrochlorides separated out. These were crystallized from ethylacetate as white shinning flaky solids.

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