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SYNTHESIS AND *IN VITRO* AMEBICIDAL ACTIVITY OF SOME N,N'-DISUBSTITUTED DIAMINE DIHYDROCHLORIDES AND N-SUBSTITUTED BENZENEPROPENAMIDES

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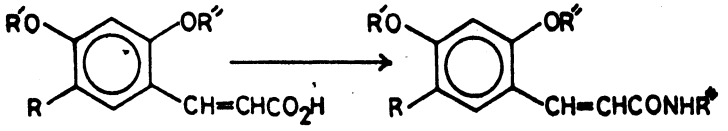
Synthesis of some N,N'-di-[3-(2,4-dialkoxy-5-alkylphenyl)propyl]-1,3-propanediamines and N-substituted 2,4-dialkoxy-5-alkylbenzenepropenamides have been described. The compounds have been tested *in vitro* for amebicidal activity against axenically grown *E. histolytica*.

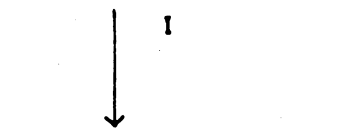
INTRODUCTION

Substituted benzenealkanamines have been reported to possess appreciable *in vitro* amebicidal activity[1–2]. The length of the alkyl side chain as well as the length of the side chain carrying the N-atom have been found to effect the activity. It has been observed[2] that the benzenealkanamines having secondary nitrogen are more active than the compounds having a primary amino group. N-Alkylation by (2,4-dialkoxy-5-alkylphenyl)propyl group seemed to enhance the amebicidal activity to a significant degree *viz*, 32 to 64 times in several cases[3]. Synthesis and *in vitro* amebicidal activity of certain diamines have been reported from our laboratory[4–5]. In continuation to our earlier work, we report the synthesis and *in vitro* amebicidal activity of certain diamines, having three carbon atom chain between two N-atoms and N-substituted-2,4-dialkoxy-5-alkylbenzenepropenamides.

2,4-Dialkoxy-5-alkylbenzenepropanoic acids(II)[6] [prepared from the corresponding 2,4-dialkoxy-5-alkylbenzaldehydes by Knoevenagel reaction followed by reduction with 3% Na-Hg] were converted into acid chlorides with $SOCl_2$ and condensed with 1,3-diaminopropane in dry benzene. The resulting diamines(III) were reduced with lithium aluminium hydride and the diamines isolated as dihydrochlorides(IV). 2,4-Dialkoxy-5-alkylcinnamic acids(I) were also converted into acid chlorides with $SOCl_2$ and condensed with various amines in dry benzene to get various benzenepropenamides(V). The structures were established on the basis of their elemental analysis and spectral data (IR and ^1H NMR).



I V



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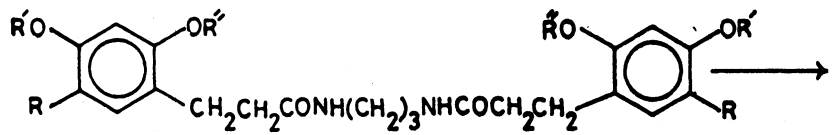
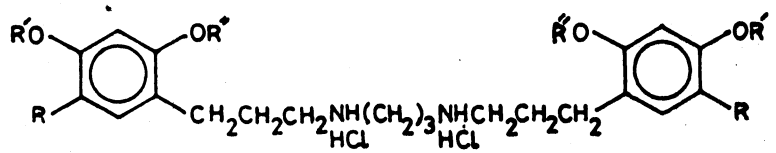


III



IV

IV_a: R = R″ = Et; R′ = Me; IV_b: R = R′ = Et; R″ = Me; IV_c: R = Pr^n; R = Et; R′ = Me;
IV_d: R = Pr^n; R′ = Et; R″ = Me.
R = R″ = Et; R′ = Me; V_a: R‴ = Bu^n; V_b: R‴ = Benzyl; V_c: R‴ = 2 Phenylethyl
R = R′ = Et; R″ = Me; V_d: R‴ = Bu^n; V_e: R‴ = Benzyl V_f: R‴ = 2 Phenylethyl
R = Pr^n; R″ = Et; R′ = Me; V_g: R‴ = Bu^n; V_h: R‴ = Benzyl; V_i: R‴ = 2-Phenylethyl
R = Pr^n; R′ = Et; R″ = Me; V_j: R‴ = Bu^n; V_k: R‴ = Benzyl; V_l: R‴ = 2-Phenylethyl

EXPERIMENTAL

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

N,N'-di-[3-(2,4-dialkoxy-5-alkylphenyl)propanoyl]-1,3- propanediamines (III)

2,4-Dialkoxy-5-alkylbenzenepropanoic acids (II, 0.2 mol) were dissolved in dry benzene (25 ml) and refluxed with distilled $SOCl_2$ (0.3 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 1,3- diaminopropane (0.1 mol). The mixtures were refluxed for 0.5 hr., cooled and washed first with $NaHCO_3$ solution and then with 6% HCl. These were dried over anhydrous $CaCl_2$, benzene was distilled off and the compounds (III) crystallized from benzene-pet. ether, m.pt.: a 135°; b 121°; c 119°; d 131°. Their IR spectra in KBr showed prominent bands at ν cm^{-1}: 3270–3260 (N–H stretch), 1640–1635 ()C=0 stretch), 1545 ()C=0 bend).

N,N'-di-[3-(2,4-dialkoxy-5-alkylphenyl)propyl]-1,3- propanediamine dihydrochlorides (IV)

Compound III (0.1 mol) in dry ether was added to a slurry of lithium aluminium hydride (8 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 2–3 hrs and left overnight. Excess of lithium aluminium hydride was destroyed by dropwise addition of 15% NaOH solution. The ethereal layer was dried over anhydrous Na_2SO_4 and KOH. Dry HCl was passesd and the solution allowed to stand when the diamine dihydrochloride separated as a white solid which was crystallized from methanol-ethyl acetate, m.pt.: a 178°; b 181°; c 170–171°; d 163°. Their IR spectra in KBr showed the bands at ν cm^{-1}: 3000–2700 (N–H stretch), 1585–1580 and 1510–1500 (N–H bend). Their ^1H NMR in TFA showed the following signals: δ 0.96–1.03 (t, $-CH_3$ groups), 1.4 (t, $-OCH_2-CH_3$ and m, $-CH_2-$ groups), 2.0–2.13 (m, Ar–CH_2–CH_2–CH_2–NH–), 2.33–2.83 (m, Ar–CH_2–CH_2– and Ar–CH_2–CH_2–CH_2–NH–), 2.83–3.60 (m, $-CH_2$–NH–CH_2–CH_2–CH_2–NH–CH_2–), 3.96 (S, $-OCH_3$), 4.16 (q, $-OCH_2-CH_3$), 6.60 (2H, S, Ar–*H*), 6.85 (2H, S, Ar–*H*).

N-substituted 2,4-dialkoxy-5-alkylbenzenepropenamides (V)

2,4-Dialkoxy-5-alkylcinnamic acids (I, 0.1 mol) were converted into acid chlorides and condensed with various amines (0.1 mol) by the procedure as for III. The resulting benzenepropenamides were crystallized from benzene-pet. ether, m.pt.: a 104°; b 93°; c 122°; d 118–119°; e 138°; f 141°; g 98°; h 94–96°; i 130°; j 110–111°; k 98°; l 120°. Their IR spectra in KBr showed prominent bands at ν cm^{-1}: 3270–3260 (N-H stretch), 1665–1650 (N-arylamide)C=O stretch), 1635–1630 (N-alkylamide)C=O stretch), 1550–1530 ()C=O bend).

AMEBICIDAL ACTIVITY

The compounds were tested *in vitro* for their minimum inhibitory concentrations (MIC) against axenically grown *E. histolytica* by the cavity slide method[7]. MIC values of diamines are in the range of 31.25 to 125 μg/ml (controlled value

of emetine hydrochloride being 15.6 μg/ml). Benzenepropenamides exhibited much less activity, MIC values being in the range 500–1000 μg/ml.

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