Synthesis and Activity of Some N-Substituted α-(2-*n*-Hexyl-4,5-dimethoxyphenyl)ethylamines against *Entamoeba histolytica*

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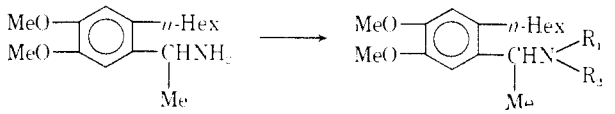
The synthesis of α-(2-*n*-hexyl-4,5-dimethoxyphenyl)-ethylamine (I), which can be regarded as a hypothetical fragment of emetine, has been reported.[1] Although the *in vitro* activity of this compound against *Entamoeba histolytica* is comparable to that of emetine, its *in vivo* activity has been found to be very weak.[2] It is quite probable that the compound undergoes some change in the system and the resultant products are inactive. In the absence of knowledge of the cause of this difference in activity it was considered worthwhile to synthesize N-dichloroacetyl (II), N-carbamoyl (III), N-ethyl (IV), and N,N-dimethyl (VI) derivatives of I for additional tests.



I

II, $R_1 = H$; $R_2 = COCHCl_2$
III, $R_1 = H$; $R_2 = CONH_2$
IV, $R_1 = H$; $R_2 = Et$
V, $R_1 = R_2 = Me$

Condensation of I with methyl dichloroacetate gave II[3] while the interaction of I with KCNO in dilute EtOH in the presence of AcOH furnished III. Acetylation of I and subsequent reduction of the acetyl derivative led to IV. I was refluxed with HCO_2H–CH_2O to provide V.[4]

Compounds II and III, and the hydrochlorides of IV and V have been evaluated for their activity. None of the compounds killed *E. histolytica* at a concentration of 1×10^{-3} *in vitro* while emetine hydrochloride is active at a dilution of 1:256,000.[5] Because of this low activity the compounds have not been tested *in vivo*.

Experimental Section[6]

N-Dichloroacetyl-α-(2-*n*-hexyl-4,5-dimethoxyphenyl)ethylamine (II).—After heating a mixture of I (1 mole) and $CHCl_2COOMe$ (1.5 moles) on a steam bath for 3 hr, excess ester was removed under reduced pressure and the product was refluxed with petroleum ether (bp 60–80°) to remove the unreacted amine.[3] A solution of the crude product in PhH–petroleum ether (1:1) was chromatographed on adsorbent Al_2O_3 which was eluted with the same solvent and the product was crystallized from PhH–petroleum ether, mp 118°. *Anal.* ($C_{18}H_{27}Cl_2NO_3$) C, H, N.

N-Carbamoyl-α-(2-*n*-hexyl-4,5-dimethoxyphenyl)ethylamine (III).—To a solution of I·HCl (1 mole) in the minimum amount of H_2O, a solution of KCNO (2.4 moles) in the minimum amount of dilute EtOH was added followed by the addition of AcOH (2.4 moles), and the mixture was left overnight in a closed flask. The product was filtered and crystallized from dilute EtOH as fine needles, mp 122°. *Anal.* ($C_{17}H_{28}N_2O_3$) C, H, N.

N-Ethyl-α-(2-*n*-hexyl-4,5-dimethoxyphenyl)ethylamine (IV).—The amine I (1 mole) was heated with Ac_2O (1.2 moles) on a water bath with 3–4 drops of pyridine for 2 hr to give the acetyl derivative which was crystallized from petroleum ether as colorless needles, mp 91–93°. The Ac derivative (1 mole) was reduced with LAH (1.2 moles) in dry Et_2O for 6 hr; the amine boiled at 152–154° (0.8 mm). It was converted into the hydrochloride and crystallized from EtOAc as fine needles, mp 110°. *Anal.* ($C_{18}H_{32}ClNO_2$) C, H, N.

N,N-Dimethyl-α-(2-*n*-hexyl-4,5-dimethoxyphenyl)ethylamine (V).—A mixture of I (1 mole), HCO_2H (90%, 6.5 moles), and CH_2O (40%, 1.4 moles) was heated on a steam bath for 24 hr,[4] cooled, acidified with concentrated HCl, and evaporated under reduced pressure. The mass was made alkaline and extracted (Et_2O). The amine boiled at 176–178° (1.5 mm) and was converted into the hydrochloride which crystallized from EtOAc as fine needles, mp 158–160°. *Anal.* ($C_{18}H_{32}ClNO_2$) C, H, N.

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A Novel Synthesis of N-Dialkylaminoalkylbenzimidazoles[1]

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Although numerous 2-dialkylaminoalkyl-substituted benzimidazoles have been mentioned to possess anesthetic and analgetic activity,[3–7] few studies have been reported on the 1- or N-substituted dialkylaminoalkylbenzimidazoles. Members of this class have been prepared and screened, largely without success, for antimalarial activity.[8–10]

We wish to report the extension of Sardesai and Sunthankar's[11] diethyl ethoxymethylenemalonate (EMME) (**1**) procedure as a facile, one-step route to 1-alkylated benzimidazoles. In the original report, EMME and *o*-phenylenediamines were allowed to react thermally and fractionated to produce mixtures of benzimidazole and benzimidazolone with the latter in vast predominance. We have prepared a series of monoalkylated *o*-phenylenediamines and treated them in this fashion and have obtained the corresponding N-alkylbenzimidazoles as the sole products. This procedure circumvents the classic formic acid–HCl

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