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

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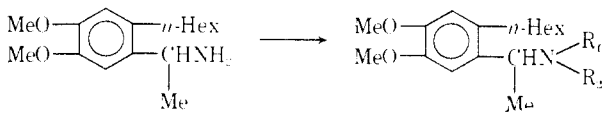
The synthesis of α-(2-*n*-hexyl-4,5-dimethoxyphenyl)-ethylamine (I), which can be regarded as a hypothetical fragment of emetine, has been reported.[1] Although the *in vitro* activity of this compound against *Entamoeba histolytica* is comparable to that of emetine, its *in vivo* activity has been found 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.* ($C_{19}H_{34}ClNO_2$) C, H, N.

Acknowledgment.—The authors' thanks are due to the Director, Central Drug Research Institute, Lucknow, for the testing of the compounds.

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(4) G. Childs and E. J. Forbes, *J. Chem. Soc.*, 2024 (1959).
(5) Screening of the compounds has been carried out by the Central Drug Research Institute, Lucknow, India.
(6) Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical values. All melting points are corrected and were determined in a Gallenkamp apparatus. Boiling points are uncorrected.

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[10] 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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(2) Undergraduate research participant.
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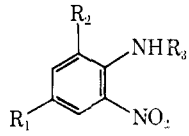
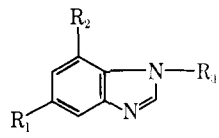
TABLE I



Compd	R_1	R_2	R_3	Yield, %	Bp (mm) or mp, °C	Formula[b]
2a	Cl	H	$(CH_2)_2NEt_2$	80	48–49	$C_{12}H_{18}ClN_3O_2$
2b	Cl	H	$(CH_2)_3NEt_2$	84	35–36	$C_{13}H_{20}ClN_3O_2$
2c	H	Cl	$CH(CH_3)(CH_2)_3NEt_2$	79	160–163 (0.2)	$C_{15}H_{24}N_3O_2$[a]
2d	CH_3	H	$(CH_2)_2NEt_2$	80	169–174 (1.2)	$C_{13}H_{21}N_3O_2$
2e	CH_3	H	$CH(CH_3)(CH_2)_3NEt_2$	75	182–185 (1.3)	$C_{17}H_{26}N_3O_2$

[a] Preparation as described by A. Raychaudhury, A. Bose, and V. Basu, *J. Indian Chem. Soc.*, **35**, 361 (1958), and properties are in agreement with those reported. [b] All compounds except **2c** were analyzed for N.

TABLE II



Compd	R_1	R_2	R_3	Yield, %	Bp (mm), °C	Formula[a]
3a	Cl	H	$(CH_2)_2NEt_2$	52	205–210 (8)	$C_{13}H_{18}ClN_3$
3b	Cl	H	$(CH_2)_3NEt_2$	64	196–199 (1.8)	$C_{14}H_{20}ClN_3$
3c	H	Cl	$CH(CH_3)(CH_2)_3NEt_2$	51	155–157 (0.18)	$C_{16}H_{24}ClN_3$
3d	CH_3	H	$(CH_2)_2NEt_2$	29	140–145 (0.20)	$C_{14}H_{21}N_3$
3e	CH_3	H	$CH(CH_3)(CH_2)_3NEt_2$	35	177–182 (0.60)	$C_{17}H_{27}N_3$

[a] All compounds were analyzed for C, H, N.

technique of Phillips,[12,13] which normally requires a neutralization and solvent extraction step to isolate the oily 1-dialkylaminoalkylbenzimidazoles.

The monoalkylated *o*-phenylenediamines were prepared by displacement of the appropriate side-chain amine onto the corresponding *o*-chloronitrobenzene (see Table I). These nitroanilines were reduced by $SnCl_2$ and used directly in the benzimidazole synthesis (see Table II). A mechanistic interpretation for the cycle-forming step would anticipate the double addition of the two adjacent NH functions and elimination of malonate. Although 1:1 noncyclic adducts have not been detected in this synthesis, other investigators have claimed their preparation from EMME and nonalkylated *o*-phenylenediamines under somewhat milder reaction conditions.[14] These workers noted that the 1:1 adducts in which they were primarily interested underwent ready ring closure to benzimidazoles. The other product in the cyclization–fragmentation, diethyl malonate, can be isolated as the lowest boiling component in the distillation and identified by nmr and ir spectral comparison with authentic material.

1-(4-Diethylamino-1-methylbutyl)-5-methylbenzimidazole (**3e**) and 1-(2-diethylaminoethyl)-5-methylbenzimidazole (**3d**) were submitted for evaluation in a standard Irwin neuropharmacological profile.[15] Compounds were administered as a single intraperitoneal injection in aqueous medium to four mice. Compound **3e** was both inactive and nontoxic at 1000-mg/kg dose. Moderate CNS depression and no toxicity was evident for **3d** at the 1000-mg/kg level and was reflected in suppression of alertness, reflex action, motor activity, and muscle tone. Between 5 and 15 min after dosing, all animals displayed significant tremors and convulsions accompanied by moderate hypothermia (average depression of body temperature = 3°) and mydriasis.

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(15) Testing was carried out by Dr. T. O. King, Bio/dynamics Inc., East Millstone, N. J.

Experimental Section[16]

N-Alkylated *o*-Nitroanilines (2).—Equimolar amounts of the dialkylaminoalkylamine and the *o*-chloronitrobenzene (either 2,3-dichloro-, 2,5-dichloro-, or 2-chloro-5-methylnitrobenzene) were heated at reflux for 3 hr. The material was poured into water, adjusted to strong basicity with aqueous NaOH and extracted thoroughly (Et_2O). The residue from the concentrated ethereal phase was either vacuum distilled or, in the case of solid products, was recrystallized from 95% EtOH. Results appear on Table I.

N-Substituted Benzimidazoles (3).—A solution of 0.1 mol of the alkylated nitroaniline in 150 ml of concentrated HCl (0.1 mole/150 ml) was added dropwise to a chilled, well-stirred solution of $SnCl_2 \cdot 2H_2O$ (0.4 mole in 175 ml of HCl). Temperature was maintained at 10° or less during the addition after which the mixture was allowed to warm to ambient temperature. After being stirred at room temperature for 2 hr, the contents of flask were diluted with 1 l. of ice–water, made strongly basic with 50% aqueous NaOH, and extracted thoroughly with Et_2O. The dried extract was evaporated *in vacuo* and the resultant oily diamine was used directly in the cycle-forming reaction. Distillation of these diamines before treatment with EMME gave no significant improvement in yields.

In general, the crude diamine and an equimolar quantity of EMME were heated on a steam cone until the theoretical amount of EtOH was evolved. The oily adduct was then added to refluxing Ph_2O and heated at that temperature for 20–30 min. Ph_2O was removed by distillation and the benzimidazole was fractionated under vacuum. The physical properties and yields (based on initial N-substituted *o*-nitroaniline) are shown in Table II.

(16) Combustion analyses were performed by Dr. George I. Robertson, Jr., Florham Park, N. J. Analyses indicated by the symbols of the elements were within ±0.4% of theoretical values.