Histamine Releasers. I. Structure of the Dimer Formed from *p*-Methoxy-N-methylphenethylamine and Formaldehyde[1]

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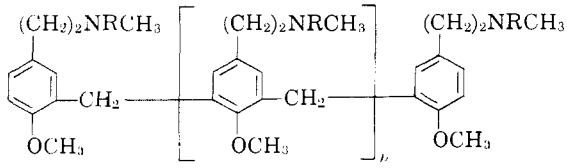
A confirmation of the structure proposed for the dimer (Ia) formed in the synthesis of a potent histamine releaser reported by Baltzly, *et al.*,[1] has been achieved. This was accomplished by converting Ia to the bis-N,N-dimethyl derivative (Ib) which was found to be identical with Ib prepared by an unequivocal synthesis. Neither Ia nor Ib showed any ability to release histamine in dogs.

A family of potent histamine releasers was first reported in 1949 by Baltzly, *et al.*,[1] and one of the compounds has since been widely used by investigators studying the mechanism of histamine release. Despite its importance, no attempts to firmly establish the structure of this ill-defined substance have been reported. The material was obtained by the condensation of 4-methoxy-N-methylphenethylamine and formaldehyde in the presence of hot 6 *N* hydrochloric acid. Several closely related compounds of proposed structures I (n = 0, 1, 2) were obtained depending on the time allowed for the reaction. A fraction rich in the trimer (Ic) appeared to be the active depressor substance. The dimer (Ia) was isolated, reasonably well characterized, and found to possess only weak depressor activity.

As a first approach to establish the structure of the trimer we sought to prepare the dimer (Ia) by an unambiguous route (II–VI). This would not only serve as a proof of structure for Ia, but also as a model system for a later synthesis of the trimer (Ic). We were unable to obtain Ia by this sequence, but were able to prepare the N,N-dimethyl compound Ib as the crystalline dipicrate. The literature[1] preparation of Ia was repeated and the crystalline hydrochloride salt so obtained was converted to the methylurethan (Id). The urethan was reduced with lithium aluminum hydride to afford the N,N-dimethyl analog also as the dipicrate. A mixture melting point comparison of the independently obtained picrates of Ib showed them to be identical.

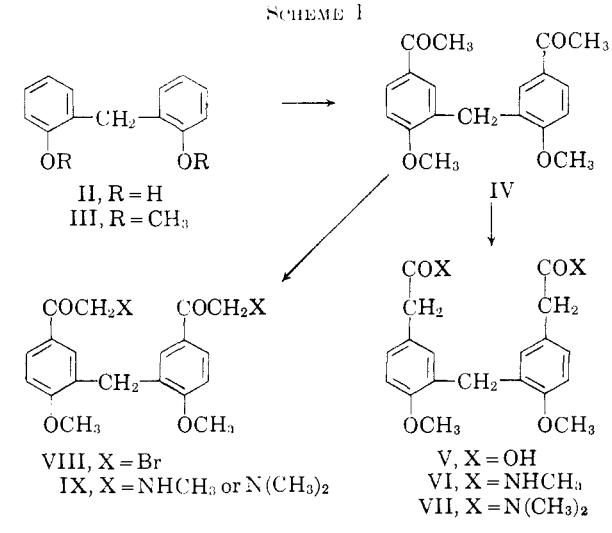


Ia, R = H; n = 0
b, R = CH_3; n = 0
c, R = H; n = 1
d, R = $COOCH_3$; n = 0

We began our synthesis in the dimer series with the commercially available compound, bis(2-hydroxyphenyl)methane (II). The diphenol was methylated with methyl iodide and potassium carbonate to afford the dimethoxy compound (III) in 73% yield. The ether (III) was found to be remarkably resistant to chloromethylation[2] (stannic chloride–chloromethyl ether or formaldehyde–hydrochloric acid). In addition, attempts to acetylate III under the usual Friedel–Crafts conditions (acetyl chloride with catalysis by stannic or aluminum chloride) or with trifluoroacetic anhydride–acetic acid[3] afforded only unchanged starting material. We are at a loss to explain this lack of reactivity of III, since aromatic systems containing methoxyl groups are normally quite reactive.

The treatment of III with trichloroacetonitrile under conditions of the Hoesch reaction[4] gave crystalline, but impure material which appeared to have undergone attack on only one of the aromatic rings. However, acetylation of III with acetic anhydride and polyphosphoric acid[5] produced the diacetyl compound (IV) in 60% yield (see Scheme I). The ultraviolet spectrum of IV in alcohol showed maxima at 230 and 275 mμ, characteristic of *p*-methoxyacetophenones; the *o*-methoxy ketone would be expected to show a single peak near 240 mμ.[6]

Scheme I



The diketone IV was treated with sulfur and morpholine under the conditions of Kindler–Peschke[7] modifi-

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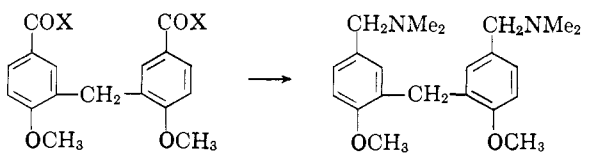
cation of the Wilgerodt reaction to yield the bisacetic acid compound (V) after hydrolysis of the intermediate thiomorpholineamide. The acid V was converted to its N-methyl- (VI) and N,N-dimethylamides (VII) in the usual manner and these were in turn reduced with lithium aluminum hydride. A crystalline salt of the syrupy dimer Ia could not be obtained; however, the dimethylamino analog Ib was isolated as its dipicrate. The purity of Ia and Ib from the hydride reductions was probably affected by side reactions involving the α-methylene group in the amides VI and VII.

An alternate route was to have proceeded through reduction of a dialkylamino ketone (IX). It was discarded in favor of the above procedure even though the bis(bromo ketone) VIII was readily formed by bromination of IV with phenyltrimethylammonium tribromide.[8]

When the diketone IV was oxidized with warm aqueous methanolic hypochlorite solution the dicarboxylic acid X was obtained. Its dimethylamide XI was prepared and reduced with lithium aluminum hydride to yield the benzyldimethylamine XII. The bismethiodide salt of XII was also prepared and, together with Ia, Ib, and XII, was evaluated for depressor and/or histamine-releasing activity.



X, X = OH
XI, X = NMe2
XII

Biological Results.—The four compounds (Ia, Ib, XII, and the bismethiodide of XII) were tested for their ability to promote release of histamine in dogs. The animals were anesthetized and their blood pressures, heart rates, and respiratory rates were continuously measured. Blood samples (2–3 ml) were obtained prior to and at 2- and 30-min intervals following the intravenous administration of 100-, 250-, and 500-μg/kg doses of the experimental compounds. Histamine levels were evaluated from these using the method described by Shore, *et al.*[9]

Aqueous solutions of the hydrochloride salts were used for Ia, Ib, and XII, while the methiodide of XII was injected as an aqueous suspension. The syrupy hydrochloride of Ib was prepared by stirring the bispicrate in 90% methanol with excess Dowex 2 (chloride) resin.

None of the four compounds showed any significant effect on the animals' blood pressures or histamine levels. Baltzly, *et al.*,[1] reported weak activity for Ia and Ib.

Experimental Section

Bis(2-methoxyphenyl)methane (III).—To 10.0 g (50 mmoles) of bis(2-hydroxyphenyl)methane (Aldrich Chemical Co.) in 93 ml of acetone was added 27.6 g (0.2 mole) of pulverized K_2CO_3 and 50 ml (0.8 mole) of methyl iodide. The mixture was refluxed for 70 hr. The supernatant was decanted, and the white, solid material was washed three times with acetone. The acetone was evaporated *in vacuo* to yield an orange syrup which was taken up in ethyl ether and washed with water. The ethereal solution was separated, dried ($MgSO_4$), and evaporated *in vacuo* to yield 10.1 g of syrup which crystallized upon standing. The material was recrystallized from petroleum ether (bp 30–60°); yield 8.27 g (73%), mp 53–55°.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.06. Found: C, 78.9; H, 6.97.

Bis(2-methoxy-5-acetylphenyl)methane (IV).—To 4.4 g (19.3 mmoles) of bis(2-anisyl)methane in approximately 90 ml of polyphosphoric acid was added 9.24 ml (96.4 mmoles) of acetic anhydride. The mixture was stirred at 60° for 3 hr, chilled, and diluted with approximately 50 ml of water. The acid mixture was alkalized in the cold with concentrated NH_4OH (pH 8); the tan solid was collected by filtration and thoroughly washed with cyclohexane; yield 3.6 g (60%), mp 115–117°. An analytical sample melted at 111–113°; λ_{max}^{EtOH} 230 mμ (ϵ 26,950), 275 (28,600).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.45. Found: C, 72.8; H, 6.61.

Bis(2-methoxy-5-carboxymethylphenyl)methane (V).—A mixture of 4.0 g of IV, 1.2 g of sulfur, and 4 ml of morpholine was stirred at 125–130° for 15 hr. The mixture was evaporated to dryness *in vacuo*, and the residue was refluxed with 80 ml of acetic acid and 40 ml of concentrated HCl for 15 hr. Sodium hydroxide (10%) was added until a pH of about 10 was reached. A small amount of insoluble material was removed by filtration and the filtrate was acidified to pH 2. The resulting precipitate was removed and the aqueous portion was extracted with four 25-ml portions of ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to leave a yellow solid. Trituration with ethyl ether afforded 0.91 g of white crystals, mp 177–181°. Recrystallization from toluene of material from another run gave an analytical sample, mp 183–185°.

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.3; H, 5.85. Found: C, 65.7; H, 5.95.

N-Methylamide of Bis(2-methoxy-5-carboxymethylphenyl)methane (VI).—A mixture of 0.76 g of V and 10 ml of α,α-dichloromethyl methyl ether[10] was refluxed 15 min and evaporated *in vacuo*. Benzene (20 ml) was added and also evaporated to dryness. The residual acid chloride was taken up in 25 ml of CH_2Cl_2, chilled to 0–5°, and treated with a slow stream of gaseous methylamine for 15 min. The flask was stoppered and allowed to stand 15 hr. The solvent was removed *in vacuo*, and the residue was stirred with 20 ml of water. The solid was collected and dried to leave 0.75 g. A recrystallization from ethanol yielded 0.33 g of VI, mp 186–189.5°.

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.07; N, 7.56. Found: C, 67.9; H, 7.20; N, 7.49.

N,N-Dimethylamide of Bis(2-methoxy-5-carboxymethylphenyl)methane (VII).—To a solution of the acid chloride, prepared from 0.797 g (2.1 mmoles) of V and $SOCl_2$, in 10 ml of anhydrous CH_2Cl_2 was added 5 ml of anhydrous dimethylamine. The mixture, after standing at room temperature for 20 hr, was washed with water, and the methylene chloride layer was separated and dried ($MgSO_4$). Evaporation *in vacuo* yielded 0.895 g of yellow-brown gum. The gum was chromatographed on 30 g of silica gel in benzene. Elution with acetone and evaporation *in vacuo* gave 0.42 g (50%) of a pale yellow gum. An infrared spectrum of the sample showed amide C=O at 6.0 μ. This material was suitable for use in the next step.

Bis[2-methoxy-5-(β-dimethylaminoethyl)phenyl]methane Dipicrate (Ib).—A mixture of 756 mg of the dimethylamide VII, 434 mg of $LiAlH_4$, and 25 ml of tetrahydrofuran (THF) was stirred at reflux for 13 hr. The excess hydride was decomposed with ethanol and water, and the solvent was removed *in vacuo*. The residue was partitioned between water and 1-butanol. The butanol was dried ($MgSO_4$) and evaporated *in vacuo* to leave 620 mg of yellow syrup. Attempts to prepare the hydrochloride salt gave only hygroscopic gums; however, the dipicrate (1.00 g) was prepared by treatment with 844 mg of picric acid in hot aqueous alcohol. A recrystallization from aqueous 2-methoxyethanol yielded 0.62 g of Ib, mp 85–90°.

Anal. Calcd for $C_{35}H_{40}N_8O_{16}\cdot H_2O$: C, 49.6; H, 4.90; N, 13.2. Found: C, 49.3; H, 4.90; N, 13.8.

A portion (50 mg) was recrystallized twice from 80% 2-methoxyethanol to afford 6 mg, mp 199–202°. Admixture with Ib dipicrate (mp 198–201°) prepared independently from Ia

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(10) H. Gross and A. Rieche, *Ber.*, **94**, 544 (1961).

(see below) showed no melting point depression (mp 198–202°). The infrared spectra as Nujol mulls were also very similar to one another. On occasion, another crystal form of the picrate, mp 167–170°, was obtained by recrystallization from 80% 2-methoxyethanol.

Anal. Calcd for $C_{35}H_{40}N_8O_{15}$: C, 50.7; H, 4.83; N, 13.5. Found: C, 50.5; H, 4.85; N, 13.8.

Methylurethan of the Dimer Id and Reduction to Ib.—To an ice-cold, stirred mixture of 300 mg of Ia dihydrochloride (prepared as described by Baltzly, *et al.*[1]), 10 ml of 1 *N* NaOH, and 10 ml of chloroform was slowly added 0.25 ml of methyl chloroformate. Stirring was continued for 1 hr at room temperature. The mixture was acidified with concentrated HCl and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with another 10 ml of chloroform. The chloroform was dried ($MgSO_4$) and evaporated *in vacuo* to leave 333 mg (100%) of a syrup whose infrared spectrum was in agreement with Id: λ_{max}^{film} 5.90 μ (C=O of urethan).

The urethan (320 mg) was reduced with 0.60 g of $LiAlH_4$ in THF solution by refluxing for 16 hr. The solvent was evaporated and after decomposition of the hydride mixture with water, the amine Ib was extracted into ether. The ether was evaporated to yield 210 mg of free base as a syrup. The dipicrate was prepared to yield 390 mg, mp 187–198°. Recrystallization from 90% 2-methoxyethanol gave 181 mg, mp 198–201°.

Anal. Calcd for $C_{35}H_{40}N_8O_{16}$: C, 50.7; H, 4.83; N, 13.5. Found: C, 50.6; H, 4.82; N, 13.4.

Bis(2-methoxy-5-bromoacetylphenyl)methane (VIII).—To a mixture of 2.0 g (6.4 mmoles) of bis(2-methoxy-5-acetylphenyl)-methane in 50 ml of THF was added 4.6 g (12.2 mmoles) of trimethylphenylammonium tribromide. The mixture was stirred at room temperature for 3.5 hr and evaporated *in vacuo*, and the yellow solid was washed thoroughly with water. The crude material (2.4 g) was collected after a benzene wash. Recrystallization from 2-methoxyethanol afforded 1.25 g (41%), mp 144–147°.

Anal. Calcd for $C_{19}H_{18}Br_2O_4$: C, 48.5; H, 3.83; Br, 34.1. Found: C, 48.2; H, 3.80; Br, 33.9.

Bis(2-methoxy-5-carboxyphenyl)methane (X).—To 60 ml of warm (60°) "Sanichlor" bleach was added 2.54 g (8.1 mmoles) of bis(2-methoxy-5-acetylphenyl)methane in 200 ml of methanol. The mixture was stirred at 60° for 2 hr, then 10-ml portions of bleach were added until a persistent starch–iodide test was obtained. The mixture was then evaporated *in vacuo* to near dryness, taken up in water, and treated with sodium bisulfite. The resulting suspension was acidified to pH 2 with 6 *N* HCl, and the solid was collected by filtration and washed with water. The white crystalline material was triturated with absolute methanol, yielding 2.19 g (85%), mp >300.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 64.5; H, 5.10. Found: C, 64.1; H, 5.11.

Bis(2-methoxy-5-dimethylcarbamoylphenyl)methane (XI).—A mixture of 0.3 g (0.95 mmole) of bis(2-methoxy-5-carboxyphenyl)methane and 5 ml of $SOCl_2$ was refluxed 6 hr and evaporated *in vacuo*. The acid chloride was freed of $SOCl_2$ by the addition and evaporation (*in vacuo*) of a few milliliters of anhydrous benzene. To 0.33 g (0.93 mmole) of the acid chloride in 8 ml of cold CH_2Cl_2 was added, dropwise, 2 ml of anhydrous dimethylamine in 2 ml of cold methylene chloride. After standing at room temperature 15 hr, the mixture was washed with water, and the CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated *in vacuo* to yield 0.24 g of gummy material. When treated with ether, the gum yielded 0.18 g of yellow crystals. Recrystallization from benzene–cyclohexane gave 0.13 g (38%), mp 119–122°. An analytical sample had mp 123–125°.

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.07; N, 7.56. Found: C, 67.8; H, 7.14; N, 7.20.

Bis(2-methoxy-5-dimethylaminomethylphenyl)methane Dihydrochloride (XII).—To a chilled suspension of 0.74 g (19.4 mmoles) of $LiAlH_4$ in 20 ml of anhydrous THF was added 1.2 g (3.2 mmoles) of bis(2-methoxy-5-dimethylcarbamoylphenyl)-methane. The mixture was refluxed 12 hr and chilled, and the remaining unchanged hydride was decomposed by the addition of absolute ethanol followed by a few milliliters of water. The mixture was evaporated *in vacuo* to near dryness. The white suspension was washed thoroughly with ethyl ether and filtered, and the ethereal extract was separated and dried ($MgSO_4$). Evaporation *in vacuo* yielded a clear gum, which, when taken up in chilled ethyl ether and saturated with dry HCl, yielded a white crystalline solid. Three recrystallizations from 2-propanol gave 0.2 g (15%) of XII, mp 212–215°.

Anal. Calcd for $C_{21}H_{30}N_2O_2 \cdot 2HCl$: C, 60.7; H, 7.72; N, 6.75. Found: C, 60.4; H, 7.80; N, 6.48.

The bismethiodide was prepared by stirring XII with an excess of methyl iodide for 3 days. An analytical sample, mp >300°, was obtained by recrystallization from aqueous 2-methoxyethanol.

Anal. Calcd for $C_{23}H_{36}I_2N_2O_2$: C, 44.1; H, 5.75; I, 40.6. Found: C, 44.4; H, 5.87; I, 40.5.

Electronic Structures of Some N-Alkyl-Substituted Amides of Interest as Cholinesterase Inhibitors[1]

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Electronic structures were calculated for 18 N-alkyl-substituted amides which are of interest as cholinesterase inhibitors. The electron densities were calculated from molecular orbital approximations. No simple relationship was observed between the net charge at the carbonyl carbon or carbonyl oxygen and the corresponding cholinesterase inhibitory property; however, the activity increases rather smoothly as the amide nitrogen becomes more positive.

We have been interested in correlating physicochemical parameters with the cholinesterase inhibitory properties of 1-decyl-3-[(N-alkyl)- and 1-decyl-3-[(N,N-dialkyl)-substituted carbamoyl]piperidines[2] and, more recently, have initiated molecular orbital calculations to give electron densities at the atomic sites of these inhibitors. Although the calculations are inherently approximate, it is not the absolute magnitudes of the results which we emphasize. Instead, we wish to classify or rank certain homologs which vary systematically and gradually by one structural alteration at a time, and compare *relative* electron densities with biochemical response.[3] Also, we wish to evaluate quantitatively the view[4] that inhibition is related to the electro-

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