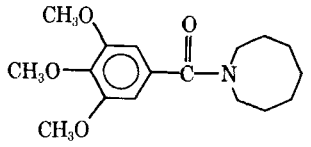
Structure–Activity Studies of New Potential Depressants 3,4,5-Trimethoxybenzamides II

HEINO A. LUTS

Abstract □ A group of 3,4,5-trimethoxybenzamides of various amines was synthesized and subjected to general pharmacological screening. The structures of Compounds 7, 8, 9, and 10 show strong depressant properties. A hypothesis is provided for the possible difference in activity of the various substituents on the amide nitrogen.

Keyphrases □ 3,4,5-Trimethoxybenzamides—synthesis, evaluation as potential depressants, structure–activity relationships □ Depressants, new potential—structure–activity relationships, synthesis, evaluation, 3,4,5-trimethoxybenzamides □ Structure–activity relationships—3,4,5-trimethoxybenzamides, potential depressants

In 1963, 3,4,5-trimethoxybenzoylheptamethyleneimine was synthesized and tested and, subsequently, the results were published (1). The compound was shown to



3,4,5-trimethoxybenzoylheptamethyleneimine

be a stimulant-antidepressant, and it exhibited no analgesic action. Since that time, several other workers have repeated the studies with the same findings (2, 3).

In continuation of these studies, some new structures were prepared and pharmacologically evaluated (Table I). The compounds prepared all have —N(—C)—C linkage; no —N(—H)—C linkage was prepared because of possible hydrogen bonding formation *in vivo*. The findings indicate that in cases where the imine ring was either decreased in size (Compound 3) or enlarged (Compound 4), the compounds exhibited depressant activity. Of the structures examined, Compounds 7, 8, 9, and 10 are strong depressants, while 3 and 5 possess only medium depressant activity. In general, it can be stated that if the compounds have nitrogen atoms outside the ring, and the amine function is nonaromatic, the depressant activity is stronger. The fact that the heptamethyleneimine derivative is an antidepressant and the hexa- and octamethyleneimine relatives are not prompted a look at other possible differences. By building the molecular models (Figs. 1–3), it was noted that the hydrogen atom from the number 5 carbon atom was overlapping the nitrogen atom and likely altering the electron density.

In the canonical form, the overlapping is expected to be even more pronounced. Possibly because of this, two five-membered ring structures are observed. This is not possible with the hexa- and octamethyleneimine derivatives, and it is postulated that the proximity effect is the reason for the difference in biological activity.

The compounds were prepared according to the method previously described (1).

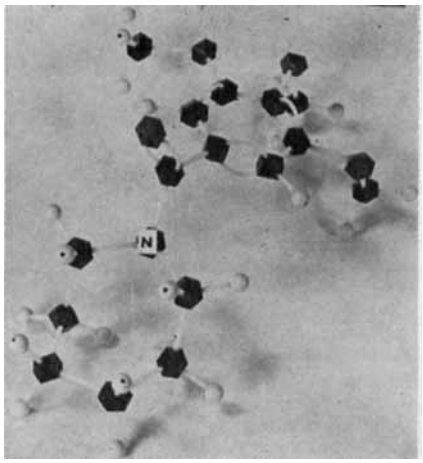


Figure 1—*3,4,5-Trimethoxybenzoylhexamethyleneimine.*

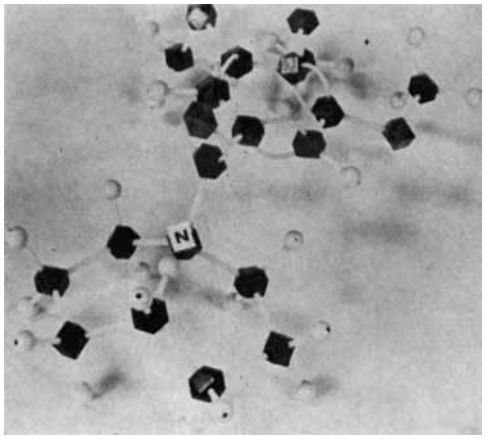


Figure 2—*3,4,5-Trimethoxybenzoylheptamethyleneimine.*

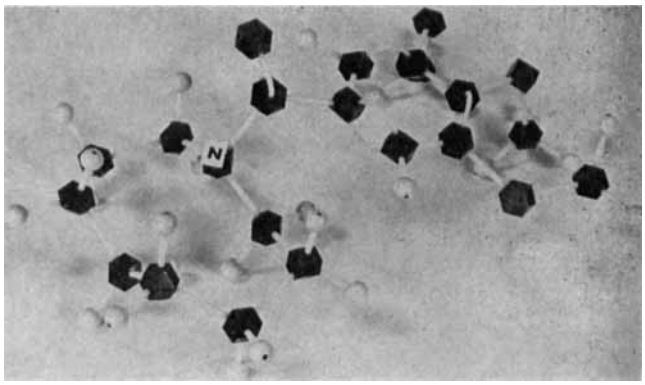
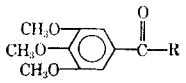
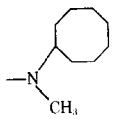
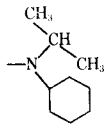
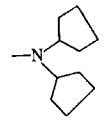
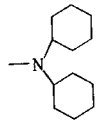
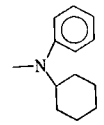


Figure 3—*3,4,5-Trimethoxybenzoyloctamethyleneimine.*

Table I—Physical Data for 3,4,5-Trimethoxybenzamide Derivatives



Compound Number	R	Formula	Melting Point	Yield, %	Analysis, % Calc.	Analysis, % Found
1		$C_{19}H_{27}NO_4$	135°	78	C, 68.44 H, 8.16 N, 4.19	C, 68.32 H, 8.16 N, 4.14
2		$C_{18}H_{25}NO_4$	111°	83	C, 67.63 H, 7.89 N, 4.38	C, 67.66 H, 7.85 N, 4.37
3		$C_{18}H_{27}NO_4$	111°	86	C, 73.73 H, 9.28 N, 4.77	C, 73.76 H, 9.30 N, 4.70
4		$C_{16}H_{23}NO_4$	75°	42	C, 41.12 H, 7.21 N, 4.35	C, 41.04 H, 7.27 N, 4.36
5		$C_{19}H_{21}NO_4$	95°	84	C, 69.70 H, 6.46 N, 4.27	C, 69.74 H, 6.49 N, 4.36
6		$C_{19}H_{21}NO_4$	98°	86	C, 69.70 H, 6.46 N, 4.27	C, 69.76 H, 6.51 N, 4.26
7		$C_{19}H_{29}NO_4$	79°	78	C, 68.03 H, 8.71 N, 4.17	C, 68.12 H, 8.69 N, 4.19
8		$C_{19}H_{29}NO_4$	69°	72	C, 68.03 H, 8.71 N, 4.17	C, 68.06 H, 8.74 N, 4.24
9		$C_{29}H_{29}NO_4$	184°	91	C, 69.13 H, 8.41 N, 4.02	C, 69.01 H, 8.37 N, 4.01
10		$C_{22}H_{33}NO_4$	172°	77	C, 70.36 H, 8.85 N, 3.72	C, 70.29 H, 8.89 N, 3.78
11		$C_{22}H_{27}NO_4$	134°	84	C, 71.52 H, 7.36 N, 3.78	C, 71.43 H, 7.88 N, 3.67

EXPERIMENTAL

General Procedure—To a solution of 0.05 mole of appropriate acid chloride in 150 ml. of benzene solution was added dropwise 0.1 mole of appropriate amine. The reactants were then refluxed for 30 min., and the crystals thus formed were separated by filtration. The benzene solution was then evaporated to dryness, and the crystalline product obtained was washed twice with petroleum ether, b.p. 30–60°.

Pharmacological Procedures—*Reserpine Antagonism*—The method utilized is a modification of that of Randall and Baydon (5). Fasted male mice were injected with 2.5 mg./kg. i.p. reserpine. After 1 hr., the mice were injected subcutaneously with each of the drugs and were observed hourly for 4 consecutive hr. The neurological deficits observed were general motor activity, miosis, and ptosis.

Hexobarbital Potentiation—A modification of the Kuhn and Van Maanen (6) method was used. Fasted male mice (S.W. strain) were administered the drugs intraperitoneally 15 min. prior to the injection of hexobarbital sodium, 100 mg./kg. i.p., and observed for their sleeping time.

Phenylquinone Writhing—The method employed was that of Hendershot and Forsaith (7). Fasted male mice (S.W. strain) were administered intraperitoneally with 0.2 ml. of phenylquinone solution (0.02%). The mice were placed in a single 1-l. beaker and ob-

Table II—Partial Pharmacological Data

Tests	Compounds, in Descending Order, Best in Each Test
Hexobarbital potentiation	9, 8, 7, 6
Phenylquinone writhing	5, 9, 8
Randall–Sellito pressure paw	9, 8, 7, 3, 10, 5
Reserpine antagonism	None
Antipyresis	7, 10, 5, 9, 8, 3

served for 10 min. The test drugs were given 20 min. prior to injection of phenylquinone.

Randall–Sellito Pressure Paw—The method employed was adapted from that of Randall and Sellito (8). Inflammation of the hindpaw of fasted Sprague-Dawley rats (body weight 100–125 g.) was induced by an injection of 0.1 ml. of 20% brewer's yeast suspension into the plantar surface. The ability of the subcutaneously administered test drugs (administered concomitantly with phlogistic agent) to affect the pressure pain interval was determined 1, 2, 3, and 4 hr. after drug administration. This test was modified to determine antipyretic activity; thus, rectal temperatures were taken prior to drug–phlogistic administration and at the designated time intervals after administration.

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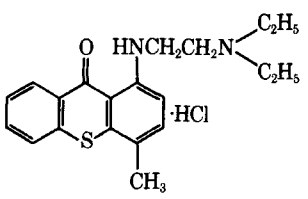
Condensed *p*-Toluidines with Aminothiazoles as Schistosomicidal Agents II

I. NABIH and M. ABBASI

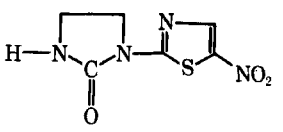
Abstract □ Compounds representing structural combinations between the two moieties necessary for the biological activity in both schistosomicidal agents, 1-(β-diethylaminoethylamino)-4-methylthiaxanthone and 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (*p*-toluidine and 5-nitrothiazole, respectively), have been synthesized. For the condensation reaction, aromatic azido acids were used followed by selective reduction of the azido groups through metallic hydrides.

Keyphrases □ *p*-Toluidines, 5-nitrothiazole—synthesis, potential schistosomicidal agents □ Schistosomicidal agents, potential—synthesis of condensed *p*-toluidines, aminothiazoles

Investigations carried out since the discovery of the schistosomicidal activity of 1-(β-diethylaminoethylamino)-4-methylthiaxanthone[1] (I) and its analogs showed that the presence of an amino side chain located on C-1 in *para*-position to the methyl group on C-4 is necessary for the biological activity of these agents (1, 2). In the recent schistosomicidal agent, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone[2] (II), the presence of the nitrothiazole group was confirmed to be an essential feature for its activity (3, 4).

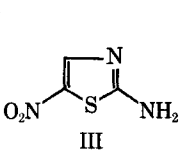


I

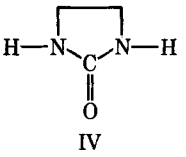


II

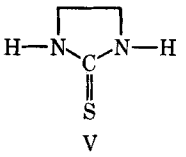
[1] Lucanthone or Miracil D.
[2] Ambilhar or Ciba 32644-Ba.



III



IV

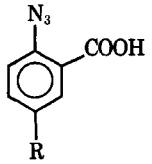


V

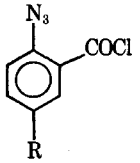
These considerations suggested the synthesis of compounds containing these necessary moieties. Both systems were designed to be connected through an amide linkage, because this may be biologically hydrolyzed to free both parts. Thus, the molecules may act as a whole or as separate components in the presence of one another.

Aromatic azido acids were used in the condensation reaction with 2-amino-5-nitrothiazole (III), 2-imidazolidinone (IV), and its thione analog, 2-imidazolidinethione (V). 2-Imidazolidinone is structurally included with 5-nitrothiazole in the schistosomicidal agent II.

The azides of anthranilic acid (VI*a*) and its 3-methyl derivative (VI*b*) were prepared by a procedure involving the addition of hydrazoic acid to the corresponding diazonium salt. The azido acid chlorides (VII*a* and VII*b*) prepared through the action of thionyl chloride upon the acids VI*a* and VI*b*, respectively, reacted readily



VI*a*: R = H
VI*b*: R = CH_3



VII*a*: R = H
VII*b*: R = CH_3