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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NEW ALKOXYBENZAMIDES—II

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Abstract—Several new derivatives of benzoic acid-morpholide and some other acid amides have been prepared and their toxicity, tranquillizing action and analgesic activity determined. Attempts were made at correlations between chemical contribution and biological activity.

IN A previous paper[1] we reported that certain amides of 3:4:5-trimethoxybenzoic acid were found to possess tranquillizing action: one of these compounds, 3:4:5-trimethoxybenzoyl-morpholine ("Trioxazin"), has been adopted by therapeutical practice, too.

In the course of our further investigations, we wanted to study whether the 3:4:5-trimethoxybenzoyl group was a necessary structural element for producing tranquillizing action, or could the same effect be brought about also by other acid amides of similar structure? In this research, morpholine was, in general, retained as the basic component, and the acid moiety was varied according to the following principles:

(1) The positions of the methoxy groups were shifted (see Table 1, nos. 7–9).

(2) The number of the methoxy groups was changed (nos. 1–4).

(3) The ethereal alkyl group was partly or completely eliminated from the structure (nos. 5 and 6).

(4) The length of the ethereal alkyl chain was increased (nos. 10–16).

(5) The alkyl part was partly substituted by an aralkyl group (nos. 17–19).

(6) Or by some basic group (no. 22).

(7) Or by an acyl group (nos. 20, 21).

(8) Nitrogen-containing substituents were introduced into the trimethoxybenzoyl group (nos. 25–27).

(9) The acid amide group was separated from the benzene ring (no. 23).

(10) And finally, two acid amide groups were introduced into the benzene ring (no. 24).

The compounds listed in Table 2 are the amides of differently substituted acids, formed with various bases.

The resulting acid amides are, in general, crystalline compounds. However, some of them were oils; such products were purified by distillation under reduced pressure. The general method of preparation consisted of reacting a benzene solution of the acid chloride with an excess of the base, e.g. morpholine; the precipitated salt was filtered off, and the acid amide produced was isolated from the solution. In some cases, however, triethylamine was used for binding the acid instead of an excess of the secondary base reaction component (Table 1, nos. 3, 7, 8).

The morpholides, denoted nos. 5, 6, 10, 11, 12, 14, 20, 22, 26 and 27, have been prepared by a method different from the general procedure described above. Mixed alkylated or acylated derivatives (nos. 10, 11, 12, 20, 22) have been obtained by the alkylation or acylation of syringic acid morpholide. 3:4:5-Tripropoxybenzoylmorpholine (no. 14) has been prepared by catalytic hydrogenation from the triallyloxy derivative (no. 15). It may be noted, that catalytic hydrogenation of the 4-allyloxy derivative (no. 11) failed to give the 3:5-dimethoxy-4-propoxy derivative (no. 10), since after the consumption of 1 mole of hydrogen, the allyl group suffered hydrogenolysis which resulted in the formation of syringic acid morpholide (no. 5). In the synthesis of piperazine derivatives (nos. 31, 33), it was important to add the acid chloride gradually into a benzene solution of excess piperazine, since formation of diacyl derivatives could not be avoided even if a large excess of the base was present. The preparation of 3:4:5-trimethoxyphenyl thioacetic morpholide (no. 30) also differed from the general procedure, as it was obtained from 3:4:5-trimethoxyacetophenone by the Willgerodt–Kindler method. The syntheses of the compounds prepared by some special method are described in detail in the experimental part.

The acids and acid chlorides used as the starting materials are mostly known compounds; some of them, however, have been synthesized now for the first time. These acids and their derivatives are discussed again in the experimental part. It should be noted here that total methylation of trihydroxybenzoic acids containing a hydroxyl group next to the carboxyl could not be achieved in a single step by dimethyl sulphate in aqueous alkaline solution, or a very poor yield was obtained. It was observed that a good yield of the trimethoxy acid could be realized also in a one-step reaction, if the methyl ester of the trihydroxy acid was acted upon by dimethyl sulphate in butanone or acetophenone,[2] in the presence of anhydrous potassium carbonate. In this way 2:3:4-trimethoxybenzoic acid and 4:5:6-trimethoxybenzene-1:3-dicarboxylic acid have been prepared.

A new route employing the Willgerodt–Kindler method has been developed for synthesizing the known 3:4:5-trimethoxy-phenylacetic acid from the readily available 3:4:5-trimethoxy-acetophenone. The process is simpler than those published so far.[3]

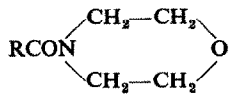
The acid chlorides were prepared from the corresponding acids, usually by means of thionyl chloride.

EXPERIMENTAL

2:3:4-*Trimethoxybenzoic acid*[4]

To a boiling and stirred solution of methyl 2:3:4-trihydroxybenzoate (68·87 g) in dry butanone (315 ml), anhydrous powdered potassium carbonate (205 g) was added during a period of 1 hr; then dimethyl sulphate (143 ml) was added during a period of 70 min, and the mixture was refluxed for 6 hr. After being cooled, 500 ml of ether and 750 ml of water were added, the reaction mixture was filtered, and the two layers of the filtrate separated. The ether solution was shaken with 6 per cent sodium hydroxide solution, the ether evaporated, and the crude oily ester (70·2 g) saponified by refluxing for 2 hr with a mixture of 33 per cent potassium hydroxyde (90 ml) and 96 per cent ethanol (300 ml). The solution was concentrated under reduced pressure, the residue diluted with water (200 ml), and acidified by the addition of concentrated hydrochloric acid. The mixture was chilled in ice-water a few hours, then the impure acid filtered by suction, and recrystallized from a mixture of water (800 ml) and

TABLE 1. MORPHOLIDES OF ALKOXYBENZOIC ACIDS



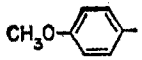
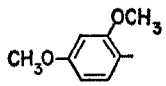
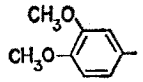
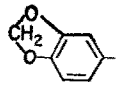
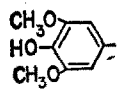
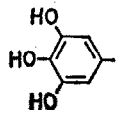
Compd.	R	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%)							
						Calcd.				Found			
						C	H	N	OCH_3	C	H	N	OCH_3
1			42–44° 162–168°/ 0·5 mm*	$C_{12}H_{15}NO_3$	221·2	65·13	6·83	6·33	14·01	65·22	7·11	6·48	13·94
2		acetone + petroleum ether (1:1)	98–99° 192–193°/ 0·6 mm	$C_{13}H_{17}NO_4$	251·2	62·2	6·77	5·57	24·7	62·18	6·84	5·57	24·03
3			180–186°/ 0·4 mm*	$C_{13}H_{17}NO_4$	251·2	62·2	6·77	5·57	24·7	62·01	7·01	5·42	24·2
4		methanol + (water 1:1)	81–83° (softens 78°)	$C_{12}H_{13}NO_4$	235·1	61·2	5·53	5·96		61·19	5·83	6·2	
5		ethanol	163–165°	$C_{13}H_{17}NO_5$	267·2	58·4	6·36	5·25	23·2	58·25	6·08	5·47	23·6
6		water	240° (softens 224°)	$C_{11}H_{13}NO_5$	239·2	55·22	5·48	5·86		55·5	5·45	5·91	

TABLE 1—*continued.*

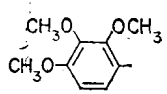
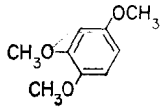
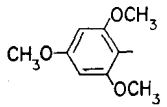
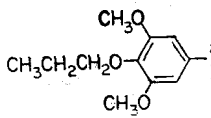
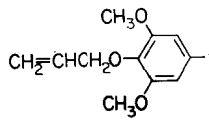
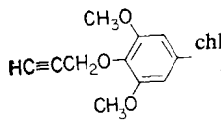
Compd.	R	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%) Calcd. C	H	N	OCH_3	Found C	H	N	OCH_3
7		water	84–86°	$C_{14}H_{19}NO_5$	281·3	59·76	6·81	4·98	33·10	59·92	7·26	4·98	32·44
8		benzene–ether	91–92° 160–162°/ 0·07 mm*	$C_{14}H_{19}NO_5$	281·3			4·98				5·05	
9		ethanol + water (1:7)	128–131°	$C_{14}H_{19}NO_5$	281·3	59·76	6·81	4·98	33·10	59·54	6·81	4·80	32·95
10		acetone + petrol (1:3)	72–74° (softens 70°)	$C_{16}H_{23}NO_5$	309·2	62·1	7·52	4·53		61·91	7·54	4·31	
11		acetone + petrol (4:5)	79–81°	$C_{16}H_{21}NO_5$	307·2	62·5	6·90	4·56		62·29	7·2	4·62	
12		chloroform + methanol (1:10)	154–155°	$C_{16}H_{19}NO_5$	305·2	63·0	6·30	4·59		62·85	6·47	4·57	

TABLE 1—*continued.*

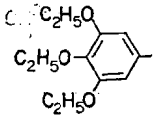
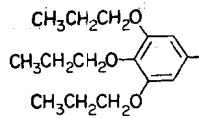
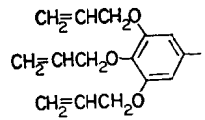
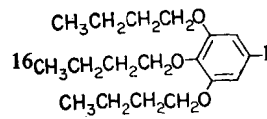
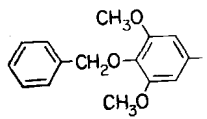
Compd.	R	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%) Calcd. C	H	N	OCH_3	Found C	H	N	OCH_3
13		petrol	76–77° (softens 73°)	$C_{17}H_{25}NO_5$	323·2			4·33	41·8 (OEt)			4·38	40·9 (OEt)
14		petroleum ether	63–65°	$C_{20}H_{31}NO_5$	365·5	65·72	8·55	3·83		65·40	8·80	4·01	
15		benzene + petroleum ether (1:6)	52–53°	$C_{20}H_{25}NO_5$	359·4	66·83	7·01	3·90		66·90	6·79	4·14	
16		petroleum ether	54–56°	$C_{23}H_{37}NO_5$	407·5	67·80	9·15	3·43		67·51	8·86	3·57	
17		benzene + petrol (1:1)	138–139°	$C_{20}H_{23}NO_5$	357·2	67·20	6·44	3·94	17·35	67·50	6·32	3·93	16·70

TABLE 1—*continued.*

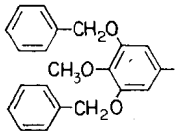
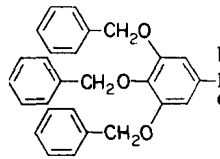
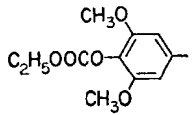
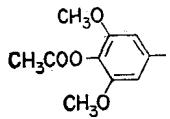
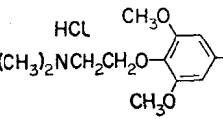
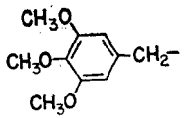
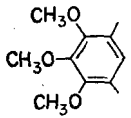
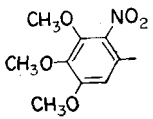
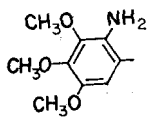
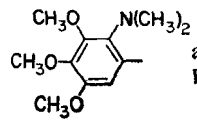
Compd.	R	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%) Calcd. C	H	N	OCH_3	Found C	H	N	OCH_3
18		methanol + benzene (5:1)	131–133°	$C_{26}H_{27}NO_5$	433·2	72·10	6·23	3·24	7·16	72·36	6·07	3·03	6·63
19		benzene + petroleum ether (3:5)	88–90° (softens 86°)	$C_{32}H_{31}NO_5$	509·4	75·42	6·13	2·75		75·70	6·54	2·72	
20		96% ethanol	147–149° (softens 145°)	$C_{16}H_{21}NO_7$	339·2	56·60	6·20	4·13		56·35	6·28	4·12	
21		methanol	136–138°	$C_{15}H_{19}NO_6$	309·2	58·30	6·21	4·53		58·02	6·14	4·34	
22		ethanol	193–195°	$C_{17}H_{27}ClN_2O_5$	374·7	54·30	7·26	7·46		54·40	7·55	7·70	

TABLE 1—*continued.*

Compd.	R	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%) Calcd. C	H	N	OCH_3	Found C	H	N	OCH_3
23		acetone + petroleum ether (2:1)	48–50°	$C_{15}H_{21}NO_5$	295·3			4·74	31·5			4·67	31·84
24		benzene + petrol (2:1)	135–136° (softens 133°)	$C_{19}H_{26}N_2O_7$	394·2			7·11	23·6			7·16	22·9
25		methanol	117–118°	$C_{14}H_{18}N_2O_7$	326·1	51·55	5·56	8·58	28·55	51·1	5·76	8·64	29·00
26†		benzene + petrol (1:2)	69–71°	$C_{14}H_{20}N_2O_5$	296·2			9·46	31·40			9·31	30·90
27		acetone + petrol (1:2)	96–99°	$C_{16}H_{24}N_2O_5$	324·2			8·65	28·70			8·71	28·40

† *p*-$CH_3C_6H_4SO_3H$ salt m.p. 203–206° (softens 197°).

TABLE 2

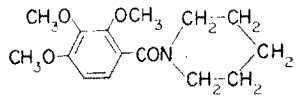
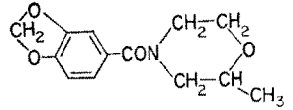
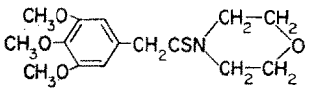
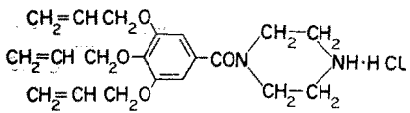
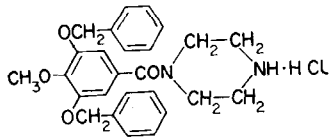
Compd.	Formula	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%)							
						Calcd.				Found			
						C	H	N	OCH_3	C	H	N	OCH_3
28		acetone + petroleum ether (1:10)	55–57°	$C_{15}H_{21}NO_4$	279·2	64·6	7·52	5·02		64·45	7·81	4·73	
29			176–183°/ 0·4 mm*	$C_{13}H_{15}NO_4$	249·1	62·70	6·06	5·62		62·40	5·64	5·74	
30		benzene	110–111°	$C_{15}H_{21}NO_4S$	311·3	57·90	6·82	4·50	29·90	57·65	7·02	4·54	29·10
31		methanol	219–221°	$C_{20}H_{27}ClN_2O_4$	394·8	60·80	6·88	7·09		60·66	6·86	6·98	
32	N:N-bis-(3:4:5-triallyloxy benzoyl)-piperazine	benzene +1 petrol (5:3)	97–100°	$C_{36}H_{42}N_2O_8$	630·3	68·30	6·71	4·44		68·54	6·78	4·23	

TABLE 2—*continued.*

Compd.	Formula	Recryst. solvent	m.p., °C b.p., °C*	Empirical formula	Mol. wt.	Analysis (%)							
						Calcd.				Found			
						C	H	N	OCH_3	C	H	N	OCH_3
33		water + 96% ethano (10:3·5)	233–235°	$C_{26}H_{29}ClN_2O_4$	469·3	66·60	6·22	5·97		66·55	6·08	5·66	
34	N,N-bis-(4-methoxi-3:5-dibenzyloxy-benzoyl)-piperazine	xylene	214–216° (softens 200°)	$C_{48}H_{46}N_2O_8$	778·4	74·1	5·96	3·60		74·33	5·84	3·53	

ethanol (80 ml) with the aid of decolorizing carbon, to yield 55·45 g of needles, m.p. 100–102°.

Anal. Calcd. for $C_{10}H_{12}O_5$ (212·2): CH_3O, 43·8. Found: CH_3O, 43·2.

3:4:5-*Triallyloxybenzoic acid*

To a boiling and stirred solution of methyl gallate (63 g) in dry butanone (225 ml) was added anhydrous powdered potassium carbonate (180 g) during 1 hr, and allyl bromide (117 ml) during 3 hr. After being refluxed for 10 hr, the mixture was cooled, filtered by suction, and the filtrate steam-distilled. The oily portion of the residue of the steam distillation was extracted with 200 ml then 50 ml of ether, and the combined ethereal extracts were washed with 100 ml of 4 per cent sodium hydroxide solution. After evaporating the ether, 104 g of a brown oil was left which consisted mostly of methyl 3:4:5-triallyloxybenzoate. Methanol (300 ml) and 10 per cent aqueous methanolic (1:1) potassium hydroxide solution (145 ml) were added to this residue, and the mixture was refluxed for 1·5 hr. The solution was evaporated under reduced pressure, the remaining material dissolved in water (500 ml), and extracted with 150 ml of ether. The aqueous alkaline layer was acidified with hydrochloric acid; an oil separated which soon became crystalline. The product was recrystallized first from a mixture of ethanol (100 ml) and water (30 ml), then from a mixture of methanol (40 ml) and water (15 ml), to yield 32·65 g of white needles, m.p. 78–79°. An ethanol solution of the product gave no colour reaction with ferric chloride.

Anal. Calcd. for $C_{16}H_{18}O_5$(290·3): C, 66·19; H, 6·25; acid value 193. Found: C, 65·90; H, 6·50; acid value 189.

3:4:5-*Triallyloxybenzoyl chloride*

A mixture of 3:4:5-triallyloxybenzoic acid (2·9 g), dry benzene (3 ml) and thionyl chloride (1·1 ml) was warmed at 50–55° for a period of 3 hr. The reaction mixture was concentrated under reduced pressure, and the residue (3·11 g) recrystallized from 2·5 ml of petroleum ether (b.p. 55–60°). The yield of crystalline needles was 0·52 g, m.p. 31–33°.

Anal. Calcd. for $C_{16}H_{17}ClO_4$ (308·8): Cl, 11·48. Found: Cl, 11·73.

Rather high losses are involved in the procedure of recrystallization; however, the acid chloride can be used for the condensation reaction with amines without any further purification.

3:4:5-*Trimethoxyphenylthioacetic acid morpholide* (*compound no.* 30)

A mixture of 3:4:5-trimethoxyacetophenone (31·8 g), sulphur powder (7·25 g), and morpholine (50 ml) was refluxed for 10 hr, then the reaction mixture was concentrated under reduced pressure. The residue was boiled for a few minutes with 300 ml of benzene, and the benzene solution was decanted from the undissolved tarry material. After being cooled, the benzene solution was washed subsequently with water (200 ml), 4 per cent hydrochloric acid (200 ml), 5 per cent ammonium hydroxyd solution (200 ml), and again with water (200 ml), then it was dried over anhydrous potassium carbonate, and the solvent was evaporated. The residue (34·75 g) was recrystallized twice from 140 ml and 30 ml of benzene, respectively, to yield 10·7 g of small sturdy needles.

3:4:5-*Trimethoxyphenylacetic acid*

The combined mother liquors from the recrystallization of the above thiomorpholide

were evaporated, and the residue (23·28 g) was refluxed for 4 hr with ethanol (130 ml), water (35 ml), and 33 per cent potassium hydroxyde (75 ml). The solvents were evaporated under reduced pressure, the residue dissolved in a mixture of 200 ml of water and 200 ml of benzene, and the two layers were separated. The aqueous alkaline solution was acidified with hydrochloric acid and extracted with 100 ml and then 50 ml of ether. The solvent was evaporated from the combined ethereal extracts, and the residue was recrystallized from 115 ml of water with the aid of decolorizing carbon, to yield 8·3 g of 3:4:5-trimethoxyphenylacetic acid, m.p. 119–120°.

Mixed melting point determination with authentic material showed no depression.

Dimethyl 4:5:6-*trihydroxybenzene*-1:3-*dicarboxylate*

A mixture of 4:5:6-trihydroxybenzene-1:3-dicarboxylic acid[5] (48·3 g), methanol (500 ml), and concentrated sulphuric acid (73 ml) was refluxed for 15 hr, and then stored at − 2° for 12 hr. The precipitated brownish crystalline material was filtered off, and boiled with 720 ml of ethyl acetate. The hot solution was decanted from the undissolved material and chilled in ice-water for 1 hr. After being filtered, the mother liquor was used for dissolving the residue which had been left behind during the first extraction. A total of 34·35 g, white needles, of the ester was obtained, m.p. 213–214°. The crystalline residue from the evaporation of the mother liquor gave an additional 5·9 g of the ester when rubbed with 100 ml of acetone.

Anal. Calcd. for $C_{10}H_{10}O_7$ (242·1): C, 49·60; H, 4·13; CH_3O, 25·60. Found: C, 49·73; H, 4·35; CH_3O, 25·25.

4:5:6-*Trimethoxybenzene*-1:3-*dicarboxylic acid*[6]

Dimethyl 4:5:6-trihydroxybenzene-1:3-dicarboxylate (30·9 g) was mixed for 5 min with dry acetophenone (127 ml) in a bath of 120–123°, and anhydrous powdered potassium carbonate (68·5 g) was added to the stirred mixture over a period of 40 min at the same temperature. The bath was heated to 135–140°, and a mixture of dimethyl sulphate (49 ml) and acetophenone (64 ml) was added dropwise at such a rate that the addition was complete in 1 hr. The stirring was continued at 135–140° over an additional period of 10 hr. After being cooled, 600 ml of water and 400 ml of ether were added, the reaction mixture was filtered if necessary, the organic layer was separated, the ether evaporated, and the acetophenone removed from the residue by steam distillation. The oily portion of the remaining material was extracted with 300 ml, then 200 ml of ether, the combined ethereal solutions washed with 100 ml of 10 per cent potassium hydroxide, filtered, and the solvent evaporated. A brown oily liquid (37·4 g) was left which consisted mostly of dimethyl 4:5:6-trimethoxybenzene-1:3-dicarboxylate. Methanol (380 ml) and 11 per cent potassium hydroxide solution (173 ml) were added, and the material saponified by refluxing for 1·5 hr. The methanol was evaporated under reduced pressure, and the residue dissolved in 250 ml of water. The solution was extracted with 200 ml of ether, and the aqueous alkaline layer acidified. The mixture was chilled at 0° for 1 hr, and the separated acid filtered by suction. The yield was 26 g, m.p. 192–193°.

The extraction of the aqueous mother liquors by means of ethyl acetate gave an additional 1·75 g of the acid, m.p. 189–192°.

Anal. Calcd. for $C_{11}H_{12}O_7$ (256·1): CH_3O, 36·4; acid value 437. Found: CH_3O, 35·8; acid value 438.

N-(4-*Hydroxy*-3:5-*dimethoxybenzoyl*)-*morpholine* (*syringic morpholide*) (*no.* 5)

Method A. N-(4-benzyloxy-3:5-dimethoxybenzoyl)-morpholine (5 g) was dissolved in a mixture of acetic acid (40 ml) and water (5 ml), and the reaction mixture was hydrogenated at room temperature and atmospheric pressure in the presence of 10 per cent palladium charcoal catalyst (1 g). A volume of 330 ml of hydrogen (18°, 1 atm) was absorbed in 45 min, then the consumption stopped. The theoretically expected hydrogen consumption was 314 ml (0°, 1 atm). The catalyst was filtered off, and the solution evaporated to dryness to give 3·67 g of almost pure syringic morpholide. For analysis, it was recrystallized from ethanol.

Method B. N-(4-acetoxy-3:5-dimethoxybenzoyl)-morpholine (acetylsyringic morpholide) (3·1 g) was dissolved by gentle warming in dry methanol (30 ml), then quickly cooled to room temperature and treated with a sodium methoxide solution (prepared from 0·25 g of sodium in 10 ml of methanol). The reaction mixture was shaken and cooled in ice-water for 1–2 min, then allowed to stand at room temperature 2·5 hr. While cooling again in ice-water, the mixture was carefully acidified with a mixture of 4 ml 20 per cent sulphuric acid and 50 ml of water, and extracted with three 50-ml portions of chloroform. The extract was dried over anhydrous magnesium sulphate, the solvent evaporated under reduced pressure at a bath temperature of 70°, and the residue recrystallized from 19 ml of anhydrous ethanol to give 2·18 g of the product.

N-(3:4:5-*Trihydroxybenzoyl*)-*morpholine*) (*gallic morpholide*) (*no.* 6)

This compound was prepared from N-(tribenzyloxybenzoyl)-morpholine in the same way as described for the preparation of syringic morpholide from N-(4-benzyloxy-3:5-dimethoxybenzoyl)-morpholine, according to method A.

N-(4-n-*propoxy*-3:5-*dimethoxybenzoyl*)-*morpholine* (*no.* 10)

Syringic morpholide (7 g) was dissolved in hot methanol (35 ml), *n*-propyl bromide (3·5 ml) was added, then under continuous stirring 47·7 per cent potassium hydroxide solution (3·4 g) was introduced dropwise, and the mixture refluxed for 8 hr. After being cooled, 120 ml of water was added, and the solution extracted with two 50-ml portions of chloroform. The extract was washed with 4 per cent sodium hydroxide, dried over anhydrous magnesium sulphate, and the chloroform removed by distillation under reduced pressure. The remaining material (7·2 g) was recrystallized from 13 ml of light petroleum mixed with 4 ml of acetone to give 3·8 g product.

Processing of the mother liquor gave an additional 1·3 g of the compound.

N-(4-*Allyloxy*-3:5-*dimethoxybenzoyl*)-*morpholine* (*no.* 11)

Syringic morpholide (13·35 g), methanol (20 ml), and allyl bromide (6·5 ml) were mixed and refluxed for 5 min, then sodium methoxide solution (60 ml) (prepared from 1·27 g of sodium in methanol was added dropwise and under continuous stirring to the boiling reaction mixture. The addition required 10 min. Refluxing was continued over a period of 4 hr, then the mixture was cooled and processed as described above for N-(4-*n*-propoxy-3:5-dimethoxybenzoyl)-morpholine. The evaporation residue (11·95 g) of the chloroform solution was recrystallized from a mixture of light petroleum (10 ml) and acetone (8 ml). The yield was 8·4 g. Processing of the mother liquor gave a further 1·3 g of the product.

Hydrogenation of N-(4-*allyloxy*-3:5-*dimethoxybenzoyl*)-*morpholine*

N-(4-allyloxy-3:5-dimethoxybenzoyl)-morpholine (1 g) dissolved in methanol (30 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10 per cent palladium charcoal catalyst (0·2 g). The material absorbed 85 ml of hydrogen (21°, 1 atm) over a period of 5 min, then consumption strongly fell back. The solution was filtered from the catalyst, the filtrate evaporated under reduced pressure, and the residue recrystallized from a mixture of acetone and light petroleum. The yield was 0·25 g, m.p. 159–161°. The resulting product melted at 162–164° when in admixture with pure authentic syringic morpholide.

N-(4-*Propargyloxy*-3:5-*dimethoxybenzoyl*)-*morpholine* (*no.* 12)

Syringic morpholide (2·67 g) was dissolved in hot methanol (12 ml), methanolic sodium methoxide solution (10 ml, prepared from 0·28 g of sodium) was added, and a mixture of propargyl bromide (1 ml) and methanol (6 ml) was added to the boiling solution over a period of 1·5 hr. After being refluxed for 5 hr, the reaction mixture was processed as described above for N-(4-*n*-propoxy-3:5-dimethoxybenzoyl)-morpholine. The evaporation residue (2·72 g) of the chloroform solution was recrystallized from a mixture of methanol (20 ml) and chloroform (2 ml) to give 2·35 g product.

N-(4-*ethoxycarbonyloxy*-3:5-*dimethoxybenzoyl*)-*morpholine* (*no.* 20)

To a cooled and stirred mixture consisting of syringic morpholide (13·8 g), 14 per cent sodium hydroxide solution (14·3 ml) and water (20 ml), there was added dropwise ethyl chloroformate (9·5 ml) during a period of 1·5 hr, and then the mixture was stirred and heated in a bath of 50–52° for an additional period of 1·5 hr. After cooling, the reaction mixture was stirred with a mixture of water (150 ml) and acetic acid (10 ml), the precipitated material filtered by suction, dried, and the crude product (15·6 g) twice recrystallized from 96 per cent ethanol (80 ml each). The yield was 12·6 g.

N-(4-*dimethylaminoethoxy*-3:5-*dimethoxybenzoyl*)-*morpholine* (*no.* 22)

Sodium (0·46 g) was dissolved in dry *iso*propanol (30 ml), finely powdered syringic morpholide (2·67 g) was added and dissolved by gentle heating, quickly cooled, and then dimethylaminoethyl chloride hydrochloride (1·44 g) was introduced in one portion, and the reaction mixture refluxed for 2 hr. After being cooled, the mixture was filtered by suction from the precipitated salt, the mother liquor was concentrated under reduced pressure, the remainder dissolved in 4 per cent hydrochloric acid (20 ml), and the solution extracted with 50 ml of ether. The acidic aqueous solution was made alkaline by the addition of 50 per cent potassium hydroxide solution (15 ml) while cooling in ice-water, and the separating oil was extracted with two 50-ml portions of ether. The extract was dried over anhydrous potassium carbonate, and the ether evaporated to leave 1·9 g of a light yellow oil which could not be crystallized or distilled.

Anal. Calcd. for $C_{17}H_{26}N_2O_5$ (338·5): N, 8·28; CH_3O, 18·35. Found: N, 8·83; CH_3O, 17·7.

The oil was dissolved in 20 ml of dry ether, and 3 ml of a 20 per cent ethanolic solution of hydrogen chloride was added. Cooling and scratching with a glass rod resulted in the crystallization of the oil, to give 1·8 g product, m.p. 163–165°. This

material was the unstable dihydrochloride. Recrystallization from 3 ml of ethanol gave 1·4 g of the pure monohydrochloride.

N-(3:4:5-*tri-n-propoxybenzoyl*)-*morpholine* (*no.* 14)

N-(3:4:5-Triallyloxybenzoyl)-morpholine (14 g) was dissolved in methanol (150 ml), and it was hydrogenated at room temperature and atmospheric pressure in the presence of 10 per cent palladium charcoal catalyst (1·4 g). The reaction mixture adsorbed 2650 ml of hydrogen (21°, 1 atm.) during a period of 2 hr; the calculated quantity was 2600 ml (0°, 1 atm). After this, the consumption of hydrogen almost completely stopped. The catalyst was removed by filtration, the mother liquor evaporated under reduced pressure, and the residue recrystallized from 17 ml of petroleum ether (b.p. 60°). The yield was 10·6 g.

N-(2-*Amino*-3:4:5-*trimethoxybenzoyl*)-*morpholine* (*no.* 26)

A mixture of N-(2-nitro-3:4:5-trimethoxybenzoyl)-morpholine (30 g), acetic acid (350 ml) and *p*-toluenesulphonic acid (21·9 g) was hydrogenated at room temperature and atmospheric pressure in the presence of palladium on carbon (10 per cent Pd) catalyst (5 g). The solid dissolved with strong evolution of heat. During the course of 100 min, 6450 ml of hydrogen (20°, 1 atm) was taken up, then the rate of absorption slowed down. The calculated volume of hydrogen was 6180 ml (0°, 1 atm). The catalyst was filtered off, the solution evaporated under reduced pressure, and the residue recrystallized from 95 per cent ethanol (100 ml), to yield 37·92 g of the *p*-toluenesulphonic acid salt, m.p. 203–206° (shrinking at 197°).

Anal. Calcd. for $C_{21}H_{28}O_8N_2S$ (468·2): C, 53·8; H, 6·02; N, 5·98; S, 6·83; CH_3O, 19·80. Found: C, 53·61; H, 6·28; N, 5·77; S, 6·29; CH_3O, 19·82.

The base could be liberated by treating the aqueous solution of the *p*-toluenesulphonic acid salt with strong alkalis. The free base was readily soluble in water, therefore its isolation required extraction by ether.

N-(2-*Dimethylamino*-3:4:5-*trimethoxybenzoyl*)-*morpholine* (*no.* 27)

A mixture of N-(2-nitro-3:4:5-trimethoxybenzoyl)-morpholine (12·18 g), acetic acid (240 ml), 36 per cent aqueous formaldehyde solution (8·7 ml), and *p*-toluenesulphonic acid (7·2 g) was hydrogenated at room temperature and atmospheric pressure in the presence of palladium on carbon (10 per cent Pd) catalyst (2 g). During the course of 16 hr, 4200 ml of hydrogen (18°, 1 atm) was absorbed, then the consumption of the gas slowed down. The material was dissolved during the process of reduction. Calculated theoretical absorption: 4180 ml hydrogen (0°, 1 atm). The catalyst was removed by filtration, the filtrate evaporated under reduced pressure, and the residue dissolved in 50 ml of water. Under cooling in ice-water, 200 ml of 20 per cent sodium hydroxide was added to the solution, and it was immediately extracted with two 200-ml portions and one 100-ml portion of chloroform. The organic layer was dried over anhydrous potassium carbonate, evaporated under reduced pressure, and the residue recrystallized from a mixture of acetone (14 ml) and light petroleum (28 ml). The yield was 5·2 g of crystalline plates.

PHARMACOLOGY

Methods

The toxicity, neurosedative and analgesic actions of the prepared compounds were studied on mice, using the methods described in our previous paper.[1]

Results

Table 3 (*a*) shows the data of toxicity and of pharmacological effects obtained with N-(3:4:5-trimethoxybenzoyl)-morpholine and other alkoxybenzoic acid morpholides. The neuro-sedative and analgesic action of the former compounds show, to a certain extent, dependence upon the number and position of the methoxy groups present. In order to maintain a tranquillizing activity, it is sufficient to have two methoxy groups in the ortho position (compound no. 3). The depressant activity becomes decreased in *p*-methoxybenzoyl derivative, and lack of the methoxy group (N-benzoylmorpholine) results in no activity at all. This latter compound showed no tranquillizing action even when administered in intraperitoneal doses of 600 mg/kg. The analgesic activities of these compounds, though decreased in comparison with the standard derivative, do not show a parallel change; thus, for example, such an activity is still apparent in benzoylmorpholine also when the tranquillizing action has completely disappeared.

Less pronounced actions on the central nervous system can, in general, be observed in the case of the isomeric compounds (nos. 2, 7, 8 and 9). A striking decrease in the neuro-sedative action is obtained also in the case when the methoxy groups are in the positions 2:4:6 or in 2:4.

In the case of piperonyl morpholide, an increase of the analgesic activity is found, parallel with an increase of toxicity. However, the neuroplegic action of the compound is nearly twice as weak as that of the reference compound.

Partial or complete omission of the ethereal alkyl moiety (4-hydroxy-3:5-dimethoxybenzoylmorpholine and gallic morpholide, respectively) results in the decrease of toxicity, and in the complete lack of central actions.

Lengthening of the ethereal alkyl chain (compounds nos. 13, 14 and 16) gives derivatives of higher toxicity. The tributoxy-derivative is about twenty-two times as toxic as the reference compound. A decreased neurodepressant activity is observed with the triethoxy-derivative, which is completely missing in the case of the tripropoxy compound, but reappears in the tributoxy analogue. An analgesic action, comparable with that of the reference compound, is shown in this class only by the triethoxy derivative.

A slight hypnotic activity is observed in the morpholine derivatives containing allyloxy groups (compounds nos. 11 and 15). These compounds are considerably more toxic. The triallyloxy derivative, for example, is five times as toxic as the reference compound. The depressant activity observed here is a consequence rather of their hypnotic than tranquillizing action.

The introduction of aralkyl groups to replace the ethereal alkyl moiety (compounds nos. 17, 18 and 19) gives derivatives of decreased toxicity, no analgesic action and of half to quarter neuroplegic activity. Similarly, weaker actions result, if the alkyl groups are replaced by acyl groups (compounds nos. 20 and 21). The central nervous action becomes suspended if basic alkyl chains are introduced into the alkoxy group, e.g. in the case of the 4-dimethylaminoethoxy derivative.

Placing a distance between the benzene ring and the carbonylmorpholide group (compound no. 23) gives a derivative which has nearly the same toxicity as the reference compound, but no activity. A similar result is obtained also in the case of further variations, for example, if two carbonylmorpholide groups are introduced into the molecule, or when the benzene ring is further substituted.

The triallyloxybenzoyl piperazine shown in Table 3 has no hypnotic activity, unlike the morpholine derivative. It is three or four times as toxic as the reference compound, its tranquillizing activity being nearly the same, however, subtoxic doses show no analgesic action.

N-(2:3:4-trimethoxybenzoyl)-piperidine is slightly more toxic than the reference compound, it has about the same tranquillizing activity, but its analgesic action is almost doubled.

Summarizing the results, it can be stated, that the neurodepressant and analgesic actions of alkoxybenzamids depend to a certain extent upon the number and positions of the methoxy groups present. To obtain neuroplegic action, it is necessary to have at least two neighbouring methoxy groups. Lack of this condition, or introduction of alkyl, aralkyl and acyl groups, or of a basic side chain into position 4 has a detrimental effect upon the activity of these compounds.

TABLE 3 (a) THE ACUTE TOXICITY, NEUROSEDATIVE AND ANALGESIC ACTION OF ALKOXYBENZOYLMORPHOLINES IN MICE

Compd.	LD_{50} (mg/kg, i.p.)	ED_{50} (50% neurosedative dose) (mg/kg, i.p.)	AD_{50} (50% analgesic dose) (mg/kg, i.p.)
N-(3:4:5-trimethoxybenzoyl)-morpholine*	1320·0	88·0	135·0
N-(3:4-dimethoxybenzoyl)-morpholine (3)	1000·0	92·0	200·0
N-(2:4-dimethoxybenzoyl)-morpholine (2)	920·0	330·0	200·0
Piperonylic acid morpholide (4)	640·0	150·0	79·0
N-(*p*-methoxybenzoyl)-morpholine (1)	720·0	200·0	170·0
N-benzoyl-morpholine	1070·0	600·0 <	160·0
N-(2:4:5-trimethoxybenzoyl)-morpholine (8)	1670·0	128·0	200·0 <
N-(2:3:4-trimethoxybenzoyl)-morpholine (7)	1100·0	132·0	200·0 <
N-(2:4:6-trimethoxybenzoyl)-morpholine (9)	1170·0	320·0	200·0 <
N-(4-hydroxy-3:5-dimethoxy-benzoyl)-morpholine (5)	1500·0 <	300·0 <	200·0 <
Gallic acid morpholide (6)	2000·0 <	300·0 <	200·0 <
N-(3:4:5-triethoxybenzoyl)-morpholine (13)	675·0	200·0	120·0
N-(3:4:5-tri-*n*-propoxybenzoyl)-morpholine (14)	96·0	40·0 <	20·0 <
N-(3:4:5-tri-*n*-butoxybenzoyl)-morpholine (16)	60·0	7·6	20·0 <
N-(3:4:5-triallyloxybenzoyl)-morpholine (15)	285·0	78·0	50·0
N-(4-allyloxy-3:5-dimethoxybenzoyl)-morpholine (11)	670·0	85·0	130·0
N-(4-propoxy-3:5-dimethoxy-benzoyl)-morpholine (10)	670·0	165·0	125·0
N-(4-propargyloxy-3:5-dimethoxy-benzoyl)-morpholine (12)	1250·0 <	145·0	100·0
N-(4-benzyloxy-3:5-dimethoxy-benzoyl)-morpholine (17)	1500·0 <	320·0	200·0 <
N-(3:5-dibenzyloxy-4-methoxy-benzoyl)-morpholine (18)	1500·0 <	320·0	200·0 <
N-(3;4:5-tribenzyloxy-benzoyl)-morpholine (19)	1500·0 <	160·0	200·0 <

TABLE 3 (a)—*contd.*

Compd.	LD_{50} (mg/kg, i.p.)	ED_{50} (50% neurosedative dose) (mg/kg, i.p.)	AD_{50} (50% analgesic dose) (mg/kg, i.p.)
N-(4-ethoxycarbonyloxy-3:5-dimetoxybenzoyl)-morpholine (20)	1750·0	400·0	200·0
N-(4-acetoxy-3:5-dimetoxy-benzoyl)-morpholine (21)	1500·0 <	400·0 <	200·0 <
N-(4-dimethylaminoethoxy-3:5-dimetoxybenzoyl)-morpholine-HCl (22)	720·0	400·0 <	200·0 <
3:4:5-Trimetoxyphenil acetic acid morpholide (23)	1200·0	300·0 <	200·0 <
3:4:5-Trimethoxybenzene-1:3-dicarboxylic acid morpholide (24)	1000·0 <	200·0 <	200·0 <
N-(2-nitro-3:4:5-trimethoxy-benzoyl)-morpholine (25)	1000·0	200·0 <	200·0 <
N-(2-amino-3:4:5-trimethoxy-benzoyl)-morpholine *p*-toluolsulfonicacid salt (26)	860·0	200·0 <	200·0 <
N-(2-dimethylamino-3:4:5-trimethoxybenzoyl)-morpholine (27)	860·0	200·0 <	200·0 <

* This compound is designated by United Works of Pharmaceutical and Dietetic Products (Budapest) under the trade name Trioxazin.

The figures in brackets refer to compounds numbered accordingly in Table 1. Owing to their spare solubility, we were not able to examine the effects of compounds 29 and 33 properly.

TABLE 3 (b) THE ACUTE TOXICITY, NEUROSEDATIVE AND ANALGESIC ACTION OF OTHER ALKOXYBENZOIC ACID DERIVATIVES IN MICE

Compd.	LD_{50} (mg/kg, i.p.)	ED_{50} (50% neurosedative dose) (mg/kg, i.p.)	AD_{50} (50% analgesic dose) (mg/kg, i.p.)
N-(3:4:5-triallyloxybenzoyl)-piperazine HCl (31)	375·0	74·0	100·0
N,N′-bis-(3:4:5-triallyloxy-benzoyl)-piperazine (32)	1500·0	200·0	200·0
N,N′-bis-(3:5-dibenzyloxy-4-metoxy-benzoyl)-piperazine (34)	1500·0	200·0	200·0
N-(2:3:4-trimetoxybenzoyl)-piperidine (28)	1080·0	82·0	64·0
3:4:5-trimethoxyphenylacetic acid thiomorpholide (30)	375·0	150·0	150·0

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