pounds, it has been shown that the net interactions observed with many guest compounds are a combination of pure spatial inclusion formation and other attractive forces. Molecules too large to be included within the cyclodextrin cavities were shown to interact with the cyclodextrins, indicating a mechanism other than pure inclusion formation for these systems (11).

Even though the mechanism involved in the interactions of the phenyl-substituted carboxylic acids with beta-cyclodextrin is believed to consist of both pure inclusion and other attractive forces, the importance of the separation between the carboxyl and phenyl groups in the net interactions observed is suggested by the experimental data. It also was shown that due to the similar magnitude of the pKa's for the various acids, differences in relative acidity could not totally account for the observed differences in these interactions, assuming the interaction is due primarily to the undissociated acid molecule. Unsaturated acids were found to be far less reactive with beta-cyclodextrin than were the corresponding saturated acids. This unique specificity shown by beta-cyclodextrin is being investigated further in these laboratories.

Even though a possible mechanism is suggested, the only manner by which the true structures of the resulting complexes can be established is by an X-ray examination of the isolated interaction products.

The large formation constants and free energies of formation for some of these systems suggest a high degree of stability for the complexes and favorable combining conditions between the acids and beta-cyclodextrin.

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Pharmacological Studies on Some New Acrylic Acid Amide Derivatives

By HUGH J. BURFORD and JAMES B. GILL

A group of newly synthesized acrylic acid amides have been evaluated pharmacologically and chemically for their similarity to the tranquilizer reserpine. The amides differ from reserpine in their behavorial depression effects in that they cause no ptosis at doses which yield decreased locomotor ability and electroshock-threshold lowering. The amides also differ markedly from reserpine in potency. Their therapeutic index (LD_{50}/TD_{50}) is about 2 compared with a value of 19 for reserpine. Finally, the amides differ from reserpine in that their TD_{50}/ED_{50} is around 1 as compared to a value of 3.5 for reserpine. The conclusion is that central nervous system depression and electroshock-threshold lowering by the amides may possibly be mediated by a similar neural mechanism. Also the role of methoxy group substitution on electroshock-threshold lowering potency is discussed.

AZLACTONES, 5,4-oxazolones, and their amide derivatives are interesting, easily synthesized compounds. They have been well studied chemically, especially in relation to the chemistry of penicillin (1–4). However, few pharmacological studies of azlactones or their derivatives have appeared. Cardiac activity was studied by Schueler and Hanna (5) and sedative properties of an amide derivative have been reported by Cronheim *et al.* (6). More recently Robison and Schueler (7) have studied substituted acrylic acid amide derivatives of unsaturated azlactones and reported them to be primarily convulsants, although one member of their series was found to be a long-acting depressant.

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The author's attention was drawn to a series of acrylic acid amides by the observation that all members of the series tested (Table II) caused significant central nervous system depression. Since the central nervous system depression was reminiscent of a tranquilizer type of sedation, studies were subsequently initiated to compare the synthetic amides with reserpine and to determine the mechanism of action of this effect.

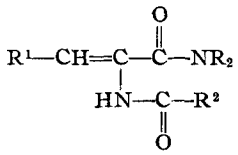
EXPERIMENTAL

Chemical Synthesis.—The unsaturated azlactones used as intermediates were prepared by reacting the appropriate acyl glycine and aldehyde in the presence of acetic anhydride and anhydrous sodium acetate, according to modification of the Erlenmeyer synthesis (2). Cooling of the reaction to 5–10° resulted in much higher yields in the case of pyridinecarboxaldehydes. Commercially unavailable acyl glycines were prepared by the regular Schotten-Baumann reaction. The azlactones were usually recrystallized from 95% ethanol.

The amides were prepared by gently refluxing the azlactones with a slight molar excess of the appropriate amine in dry benzene. The reaction was catalyzed with a small amount of ammonium chloride. The amides were usually recrystallized from benzene–tetrahydrofuran. Those amides not previously reported are shown in Table I. The yields varied from 40 to 80%.

Pharmacological Testing.—Of the compounds synthesized, those which appear in Table II have been most extensively tested pharmacologically. The compounds were screened by administering them to Carworth Farms-1 (CF-1) male mice 20–30 Gm. in doses up to 500 mg./Kg. intraperitoneally in buffered saline, and the gross effects were observed. All compounds tested revealed central nervous system depression which resembled that seen following treatment with tranquilizers. The compounds tested also caused a potentiation of the tonic phase of maximal electroshock convulsions in mice with the result that treated animals died following the

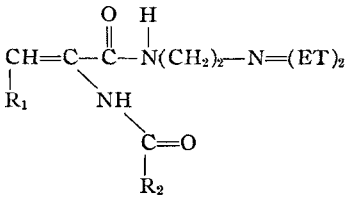
TABLE I.—SUBSTITUTED ACRYLIC ACID AMIDES



No.	R^1	R^2	NR_2	M.p., °C.[a]	Formula	Anal., %[b]	C	H	N
1	TMP[c]	Phenyl	DEEDA[d]	156–157	$C_{25}H_{33}N_3O_5$	Calcd.:	65.91	7.30	7.22
						Found:	65.87	7.39	9.23
2	TMP	Phenyl	Phenylethyl	180–181	$C_{27}H_{29}N_2O_5$	Calcd.:	70.27	6.33	6.07
						Found:	70.35	6.16	6.21
3	TMP	TMP	DEEDA	182–184	$C_{28}H_{39}N_3O_8$	Calcd.:	61.64	7.20	7.70
						Found:	61.52	7.23	7.52
4	3,5 DMP[e]	TMP	DEEDA	171–172	$C_{27}H_{37}N_3O_7$	Calcd.	62.89	7.23	8.15
						Found:	63.88	7.15	8.66
5	3 MP[f]	Phenyl	DEEDA	117–118	$C_{23}H_{29}N_3O_3$	Calcd.:	69.85	7.39	10.63
						Found:	69.59	7.40	10.76
6	3 MP	TMP	DEEDA	163–164	$C_{26}H_{35}N_3O_6$	Calcd.:	64.31	7.27	8.65
						Found:	64.14	7.21	8.89
7	2,4 DMP	Phenyl	DEEDA	112–113	$C_{24}H_{31}N_3O_4$	Calcd.:	67.74	7.34	9.88
						Found:	67.76	7.31	10.00
8	2,4 DMP	3,5 DMP	DEEDA	148–149	$C_{26}H_{35}N_3O_6$	Calcd.:	64.30	7.26	8.65
						Found:	64.09	7.14	8.87
9	4 MP	Phenyl	DEEDA	146–147	$C_{23}H_{29}N_3O_3$	Calcd.	69.85	7.39	10.63
						Found:	70.03	7.48	10.50
10	2,4 DMP	TMP	DEEDA	175–176	$C_{27}H_{37}N_3O_7$	Calcd.:	62.89	7.23	8.15
						Found:	63.01	7.19	8.33
11	3,4 DMP	TMP	DEEDA	166–167	$C_{27}H_{37}N_3O_7$	Calcd.:	62.89	7.23	8.15
						Found:	61.06	7.00	7.31
12	2 MP	TMP	DEEDA	180–181	$C_{26}H_{35}N_3O_6$	Calcd.:	64.30	7.26	8.65
						Found:	64.96	7.27	8.64
13	4-Pyridyl	Phenyl	Diallyl	153–154	$C_{21}H_{21}N_3O_2$	Calcd.:	72.60	6.09	12.10
						Found:	69.54	6.32	11.36
14	4-Pyridyl	Phenyl	Dipiperidide	278–279	$C_{34}H_{32}N_6O_4$	Calcd.:	69.37	5.48	14.28
						Found:	69.13	5.50	14.12
15	4-Pyridyl	Phenyl	Pyrrolidide	213–214	$C_{17}H_{20}N_3O_2$	Calcd.:	71.83	6.03	12.57
						Found:	71.14	6.22	13.19
16	4-Pyridyl	Phenyl	Phenyl	249–250	$C_{21}H_{17}N_3O_2$	Calcd.	73.45	4.99	12.24
						Found:	72.91	5.07	11.79
17	4-Pyridyl	Phenyl	TMP	217–218	$C_{24}H_{23}N_3O_5$	Calcd.:	66.50	5.35	9.69
						Found:	65.59	5.77	9.20
18	TMP	3-Pyridyl	DEEDA	135–140	$C_{24}H_{32}N_4O_6$	Calcd.:	63.14	7.07	12.27
						Found:	61.65	6.95	11.70

[a] Melting points are uncorrected. [b] Analyses are by Alfred Bernhardt, Max Planck Institute, Mulheim, West Germany. [c] TMP, 3,4,5-Trimethoxyphenyl. [d] DEEDA, *N,N*-Diethylethylenediamine. [e] DMP, Dimethoxyphenyl. [f] MP, Methoxyphenyl.

TABLE II.—PHARMACOLOGIC PARAMETERS OF SUBSTITUTED ACRYLIC ACID AMIDES



R_1	R_2	Compd.	LD_{50}[e]	TD_{50}[e]	$\frac{LD_{50}}{TD_{50}}$	ED_{50}[e]	$\frac{TD_{50}}{ED_{50}}$	Potency Order, ED_{50}	Time ED_{50} Test, min.
3-MPH[b]	PH[a]	*1*	78	42	1.9	50	0.84	2	7
4-MPH	PH	*2*	153	94	1.6	112	0.84	7	7
2,4-DMP[c]	PH	*3*	38	23	1.7	26	0.87	1	7
3,4,5-TMP	PH	*4*	150	70	2.1	52	1.35	3	7
2,4-DMP	3,5-DMP	*5*	145	62	2.3	98	0.63	6	7
2-MPH	3,4,5-TMP[d]	*6*	190	88	2.2	72	1.22	5	7
3-MPH	3,4,5-TMP	*7*	93	56	1.7	59	0.95	4	7
4-MPH	3,4,5-TMP	*8*	230	118	1.9	127	0.93	8	7
3,4,5-TMP	3,4,5-TMP	*9*	375	216	1.7	300	0.72	9	7
	Reserpine		102	5.2	19	1.5	3.50	0	60

[a] Ph, Phenyl. [b] MP, Methoxyphenyl. [c] DMP, Dimethoxyphenyl. [d] TMP, Trimethoxyphenyl. [e] All doses mg./Kg. i.p

administration of a maximal shock. This observation pointed up the necessity of studying threshold-shock phenomena rather than maximal shock situations. In addition, some compounds were tested for their effects on rat blood pressor responses to tyramine. The above observations constituted the preliminary steps of pharmacological testing.

Lethal Dose Determinations.—Groups of ten CF-1 male mice for each of three dose levels were used which would yield values between, but not including, 0 and 100% mortality. All doses were administered intraperitoneally. LD_{50}'s were determined by a simplified method of probits (8).

Neurotoxicity Test for Time of Peak Drug Effect.—The end point for minimal neurotoxicity was based on muscular incoordination, measured by the inability of a mouse to remain for 1 min. on a horizontal oak rod (2 cm.) rotating at 5 r.p.m. (9). Doses of the compounds corresponding to 0.9, 0.8, 0.7, and 0.6 of the LD_5 were administered to groups of ten mice each. The animals were tested each minute for a 10-min. period following injection of the compound. The test was then repeated at 20-min. intervals thereafter up to 3 hr. or until none of the animals failed the test. The time of peak minimal neurotoxicity was determined for 50% of the animals by a method of simplified probits and labeled TD_{50} (Table II).

Minimal Electroshock Threshold-Lowering Test.—Animals were shocked for minimal electroshock threshold with a Woodbury-Davenport (10) apparatus, each 48 hr. according to the method of Brown *et al.* (11). When thresholds were established, the mice, in groups of ten, were pretreated with the same doses as those used for the minimum neurotoxicity test. The animals were then shocked with a current 20% below the predetermined thresholds. The shocks were administered *via* saline-wetted corneal electrodes at the time of peak drug effect as determined from the minimum neurotoxicity test and at hourly intervals thereafter for 3 hr. The dose of drug lowering the threshold 20% in half of the animals was obtained by a simple method of probits and labeled the ED_{50} (Table II).

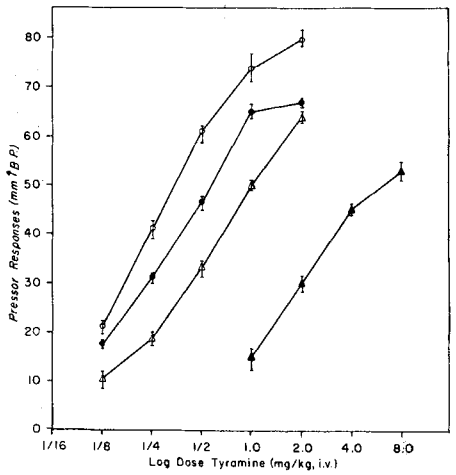


Fig. 1.—Effect of acrylic acid amide derivatives and reserpine on the tyramine pressor responses in rats. Key: O, ten normal rats; ●, compound *9*, 76 mg./Kg./day, administered for 10 days to six rats; △, compound *4*, 50 mg./Kg./day, administered for 10 days to five rats; ▲, reserpine, 1.0 mg./Kg. i.p., administered for 4 hr. to three rats.

Reserpine was also studied in comparison to the acrylic acid amide derivatives. Studies were carried out to determine the per cent threshold lowering in CF-1 male mice at various times following the intraperitoneal administration of reserpine.[1]

Tyramine Pressor Response.—Acutely, these substituted acrylic acid amides caused a transient lowering of blood pressure in pentobarbital anesthetized CFN male rats (200–300 Gm.). When administered daily in 0.5 to 0.75 LD_5 doses by the intraperitoneal route for 6 to 10 days, the pressor response to tyramine was found to be significantly lowered when compared to normal nontreated animals (Fig. 1). Rat blood pressure was recorded

[1] Reserpine was supplied by Ciba Pharmaceutical Co. Marketed as Serpasil.

from the right common carotid artery using a P 32-A Statham transducer and a Brush recorder. Doses of tyramine were administered each 15 min. in increasing doses from 1/16 to 8 mg./Kg. *via* the left jugular vein. The rises in mean blood pressure obtained were plotted *versus* the dose of tyramine administered in both normal and treated animals.

RESULTS AND DISCUSSION

Effect on Pressor Responses.—Of the compounds listed in Table II, only numbers *4* and *9* were studied for the effect of chronic administration to rats on the subsequent tyramine-pressor dose-response curve. Figure 1 summarizes the data from these experiments. The bars indicate standard errors. The upper curve represents the tyramine-pressor responses obtained in ten normal Carworth Farms male rats. The pressor responses vary from 22 mm. increase in blood pressure at 1/8 mg./Kg. to 80 mm. increase in blood pressure at 2 mg./Kg. The second curve was obtained from six animals which had been treated with α-3,4,5-trimethoxybenzoylamino-β-(3′,4′,5′-trimethoxyphenyl) acrylic acid diethylaminoethyleneamide (*9*, Table II) at a dosage level of 76 mg./Kg./day for 10 days. The pressor responses vary from 18 to 67 mm. rise in mean blood pressure at 1/8 to 2 mg./Kg. doses inclusive. The third curve was similarly obtained from five animals which had been treated with α-3,4,-5-trimethoxybenzoylamino-β-(phenyl) acrylic acid diethylaminoethyleneamide (*4*, Table II) at a dosage level of 50 mg./Kg./day for 10 days. The pressor responses vary from 10 to 63 mm. rise in mean blood pressure at 1/8 to 2 mg./Kg. doses inclusive. The bottom curve was obtained from three animals pretreated with reserpine for 4 hr. The pressure responses varied from 15 to 50 mm. rise in mean pressure from 1 to 8 mg./Kg. inclusive. It is noteworthy that the tryamine pressor curves following chronic pretreatment of rats with compounds *9* and *4* were shifted to the right significantly from the curve obtained in normal rats. The abscissa is zero for these curves at the 1/16-mg./Kg. dose. This indicates a loss of activity for tyramine due to pretreatment with the azlactone derivatives. When one compares the tyramine pressor curve obtained with reserpine with the others in Fig. 1, it is immediately evident that the reserpine curve is shifted not only down but to the right as well. This type of loss of activity of tyramine is reminiscent of competitive antagonism. Current theory would explain this effect of reserpine as being due to depletion of norepinephrine stores in the vicinity of the receptor. Furthermore, tyramine is felt to act by releasing norepinephrine which then may activate a receptor mechanism (12). The effects of the acrylic acid amides are more difficult to explain. If they are acting as nonspecific antagonists a variety of nonend organ receptor sites might be implicated. One such site may well be the sympathetic ganglion. Some of these acrylic acid amides have been demonstrated to have a ganglionic blocking action at the adrenal medulla (13). Studies are currently being planned to determine if acrylic acid amide derivatives cause depletion of peripheral catechol amine stores.

Effects on Threshold Lowering.—Before the effects of the compounds listed in Table II on electroshock threshold could be determined, the lethal dose curves and the minimal neurotoxicity data had to be obtained. These values are reported in Table II and were obtained as stated in the methods section. Also, before the threshold-lowering data obtained with the acrylic acid amide derivatives could be compared with threshold-lowering data obtained with reserpine, a study of the effects of reserpine on threshold lowering following intraperitoneal administration had to be completed. Jenney (14) first reported the ability of oral reserpine to lower electroconvulsive threshold. Chen *et al.* (15) followed with further demonstration of this phenomenon with chemical convulsants. However, a complete time study of the type needed for this work was not available in the literature. Figure 2 summarizes the data obtained in our study. Doses of reserpine ranging from 0.5 to 8.0 mg./Kg. were employed. The mice were tested for percentage threshold lowering at times up to 7.0 hr. following the intraperitoneal administration of reserpine. These data indicate a progressive increase in threshold lowering as expected. The smallest detectable value was 10% with some mice at 0.5 mg./Kg. The largest value ever achieved was 50% with the 6 and 8-mg./Kg. doses.

The studies discussed thus far were of a preliminary nature and were designed to test the effects of acrylic acid amide derivatives on the cardiovascular system and to measure the effects of intraperitoneal reserpine on convulsive threshold lowering. The studies on blood pressure revealed that the acrylic acid amide derivatives studied possessed some degree of reserpine-like effect. Therefore, subsequent work will be presented which was designed to study the effects of acrylic acid amide dervatives on convulsive threshold.

Table II summarizes the studies conducted which led to the ultimate systematic determination of the convulsive threshold-lowering effects of compounds *1–9*. The LD_{50} data were obtained on groups of

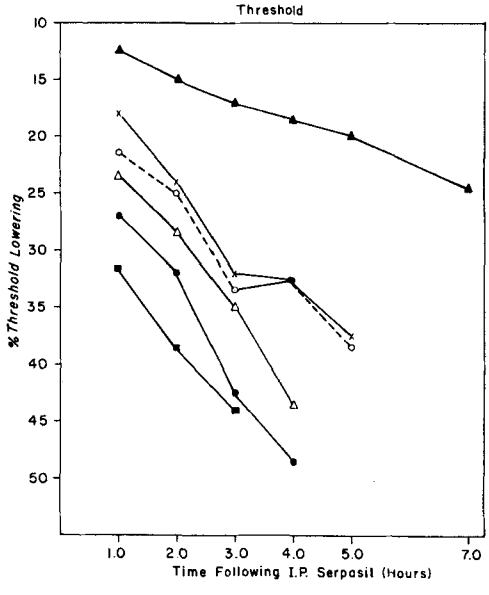


Fig. 2.—Effect of reserpine on electroshock threshold lowering in mice. Key: ▲, 0.5 mg./Kg.; ×, 1.0 mg./Kg.; ○, 2.0 mg./Kg.; △, 4 mg./Kg.; ●, 6 mg./Kg.; ■, 8 mg./Kg.

male CF-1 mice as described in the methods section. These graphic data were also extrapolated to obtain an approximate LD_5 dose for each of the compounds studied. The LD_5 doses thus obtained were used to calculate therapeutic doses for determination of peak time of minimal neurotoxicity (TD_{50}) and the determination of the dose of drug causing a 20% decrease in minimal electroshock threshold (ED_{50}). The therapeutic doses employed were arbitrarily chosen 10, 20, 30, and 40% lower than the LD_5 dose. The TD_{50} test was conducted on groups of CF-1, male mice as outlined in the methods section. The values obtained were expressed as per cent of animals which failed the test at various times after the therapeutic doses of the drug were administered. The data revealed a family of four curves whose maximum values occurred at 7 min. following drug administration. These maximum values, representing peak effectiveness for minimal neurotoxicity, were plotted *versus* the doses of the drugs used in order to obtain the values found in the TD_{50} column of Table II. The ED_{50} test was conducted on groups of male CF-1 mice as outlined in the methods to yield data expressed as percentage of animals experiencing a 20% lowering of minimal electroshock threshold at the peak time for minimal neurotoxicity (7 min.) when treated with the same therapeutic doses as calculated for the minimal neurotoxicity test. The percentage values so obtained were plotted *versus* the doses of drug used in order to obtain the values in the ED_{50} column of Table II.

The results from studies conducted using reserpine are listed in Table II for comparison with the data obtained on the nine acrylic acid amide derivatives listed. It should be pointed out that 60-min. test time for reserpine was chosen as the shortest time following administration when neurotoxic and threshold-lowering effects could be demonstrated by using reasonable therapeutic doses.

In order to facilitate interpretation of the data in Table II, the ratios LD_{50}/TD_{50} and TD_{50}/ED_{50} have been included. The therapeutic index (LD_{50}/TD_{50}) for minimal neurotoxicity for the acrylic acid amides reveals a range of values from 1.6 to 2.3. Thus, the acrylic acid amides have a rather low therapeutic index, especially when compared with reserpine (19). The LD_{50} and TD_{50} values are both rather high indicating relatively innocuous compounds of low neurotoxicity. The ratio (TD_{50}/ED_{50}) values for all nine acrylic acid amides are grouped around 1.0, ranging from 0.63 to 1.35. Since these values are so closely grouped around 1.0, the authors feel this may indicate that minimal neurotoxicity and threshold lowering are mediated *via* the same neural mechanism. All of the data in Table II concerning central nervous system depression and lowering of electroshock threshold was determined at the time of peak minimal neurotoxicity. For the acrylic acid amide derivatives, TD_{50} and ED_{50} observations were made at later times than the peak time for minimal neurotoxicity (7 min.). These observations indicated that central nervous system depression as revealed by the rotarod test and the observation of reduced locomotor activity is paralleled by a lowering of electroshock threshold. This would also indicate that a common mechanism may underlie both central depression and electroshock threshold lowering.

Because the acrylic acid amide derivatives were compared to reserpine, a final comment concerning behavorial depression in animals, receiving the two types of compounds is in order. In animals receiving reserpine the behavorial depression as revealed by ptosis and a hunched posture was noted as well as the reduced locomotor activity and electroshock threshold lowering already documented. However, in animals receiving the acrylic acid amide derivatives no ptosis was observed, although the hunched posture and general behavioral depression remained.

Relation of Methoxy Substitution to Action.—In the group of acrylic acid amides (Table II, *1–4*) substituted with phenyl at R_2, methoxy groups at positions 2 and 3 of the phenyl ring confer the greatest degree of threshold-lowering potency as revealed in the listing of ED_{50} potency. Of these two positions, *2* is the more likely to produce threshold-lowering potency. Comparing compounds *2* and *3*, we find a 7 and 1 potency order, respectively. Since the group common to these compounds is 4-methoxy, we would conclude the 2-methoxy position is the more important substitution for conferring threshold-lowering potency.

When considering compounds *6–9* of Table II, we see the effects of substituting methoxy groups on the R_1 phenyl when R_2 is a 3,4,5-trimethoxyphenyl group in each case. As in compounds *1–4*, the 2 and 3-methoxy group substitutions seem to be most important for conferring threshold-lowering potency on these acrylic acid amide derivatives.

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