Synthesis of Some Substituted Aminoacetylbenzamides for Pharmacological Study

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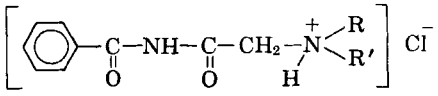
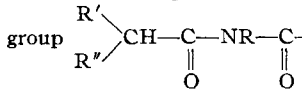
The preparation of various aminoacetylbenzamides by the condensation of chloroacetylbenzamide with the appropriate secondary amine is described. The catalytic effect of pyridine on this condensation is reported. These compounds have been prepared as potential anticonvulsants.

TABLE I.—SUBSTITUTED AMINOACETYLBENZAMIDES

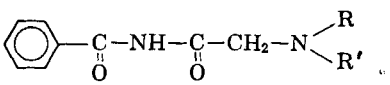


Compd.	R	R′	Yield, %	Pyridine, % Yield	M.p.,[a] °C.	N, % Calcd.	N, % Found
							14.90
1	Hydrogen	Hydrogen	38	...	95	15.71	15.00
							10.08
2	Ethyl	Ethyl	20	75	220–221	10.34	10.22
							6.87
3	Phenyl	Phenyl	...	60	241–243	7.63	8.23
							8.14
4	*n*-Butyl	*n*-Butyl	23.7	69	295–297	8.58	8.90
							6.80
5	Benzyl	Benzyl	0	72	221–222	7.09	7.28
							8.16
6	*i*-Propyl	Benzyl	0	59	219–220	8.05	7.84
							9.94
7	Ethyl	Phenyl	6.8	61	232	8.78	8.06
							9.97
8	Benzyl	Methyl	11.2	64	232–233	9.10	9.71
							9.13
9	*n*-Propyl	*n*-Propyl	26.3	70	269–270	9.37	9.69
							8.97
10	*i*-Propyl	*i*-Propyl	18	68	204–205	9.31	9.71
							8.23
11	*i*-Butyl	*i*-Butyl	29	73	276–277	8.57	8.83
							6.04
12	*n*-Heptyl	*n*-Heptyl	50	50	253–255	6.81	7.54
							10.02
13	$O(CH_2CH_2)_2$[b]		70	72	112–115	9.48	9.43
							10.04
14	$CH_2(CH_2CH_2)_2$[b]		76	78	104–105	9.90	9.27

[a] All melting points are uncorrected and were determined by use of a Thomas-Hoover capillary melting point apparatus. [b] For compounds *13* and *14*, R and R′ represent morpholino and piperidino, respectively.

THE STRANGE convulsions, trances, and other manifestations of epilepsy have been a source of suffering to humanity for centuries. At present, it hardly can be stated that epilepsy can be controlled completely. Although the drugs currently in use can reduce the incidence of epileptic seizures and, in favorable cases, control them entirely, most anticonvulsants have undesirable side effects. A review of the general structure of the anticonnulsants in clinical use at the present time will show that most of the drugs in this class contain a common group  in which R is hydrogen or alkyl and R′ and R″ are alkyl, phenyl, or hydrogen. In the most active compounds, at least one substituent (R′ or R″) is phenyl.

Clinically useful anticonvulsants having this structural feature are phenobarbital and *N*-methylphenobarbital, the hydantoins introduced by Putnam and Merrit (1), the oxazolidinediones (2), α-methyl-α-phenylglutarimide (3), 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione (4), *N*-methyl-α-phenylsuccinimide (5), phenylacetylurea (6), and *N*-acetylphenylacetamide and *N*-methyl-*N*-phenylacetamide (7). Since this structural unit is found also in the substituted aminoacetylbenzamides



these compounds were prepared as potential anticonvulsants. A suitable series could be prepared

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by reacting *N*-chloroacetylbenzamide with various amines.

EXPERIMENTAL

Chloroacetylbenzamide.—This intermediate was prepared according to the method of Cadwallader and LaRocca (8).

Preparation of Substituted Aminoacetylbenzamides.—*Aminoacetylbenzamide.*—*N*-Chloroacetylbenzamide (0.05 mole) was dissolved in 8 ml. of anhydrous benzene with the aid of heat. Dry ammonia was passed through the hot solution. On cooling, unreacted chloroacetylbenzamide precipitated and was filtered. The filtrate was evaporated until aminoacetylbenzamide precipitated. The precipitate was recrystallized three times from petroleum ether.

N-Diethylaminoacetylbenzamide Hydrochloride.—*N*-Chloroacetylbenzamide (0.05 mole) was refluxed for 5 hr. with 0.05 mole of diethylamine in 8 ml. of anhydrous benzene. Diethylaminoacetylbenzamide hydrochloride precipitated and was removed by filtration while hot. The precipitate was washed with hot benzene. The filtrate and washings were combined and distilled to remove benzene and any unreacted amine. The residue was found to be benzamide. Its presence probably was due to the hydrolysis of chloroacetylbenzamide because of the acidic nature of imino hydrogen. In an attempt to prepare the free amine, the experiment was repeated using pyridine in a molar ratio to take up the hydrogen chloride gas produced during the reaction. However, instead of free amine, the hydrochloride salt of diethylaminoacetylbenzamide precipitated. The precipitate was removed by hot filtration and washed repeatedly with hot anhydrous benzene. The yield obtained was 75%, in contrast to 20% without the pyridine, indicating that the pyridine had acted as a catalyst.

All subsequent experiments were carried out in a similar manner, with and without pyridine as a catalyst. The effects of pyridine on yield, melting points, and analytical data are summarized in Table I.

A rather extensive survey of the pharmacological properties of these compounds has been completed.[1] Although the compounds are relatively nontoxic (oral LD_{50} ranging from a minimum of 750–1000 mg./Kg. to a maximum of over 2000 mg./Kg.), they also are devoid of significant response to the tests employed. In addition to anticonvulsant activity, representative compounds were tested for systemic antibacterial, antifungal, antiparasitic, and psychotropic actions.

SUMMARY

The synthesis of 13 new substituted aminoacetylbenzamides is described, and the catalytic effect of pyridine on the condensation of secondary amines and chloroacetylbenzamide is reported. These compounds have been screened for pharmacological activity.

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[1] The authors are indebted to Dr. U. R. Schock, Abbott Laboratories, North Chicago, Ill., for the pharmacological screening data.

Modification of the Spectrophotofluorometric Determination of Griseofulvin

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The spectrophotofluorometric method of Bedford *et al.* for the determination of griseofulvin is rendered more reliable and sensitive by measuring the fluorescence in anhydrous methanol.

LEVELS OF griseofulvin in the blood of laboratory animals or humans are usually determined by the fluorometric method of Bedford *et al.* (1). The fluorescence of griseofulvin in 1% ethanol at 450 mμ (uncorrected) is measured after activation at 295 mμ (uncorrected).

Following the procedure of Bedford *et al.* (1) in the past, the authors were often unable to dissolve the residue of extracted griseofulvin in 1% ethanol, and the resulting faintly turbid suspensions gave erratic fluorescence spectra. To overcome this difficulty at first, ethanol was used (2, 3). Since ethanol is often contaminated with traces of highly fluorescent impurities, it had to be redistilled before use. Later, the procedure was modified to use reagent grade methanol instead of 1% ethanol. This offered two advantages: (*a*) the intensity of fluorescence of griseofulvin is increased nearly twofold (Table I), and (*b*) commercial reagent grade methanol does not contain fluorescent impurities. As with ethanol (2), the fluorescence maximum in methanol was shifted to 420 mμ (uncorrected) (Fig. 1). The activation maxima remained unchanged at 295 and 335 mμ (uncorrected).

The procedure of Bedford *et al.* (1) using 1%

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