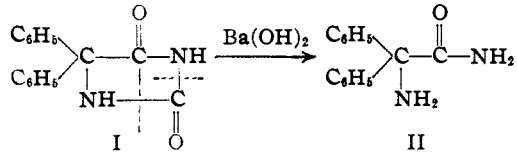
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

N,N'-Substituted α-Aminodiphenylacetamides

BY JOHN H. BILLMAN AND PHIL HARTER HIDY[1]

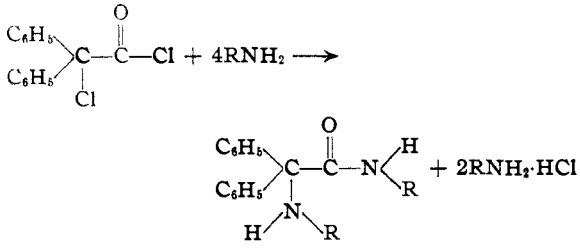
The results of the alkaline hydrolysis of 5,5-diphenylenehydantoin[2] suggest that one of the possible products from an alkaline hydrolysis of 5,5-diphenylhydantoin (I) would be α-aminodiphenylacetamide (II).



Since the biological hydrolysis of the hydantoin might also produce II, we decided to prepare α-aminodiphenylacetamide and a number of its N,N'-substituted derivatives in order to compare their anticonvulsant action with that of 5,5-diphenylhydantoin.

Although a literature search revealed that compounds of this type have never been tested pharmacologically, we felt that they should also possess antispasmodic activity because numerous amides[3] as well as derivatives of amino acids[4] are active spasmolytics.

The amides in Table I were prepared from α-chlorodiphenylacetyl chloride and the appropriate amine according to the equation



The method of Bickel[5] and modifications suggested by McKenzie[6] for the preparation of α-chlorodiphenylacetyl chloride gave only poor yields. However, we were able to obtain yields as high as 80% by varying their experimental conditions.

Pharmacological tests were made on the compounds in Table I to determine their anticonvulsant and antispasmodic activity. The unsubstituted amide II and the di-*p*-phenetidine derivative, respectively, showed anticonvulsant activities of about one-half and three-fourths that of 5,5-diphenylhydantoin. The antispasmodic tests revealed α-aminodiphenylacetamide (II) to be the most active of the compounds tested. The *n*-propylamine and the *n*-butylamine derivatives caused contraction of an isolated strip of rabbit intestine rather than relaxation.

TABLE I

SUBSTITUTED α-AMINODIPHENYLACETAMIDES

Amine used	M. p. of amide, °C.	Yield, %	Nitrogen, % Calcd.	Found
Ammonia[a]	144	18	...	...
Methylamine	118	5	11.02	10.68
Ethylamine	132	33	9.93	9.87
n-Propylamine	115	52	9.05	9.23
Diethylamine[b]	67	38	8.24	8.25
n-Butylamine	112.5	26	8.24	8.35
n-Amylamine	104	12	7.64	7.56
Aniline[a]	180	..	...	...
p-Phenetidine	121.5	57	6.01	6.25

[a] Klinger and Nickell, *Ann.*, **390**, 365 (1912). [b] Barré, *Ann. Chim.*, [10] **9**, 268 (1928).

We are deeply grateful to Eli Lilly and Company for the grant which made this work possible and to Drs. H. M. Lee, C. E. Powell and E. E. Swanson of the same company who ran the pharmacological tests.

Experimental

α-Chlorodiphenylacetyl Chloride.—To 120 g. of phosphorus pentachloride in a 500-ml. flask, immersed in an ice-water bath, is added 60 g. of benzilic acid. A ground glass jointed condenser set for downward distillation was fitted to the flask and a suction flask used as the receiver. After an interval of one to ten minutes, depending on how vigorously the reaction mixture is shaken, the evolution of hydrogen chloride begins and is allowed to proceed to completion. The mixture is then heated in an oil-bath under 12 mm. pressure at such a rate that a temperature of 145° is reached in thirty minutes, after which the flame is removed, but the vacuum is maintained until no further distillation takes place. After cooling to room temperature, the reaction mixture is poured into a mixture of 800 cc. of water and 200 cc. of ice and stirred vigorously. The pulverized lumps of crude product are dissolved without heating in 500 cc. of low-boiling petroleum ether and the solution dried as quickly as possible with anhydrous sodium sulfate. This solution is evaporated, under re-

(1) Eli Lilly Fellow.

(2) McCown and Henze, THIS JOURNAL, **64**, 689 (1942).

(3) Junkmann, *Arch. Expil. Path. Pharmakol.*, **186**, 552 (1933); **195**, 175 (1940), Halpern, *Arch. intern. Pharmacodynamine*, **59**, 149 (1938).

(4) Eisleb and Schaumann, *Deut. Med. Wochschr.*, **65**, 967 (1939); Schaumann, *Arch. Expil. Path. Pharmakol.*, **196**, 8 (1940).

(5) Bickel, *Ber.*, **22**, 1538 (1889).

(6) McKenzie and Boyle, *J. Chem. Soc.*, **119**, 1137 (1921).

duced pressure, to one-half its original volume and then cooled in a refrigerator for twelve hours. Thirty grams of α-chlorodiphenylacetyl chloride, melting at 48.5–49.5°, is obtained. Further concentration of the mother liquor yields a second crop of crystals weighing 15–25 g.; yield, 65–80%.

Preparation of N,N'-Substituted α-Aminodiphenylacetamides.—To 0.06 mole of α-chlorodiphenylacetyl chloride, dissolved in about 75 ml. of dry ether, 0.12 mole of an amine is added slowly with shaking. Ammonia, methylamine and ethylamine are added by bubbling the gas through the solution kept at 0°. The reaction mixture is allowed to stand at room temperature for three to five hours and is then filtered to remove the amine hydrochloride. The ether solution is concentrated to 25 ml., placed in a pressure bottle and 0.12 mole of amine added. After sealing the bottle the reaction mixture is maintained at 50–60° for several days. The contents are filtered and the filtrate extracted three times with 15-ml. portions of dilute hydrochloric acid. In order to extract the diphenetidine derivative it is necessary to use concentrated hydrochloric acid. The combined acid washings are almost neutralized with solid sodium carbonate and brought to neutrality with a saturated solution of the carbonate. The neutral solution is boiled gently to remove excess amine. When the odor of amine is no longer detectable, the solution is decanted and the remaining, solid or liquid, substituted α-aminodiphenylacetamide is purified by dissolving in about 25 ml. of boiling methyl alcohol and diluting with hot water until a faintly turbid solution results.

Summary

1. A modified procedure has been described for the preparation of α-chlorodiphenylacetyl chloride,

2. A number of substituted derivatives of α-aminodiphenylacetamide have been prepared. Pharmacological tests show that some of these compounds possess both anticonvulsant and antispasmodic activity.

BLOOMINGTON, INDIANA RECEIVED JANUARY 28, 1943

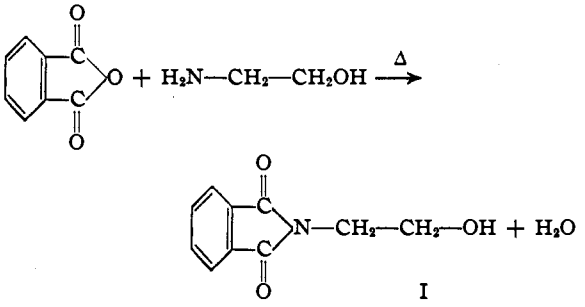
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Amino Acids. I. Glycine

BY JOHN H. BILLMAN AND EARL E. PARKER

The customary methods used for the synthesis of glycine are the amination of a halogenated acetic acid or the hydrolysis of aminoacetonitrile formed from methyleneaminoacetonitrile.[1]

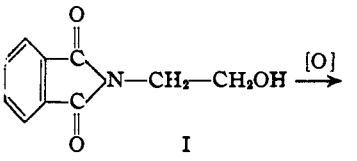
A new method for the synthesis of glycine has been developed which involves the reaction of ethanolamine and phthalic anhydride to produce β-hydroxyethylphthalimide (I) in a 99% yield.[2]



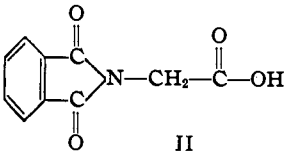
I

A study of the oxidation of β-hydroxyethylphthalimide (I) to phthalylglycine (II) was made and found to give an 89–93% yield of crude material when acidified potassium dichromate was used as the oxidizing agent.

It was unnecessary to purify the phthalylglycine which was readily hydrolyzed by refluxing

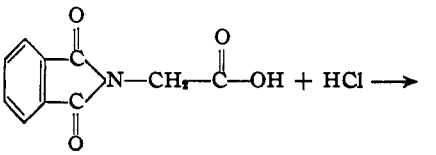


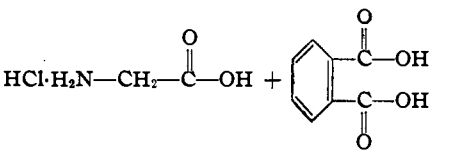
I



II

with 18% hydrochloric acid solution for ten hours. The phthalic acid formed by hydrolysis of (II) was removed by filtering the reaction mixture after cooling in an ice-water bath. Upon evaporation of the filtrate glycine hydrochloride was obtained.





The over-all yield of glycine hydrochloride from ethanolamine was 79–85%.

(1) "Organic Syntheses," Coll. Vol. I, 1941, pp. 298–301

(2) Wenker. THIS JOURNAL, 59, 422 (1937).