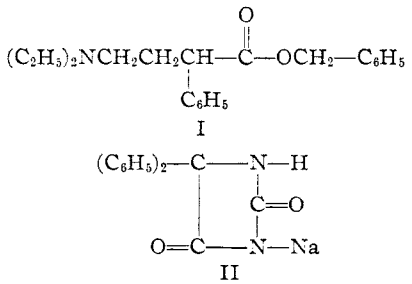
[CONTRIBUTION OF THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Anticonvulsants. V.[1] Esters of γ-Diethylamino-α-phenylbutyric Acid

BY JOHN H. BILLMAN, WALTER T. SMITH, JR.,[2,3] AND JOHN L. RENDALL[3]

One of the most important properties of a good anticonvulsant is to prevent the occurrence of convulsions and at the same time allow the patient to carry on his normal activities, while taking regular doses of the drug. Most of the compounds which have been proposed as anticonvulsants do not completely fulfill this requirement. Therefore it is desirable to investigate all series of compounds showing promise of being good anticonvulsants.

It was found by one of the authors that benzyl γ-diethylamino-α-phenylbutyrate (I) was one and one-half times more active than Dilantin (II),

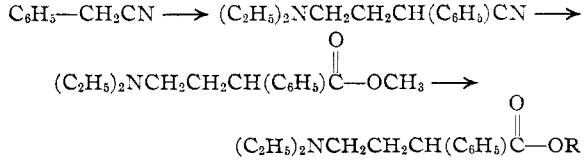


I

II

which is one of the better drugs now available for epileptics. However, this ester is not suitable for general use because of its rather high toxicity.

The purpose of this investigation was to prepare compounds closely related to benzyl γ-diethylamino-α-phenylbutyrate which might retain or improve upon the anticonvulsant activity of that compound and at the same time be less toxic. In general, esters of benzyl alcohol show undesirable toxic effects. Therefore, it was decided to use substituted benzyl alcohols and related compounds in an attempt to modify the toxicity. In all, nineteen esters of γ-diethylamino-α-phenylbutyric acid were prepared (Table I) by means of the sequence of reactions



The pharmacological tests on the esters prepared will be reported elsewhere.

TABLE I

ESTERS OF γ-DIETHYLAMINO-α-PHENYLBUTYRIC ACID

	Alcohol used	Yield, %	B. p. °C.	Mm.	% Nitrogen Calcd.	% Nitrogen Found	Moles of alcohol[a]	Time of heating, hr.
1	Benzyl	88	185–187	3	4.31	4.34	0.20	6
2	*o*-Chlorobenzyl	70	200–205	1	3.89	3.79	.20	6
3	*p*-Chlorobenzyl	78	165–167	1	3.89	3.85	.20	6
4	*m*-Methylbenzyl	53	203–205	2	4.13	4.01	.17	6
5	*o*-Methoxybenzyl	65	177–180	1	3.75	3.53	.20	88[b]
6	*p*-Methoxybenzyl	68	209–212	1.5	3.75	3.97	.20	6
7	Piperonyl	57	184–187	1	3.79	3.88	.16	6
8	*o*-Ethoxybenzyl	32	191–195	1	3.79	3.68	.20	6
9	3,4-Diethoxybenzyl	41	150–153	1.5	3.39	3.30	.18	6
10	α-Butylbenzyl	16	178–180	1	3.67	3.51	.20	6[c]
11	Hexahydrobenzyl	29	157–160	1	4.23	4.40	.11	83
12	Cinnamyl	74	200–204	1	3.99	4.02	.40	24
13	Dihydrocinnamyl	49	181–185	1	3.96	3.99	.40	24
14	β-Phenylethyl	63	170–173	1	4.13	4.21	.42	24
15	α-Naphthylmethyl	70	230–235	1	3.73	3.79	.20	28
16	Allyl	84	115–118	0.5	5.40	5.54	2.20	72[d]
17	*n*-Amyl	53	113–118	1	4.59	4.55	0.40	42[e]
18	Tetrahydrofurfuryl	25	173–175	1	4.39	4.47	.20	6
19	γ-Diethylamino-β,β-dimethylpropyl	33	118–121	0.5	7.43	7.44	.11	78

[a] Ten grams (0.04 mole) of methyl γ-diethylamino-α-phenylbutyrate were used with the number of moles of alcohol indicated. [b] Heating for sixteen hours gave a 24% yield. [c] Longer heating did not increase the yield. [d] This reaction mixture was heated on a steam-bath. [e] Reaction temperature, 120°.

Acknowledgment.—The authors wish to thank Eli Lilly and Company for the grant which made this work possible.

Experimental

γ-Diethylamino-α-phenylbutyronitrile.—In a 1-liter 3-necked flask fitted with wire stirrer, a reflux condenser

(1) Paper IV, Billman, Ward and Hidy, THIS JOURNAL, **67**, 130 (1945).

(2) Submitted to the Faculty of the Graduate School in partial fulfilment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(3) Eli Lilly Fellow.

and a device for adding solids[4] was placed 94 g. (0.80 mole) of benzyl cyanide, 110 g. (0.80 mole) of β-diethylaminoethyl chloride, and 270 ml. of benzene (dried over potassium hydroxide). To this was added slowly 32 g. (0.80 mole) of sodium amide while the flask was kept well cooled in an ice bath. The contents was then allowed to warm up to room temperature and finally heated in an oil-bath at 80° for one hour. The reaction mixture was allowed to stand overnight and then treated with 150 ml. of water with stirring. The two layers which formed were separated and the benzene layer was dried over "Drierite." Evaporation of the solvent and distillation of the residue gave 128 g. of γ-diethylamino-α-phenylbutyronitrile, b. p. 120–122° (1 mm.). This yield is 74%.

The above preparation is an improvement on the method of Eisleb,[5] giving a 14% increase in yield.

Methyl γ-Diethylamino-α-phenylbutyrate.—A solution of 86.6 g. (0.40 mole) of γ-diethylamino-α-phenylbutyronitrile in 80 g. each of water, sulfuric acid and glacial acetic acid was refluxed for thirty-five hours in an oil-bath kept at 130°. The water and acetic acid were removed by distillation under reduced pressure. Two 100 ml. portions of methanol were added and also removed under reduced pressure. To the residue was added 240 ml. of methanol and 120 ml. of sulfuric acid. The solution was refluxed for nine and one-half hours, cooled, poured onto ice and made strongly alkaline with ammonium hydroxide. The ester was extracted with three-200 ml. portions of ether. The extracts were dried over "Drierite" and distilled. The yield was 83.8 g. or 84% of theory; b. p. 130–135° (3 mm.), $n^{25}D$ 1.495.

***p*-Chlorobenzyl γ-Diethylamino-α-phenylbutyrate.**—In a 50-ml. Erlenmeyer flask was placed 28.5 g. (0.20 mole) of *p*-chlorobenzyl alcohol, 10 g. (0.04 mole) of methyl γ-diethylamino-α-phenylbutyrate, and about 0.3 g. of solid sodium ethoxide. The flask was heated for sixteen hours in an oil-bath maintained at 150°. The excess alcohol was removed by distillation. The *p*-chlorobenzyl ester was collected at 165–167° (1 mm.) and weighed 11.2 g. The yield was 78% based on methyl ester of 48.5% based on phenylacetonitrile.

3,4-Diethoxybenzyl γ-Diethylamino-α-phenylbutyrate.—This ester could not be directly distilled from the the reaction mixture. It was extracted from the reaction mixture with 5% hydrochloric acid. The acid solution was then made alkaline with ammonium hydroxide and extracted with ether. The ester could then be distilled after evaporating off the ether.

Substituted Benzyl Alcohols.—Most of the substituted benzyl alcohols were prepared by the reduction of the corresponding benzaldehydes by the method of Adams and Carothers.[6]

Summary

Nineteen new esters of γ-diethylamino-α-phenylbutyric acid have been prepared to be tested for antispasmodic and anticonvulsant activity. The best method for the preparation of these compounds was found to be by the use of an ester interchange reaction, using the methyl ester as the starting compound.

(4) Swift and Billman, *Ind. Eng. Chem.*, **17**, 600 (1945).

(5) Eisleb, *Ber.*, **74B**, 1433 (1941).

(6) Carothers and Adams, THIS JOURNAL, **45**, 1071 (1923); **46**, 1680 (1924).

NEW HAVEN, CONN. RECEIVED MAY 13, 1947

NOTES

Rearrangement in the Reaction between Benzylmagnesium Chloride and Ethyl Sulfate

BY JEROME G. BURTLE AND R. L. SHRINER

During a study of the influence of emulsifying agents on the oxidation of alkyl benzenes, it was observed that the alkaline permanganate oxidation of 6 g. of *n*-propylbenzene produced 0.3 g. of terephthalic acid in addition to benzoic acid. Investigation disclosed that this sample of *n*-propylbenzene had been made by the reaction between benzylmagnesium chloride and ethyl sulfate[1] and that it had been collected over a rather wide boiling point range, 155–160° (uncor.). The question arose as to whether the terephthalic acid was formed by the oxidation of *p*-ethyltoluene formed by a *para*-rearrangement during the course of the Grignard reaction, or whether it came from impurities in the benzyl chloride used to make the Grignard reagent. Since benzyl chloride is produced by chlorination of boiling toluene, any *p*-chlorotoluene present would form *p*-tolylmagnesium chloride which would also form *p*-ethyltoluene by reaction with ethyl sulfate. The latter explanation was excluded by repeating the preparation with carefully purified benzyl chloride which was shown to contain no *p*-chlorotoluene by the fact that no *p*-chlorobenzoic acid was produced by oxidation. Also a purified sample of benzaldehyde was converted to benzyl alcohol by the Cannizzaro reaction and this benzyl alcohol (which was halogen free) converted to benzyl chloride which was then used for the preparation of *n*-propylbenzene. In each case, oxidation of the fraction corresponding to *n*-propylbenzene produces terephthalic acid.

The boiling points of *n*-propylbenzene, *o*-ethyltoluene and *p*-ethyltoluene lie rather close together and repeated fractional distillation failed to give any pure fractions of either *o*-ethyltoluene or *p*-ethyltoluene. Apparently the three compounds show a marked tendency to co-distil. The presence of *p*-ethyltoluene was shown by oxidation with alkaline potassium permanganate solution and separation of the terephthalic acid from benzoic acid by means of its very low solubility in hot water. No phthalic acid could be separated

(1) "Organic Syntheses," Coll. Vol. 1, 471 (1941).