

pound V did not react with magnesium; however, by using an equivalent amount of methyl iodide, the reaction proceeded to a limited extent. The gases evolved were absorbed in a bromine-carbon tetrachloride trap. The carbon tetrachloride solution was washed with sodium bisulfite and after removal of the carbon tetrachloride 2 g. of liquid was collected, b. p. 120–140°,  $n_D^{20}$  1.5350. The S-alkylisothioureia picrate derivative prepared<sup>28</sup> from this material was identical to that prepared from an authentic sample of ethylene bromide (m. p. and mixed m. p. 254°).

### Summary

1. High yields of acetals were obtained by treating dihydropyran with phenol, *p*-bromophenol, resorcinol, catechol, hydroquinone, trimethylene chlorohydrin, ethylene bromohydrin and pentamethylene glycol.

(23) Levy and Campbell, *J. Chem. Soc.*, 1442 (1939).

2. The formation of acetals by the acid catalyzed addition of hydroxyl compounds to  $\alpha,\beta$ -unsaturated ethers such as dihydropyran, has been shown to be a useful method of protecting the hydroxyl group in reactions effected in basic media.

3. The acetals obtained from phenol, resorcinol, catechol and hydroquinone were converted in good yield to salicylic acid and the corresponding dihydroxybenzoic acids by metalation, carbonation and subsequent acid hydrolysis, thus establishing the position of metalation.

4. Other reactions of aliphatic acetals are described.

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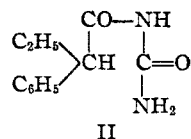
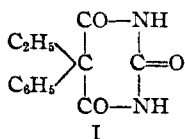
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[CONTRIBUTION FROM ABBOTT LABORATORIES]

## Anticonvulsant Drugs. II. Some Acylureas<sup>1</sup>

BY M. A. SPIELMAN, A. O. GEISZLER AND W. J. CLOSE

Phenobarbital (I) is widely used in the treatment of epilepsy. 2-Phenylbutyrylurea (II) may



be considered an "open" model of the barbiturate, less one carbon atom. A sample of the ureide (II) was tested by the methods used in our earlier work, and it was found to have definite anticonvulsant properties. The acylureas prepared as a consequence of this observation are described in the following report.

Although most of our acylureas are new, the type of compound is old. Many have been synthesized as possible hypnotics<sup>2</sup> or simply as solid derivatives of low-melting acids.<sup>3</sup> They are made by allowing an acid halide<sup>2,4</sup> or anhydride<sup>6</sup> to react with urea, or by condensing an ester with urea in the presence of a base.<sup>3</sup> They have appeared as by-products in the synthesis and degradation of barbiturates.<sup>2,6</sup>

The pharmacological examination of our ureides was carried out by G. M. Everett and R. K. Richards of this Laboratory, and we are indebted to them for the evaluations given in Table I, the de-

tails of which will be published elsewhere. Anticonvulsant effects were measured by the ability of the presumptive drugs to suppress or modify the convulsions induced in mice by electroshock or by injection of Metrazol. The following is the scale of activity used in the table.

3. Good protection at a dose level which provokes no toxic symptoms.

2. Protection only at levels which bring out toxic effects such as depression, ataxia, excitement, etc.

1. Incomplete protection, even at toxic levels.

Table I lists the activities of the compounds along with the melting points and analytical data for those which are new. The few ureides which we prepared from straight-chain aliphatic acids are neither new nor active and hence are not included in the Table. Among the aliphatic ureides the highest activity is found in those derived from secondary and tertiary acids of about seven carbon atoms. As molecular weight rises the anticonvulsant potency declines, and the compounds tend to become hypnotic. In the aromatic series phenacetylurea appears to be best. It is interesting that the isoster,  $\alpha$ -thienylacetylurea, is practically inactive.

### Experimental Part<sup>7</sup>

With the exception of the substances described below, no new compounds were involved as intermediates in the synthesis of the acylureas. Some of the aliphatic acid chlorides were contributed by K. E. Hamlin who prepared them in connection with a different project.

2-(*p*-Chlorophenyl)-butyronitrile.—Ten grams of sodium was converted to sodamide in 300 cc. of liquid ammonia with 0.1 g. of ferric nitrate catalyst. The ammonia was replaced by 200 cc. of toluene and 58 g. of *p*-chlorophenylacetonitrile was added. Fifty grams of ethyl bromide was dropped in with stirring and cooling. The product, after

(7) Microanalyses by E. F. Shelberg and staff.

(1) Preceding paper by Spielman and Everett, *THIS JOURNAL*, **70**, 1021 (1948). Presented in part at the First National Medicinal Chemistry Symposium, Ann Arbor, Michigan, June 18, 1948.

(2) Volwiler and Tabern, *THIS JOURNAL*, **58**, 1352 (1938); Blicke and Centolella, *ibid.*, **60**, 2923 (1938); German Patent 249,241; Fränkel, "Arzneimittelsynthese," Julius Springer, Berlin, 1927, pp. 498, 507.

(3) Stendal, *Compt. rend.*, **196**, 1810 (1933).

(4) Stoughton, *J. Org. Chem.*, **2**, 514 (1938); *THIS JOURNAL*, **61**, 408 (1939); Fischer and Dilthey, *Ann.*, **335**, 365 (1904).

(5) Werner, *J. Chem. Soc.*, **109**, 1127 (1916).

(6) Barnes and McElvain, *THIS JOURNAL*, **59**, 2348 (1937).

TABLE I  
 ANTICONVULSANT ACYLUREAS,  $\text{AcNHCONH}_2$ 

Acyl	M. p., °C.	Formula	Nitrogen, %		Anticonvulsant potency	
			Calcd.	Found	Electro-shock	Metrazol
Isobutyryl					0	2
Pivaloyl					2	2
2-Methylbutyryl					1	2
Isovaleryl					2	2
Isocaproyl	183-184	$\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$	17.7	17.8	0	0
3-Methylvaleryl	200-202	$\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$	17.7	17.6	0	0
2-Methylvaleryl					1	1
2-Ethylbutyryl					2	2
2,2-Dimethylbutyryl					2	2
2-Methylisovaleryl	161-162	$\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$	17.7	17.7	0	2
2-Ethyl-2-methylbutyryl	136-137	$\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$	16.3	16.2	0	2
2,3-Dimethylvaleryl	142-144	$\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$	16.3	15.8	0	0
3-Methylcaproyl					0	0
2-Ethylvaleryl					1	2
2-Ethylisovaleryl	200-201	$\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$	16.3	16.3	2	3
2-Ethylcaproyl					1	1
2- <i>n</i> -Propylvaleryl					0	0
Isoheptanoyl	190-191	$\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$	16.3	16.2	0	0
4-Ethylcaproyl	173-174	$\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$	15.0	14.8	0	0
2-Ethyl-3-methylvaleryl					0	2
3,4-Dimethylcaproyl	145-147	$\text{C}_9\text{H}_{18}\text{N}_2\text{O}_2$	15.0	14.9	0	0
3-Ethylheptanoyl	158-159	$\text{C}_9\text{H}_{18}\text{N}_2\text{O}_2$	14.0	14.2	0	0
2-Ethyl- $\Delta^4$ -pentenoyl	194-195	$\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$	16.5	16.5	1	2
2- <i>n</i> -Butyl- $\Delta^4$ -pentenoyl					1	1
2-Isopropyl- $\Delta^4$ -pentenoyl					2	2
2-Allyl- $\Delta^4$ -pentenoyl	154-156	$\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2$	15.4	15.3	1	1
Hexahydrobenzoyl					0	0
Cyclohexylacetyl					0	0
Benzoyl					2	0
Phenacetyl					3	2
2-Phenylpropionyl	158-159	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$	14.6	14.3	2	0
3-Phenylpropionyl	220-221	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$	14.6	14.4	0	0
2-Phenylbutyryl					3	0
2-Phenylisobutyryl	124-126	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$	13.6	13.6	2	2
<i>o</i> -Tolylacetyl	228-230	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$	14.6	14.3	0	0
<i>m</i> -Tolylacetyl	211-213	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$	14.6	14.5	0	0
<i>p</i> -Tolylacetyl	224-226	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$	14.6	14.3	2	1
2-Phenylvaleryl	151-152	$\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$	12.7	12.5	2	2
2-Phenylisovaleryl	178-181	$\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$	12.7	12.8	0	0
<i>p</i> -Ethylphenacetyl	200-202	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$	13.6	13.4	0	0
4-Phenylbutyryl	173-174	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$	13.6	13.5	0	0
2-Phenylcaproyl	153-154	$\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$	12.7	12.7	0	0
2-Phenyl- $\Delta^4$ -pentenoyl					2	3
1-Naphthylacetyl	250-251	$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$	12.3	12.0	0	0
2-Naphthylacetyl	232-234	$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$	12.3	12.1	0	0
Diphenylacetyl					0	0
<i>o</i> -Chlorophenacetyl	244-246	$\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2$	13.2	12.9	0	0
<i>p</i> -Chlorophenacetyl	228-230	$\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2$	13.2	13.0	0	0
2-( <i>p</i> -Chlorophenyl)-butyryl	142-145	$\text{C}_{11}\text{H}_{13}\text{ClN}_2\text{O}_2$	11.8	11.8	2	2
2-Thienylacetyl	203-204	$\text{C}_7\text{H}_8\text{N}_2\text{O}_2\text{S}$	15.2	14.9	1	0
2-Furylacetyl	186-187	$\text{C}_7\text{H}_8\text{N}_2\text{O}_3$	16.7	16.8	0	0
Phenoxyacetyl	180-181	$\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3$	14.4	14.3	0	0
2-Phenoxybutyryl	157-158	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3$	12.6	12.7	0	0

isolation in the usual way, boiled at 102-107° at 0.5 mm. The yield was 71%;  $n_D^{25}$  1.5243. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{10}\text{ClN}$ : N, 7.8. Found: N, 7.0, 7.2. It was evidently not quite pure but served satisfactorily in the next step.

2-(*p*-Chlorophenyl)-butyric Acid.—The above nitrile was hydrolyzed by boiling 25 g. for two days with 50 cc. of alcohol, 100 cc. of water and 10 g. of potassium hydroxide. After crystallization, once from dilute alcohol and twice from cyclohexane-petroleum ether, it melted at 83-85°.

