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°, $n^{20}D$ 1.5350. The S-alkylisothiourea picrate derivative prepared[23] 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.

2. The formation of acetals by the acid catalyzed addition of hydroxyl compounds to α,β-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.

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

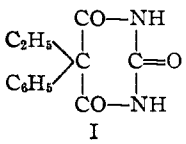
MINNEAPOLIS 14, MINNESOTA RECEIVED JULY 9, 1948

[CONTRIBUTION FROM ABBOTT LABORATORIES]

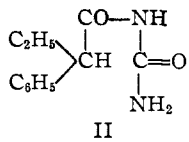
Anticonvulsant Drugs. II. Some Acylureas[1]

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



I



II

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[2] or simply as solid derivatives of low-melting acids.[3] They are made by allowing an acid halide[2,4] or anhydride[5] to react with urea, or by condensing an ester with urea in the presence of a base.[3] They have appeared as by-products in the synthesis and degradation of barbiturates.[2,6]

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 details 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, α-thienylacetylurea, is practically inactive.

Experimental Part[7]

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

(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 (1936); 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).

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

TABLE I

ANTICONVULSANT ACYLUREAS, AcNHCONH$_2$

Acyl	M. p., °C.	Formula	Nitrogen, % Calcd.	Found	Anticonvulsant potency Electro-shock	Metrazol
Isobutyryl					0	2
Pivaloyl					2	2
2-Methylbutyryl					1	2
Isovaleryl					2	2
Isocaproyl	183–184	$C_7H_{14}N_2O_2$	17.7	17.8	0	0
3-Methylvaleryl	200–202	$C_7H_{14}N_2O_2$	17.7	17.6	0	0
2-Methylvaleryl					1	1
2-Ethylbutyryl					2	2
2,2-Dimethylbutyryl					2	2
2-Methylisovaleryl	161–162	$C_7H_{14}N_2O_2$	17.7	17.7	0	2
2-Ethyl-2-methylbutyryl	136–137	$C_8H_{16}N_2O_2$	16.3	16.2	0	2
2,3-Dimethylvaleryl	142–144	$C_8H_{16}N_2O_2$	16.3	15.8	0	0
3-Methylcaproyl					0	0
2-Ethylvaleryl					1	2
2-Ethylisovaleryl	200–201	$C_8H_{16}N_2O_2$	16.3	16.3	2	3
2-Ethylcaproyl					1	1
2-*n*-Propylvaleryl					0	0
Isoheptanoyl	190–191	$C_8H_{16}N_2O_2$	16.3	16.2	0	0
4-Ethylcaproyl	173–174	$C_9H_{18}N_2O_2$	15.0	14.8	0	0
2-Ethyl-3-methylvaleryl					0	2
3,4-Dimethylcaproyl	145–147	$C_9H_{18}N_2O_2$	15.0	14.9	0	0
3-Ethylheptanoyl	158–159	$C_{10}H_{20}N_2O_2$	14.0	14.2	0	0
2-Ethyl-Δ^4-pentenoyl	194–195	$C_8H_{14}N_2O_2$	16.5	16.5	1	2
2-*n*-Butyl-Δ^4-pentenoyl					1	1
2-Isopropyl-Δ^4-pentenoyl					2	2
2-Allyl-Δ^4-pentenoyl	154–156	$C_9H_{14}N_2O_2$	15.4	15.3	1	1
Hexahydrobenzoyl					0	0
Cyclohexylacetyl					0	0
Benzoyl					2	0
Phenacetyl					3	2
2-Phenylpropionyl	158–159	$C_{10}H_{12}N_2O_2$	14.6	14.3	2	0
3-Phenylpropionyl	220–221	$C_{10}H_{12}N_2O_2$	14.6	14.4	0	0
2-Phenylbutyryl					3	0
2-Phenylisobutyryl	124–126	$C_{11}H_{14}N_2O_2$	13.6	13.6	2	2
o-Tolylacetyl	228–230	$C_{10}H_{12}N_2O_2$	14.6	14.3	0	0
m-Tolylacetyl	211–213	$C_{10}H_{12}N_2O_2$	14.6	14.5	0	0
p-Tolylacetyl	224–226	$C_{10}H_{12}N_2O_2$	14.6	14.3	2	1
2-Phenylvaleryl	151–152	$C_{12}H_{16}N_2O_2$	12.7	12.5	2	2
2-Phenylisovaleryl	178–181	$C_{12}H_{16}N_2O_2$	12.7	12.8	0	0
p-Ethylphenacetyl	200–202	$C_{11}H_{14}N_2O_2$	13.6	13.4	0	0
4-Phenylbutyryl	173–174	$C_{11}H_{14}N_2O_2$	13.6	13.5	0	0
2-Phenylcaproyl	153–154	$C_{12}H_{16}N_2O_2$	12.7	12.7	0	0
2-Phenyl-Δ^4-pentenoyl					2	3
1-Naphthylacetyl	250–251	$C_{13}H_{12}N_2O_2$	12.3	12.0	0	0
2-Naphthylacetyl	232–234	$C_{13}H_{12}N_2O_2$	12.3	12.1	0	0
Diphenylacetyl					0	0
o-Chlorophenacetyl	244–246	$C_9H_9ClN_2O_2$	13.2	12.9	0	0
p-Chlorophenacetyl	228–230	$C_9H_9ClN_2O_2$	13.2	13.0	0	0
2-(*p*-Chlorophenyl)-butyryl	142–145	$C_{11}H_{13}ClN_2O_2$	11.8	11.8	2	2
2-Thienylacetyl	203–204	$C_7H_8N_2O_2S$	15.2	14.9	1	0
2-Furylacetyl	186–187	$C_7H_8N_2O_3$	16.7	16.8	0	0
Phenoxyacetyl	180–181	$C_9H_{10}N_2O_3$	14.4	14.3	0	0
2-Phenoxybutyryl	157–158	$C_{11}H_{14}N_2O_3$	12.6	12.7	0	0

isolation in the usual way, boiled at 102–107° at 0.5 mm. The yield was 71%; $n^{25}D$ 1.5243. *Anal.* Calcd. for $C_{10}H_{10}ClN$: 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°.

Anal. Calcd. for $C_{10}H_{11}ClO_2$: C, 60.5; H, 5.5. Found: C, 60.8; H, 5.7.

All acylureas were made by either of two methods which were used interchangeably with little difference in yield. In the first, an acid chloride was allowed to react with urea in the absence of solvent.[2] Reaction began spontaneously or upon brief warming and was completed by heating on the steam-bath. In the second method, due to Stoughton,[4] the acid chloride was added to urea in refluxing benzene. The trace of sulfuric acid used by Stoughton was found to be unnecessary in our work. An example of each procedure is given.

Isocaproylurea by the Dry Urea Method.—Twelve grams of urea was powdered and mixed with 11.8 g. of isocaproyl chloride. A vigorous reaction was initiated by cautious warming. When it had subsided the mixture was heated two hours on the steam-bath, cooled, triturated with water and separated by filtration. The solid was crystallized from alcohol to give 10.0 g., m. p. 182–184°, and a second crop of 1.5 g., m. p. 178–184°. Recrystallization brought the m. p. of the colorless blades to 183–184°.

2-Ethylvalerylurea by the Benzene Method.—To a boiling, stirred mixture of 10 cc. dry benzene and 7.5 g. of urea was added dropwise 9.2 g. of 2-ethylvaleryl chloride. Stirring and refluxing were continued for four hours. After cooling, the solid was removed by filtration, washed with petroleum ether, sucked dry, washed with sodium bicarbonate solution and again with water. Recrystallization from alcohol gave 8.0 g. of ureide melting at 204–206°.

Summary

A series of acylureas has been prepared and tested for anticonvulsant activity. In the aliphatic series the optimum effect upon experimental animals is reached with those derived from secondary and tertiary branched acids of about seven carbon atoms. In the aromatic series phenacetylurea is best; activity seems to diminish with any sort of aromatic substitution.

NORTH CHICAGO, ILLINOIS RECEIVED AUGUST 19, 1948

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

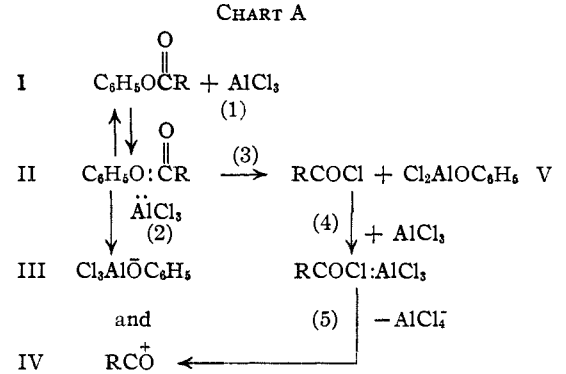
The Mechanism of the Fries Reaction[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Three principal mechanisms have been advanced for the Fries reaction.[2] Fries and v. Auwers[3] regarded it as a true rearrangement. Cox[4] and Skraup believed the phenolic ester to be cleaved by aluminum chloride to liberate acyl chloride which then reacts as in the Friedel–Crafts synthesis. Rosenmund and Schnurr[5] wrote the reaction as a bimolecular acylation in which one molecule of ester serves as an acylating agent for another. All three mechanisms have been defended by their proponents on the basis of inconclusive evidence.

Examination of the Skraup–Cox and Rosenmund–Schnurr mechanisms in the light of present views on the nature of acid catalysis[6] shows them to be identical for practical purposes. In Chart A is shown what we believe to be the main line (Steps 1–2) in the formation of active fragments (III and IV). The oxo-carbonium ion,[7] IV, is the cationic intermediate in both schemes. Its attack on a molecule of ester, I, expresses Rosenmund's view, while its formation by the circuitous route of Steps 3–5 amounts to the Skraup–Cox mechanism. It is obvious that under the conditions of the reaction experimental discrimination among the possible basic fragments, I, III, V and the phenolate anion suggested by Luder and Zuffanti is impossible.[8]

CHART A



The remaining decision is whether the reaction is intramolecular or intermolecular.[9] While an intramolecular rearrangement of the acyl group to

(1) This paper was presented before the Organic Division of the American Chemical Society, New York Meeting, September, 1947.

(2) For reviews of the literature see Blatt, *Chem. Revs.*, **27**, 429 (1940), and "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1943, p. 342.

(3) v. Auwers and Mauss, *Ber.*, **61**, 1495 (1928); *Ann.*, **464**, 293 (1928).

(4) Cox, THIS JOURNAL, **52**, 352 (1930).

(5) Rosenmund and Schnurr, *Ann.*, **460**, 96 (1927).

(6) *Cf.* Luder and Zuffanti, "The Electronic Theory of Acids and Bases," John Wiley and Sons, New York, N. Y., 1946. Chart A of this paper is essentially similar to that shown by Luder and Zuffanti, p. 123.

(7) For this term see Newman and Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

(8) As will be shown subsequently, it is probable that coördination of the ester (I) with aluminum chloride is essentially complete when the latter is in excess. Therefore, it is unlikely that free ester is available as an intermediate. The significant participation of phenolate anion is also improbable since it would require dissociation of aluminum chloride from a relatively strong base when it apparently combines extensively with the ester which is a weaker one.

(9) While the classical definition of a rearrangement implies nothing as to mechanism it is evident that Rosenmund in declaring that the Fries was not a *rearrangement* and v. Auwers in maintaining it to be a "true rearrangement" were using a more rigid definition, presumably that of an *intramolecular rearrangement*. Since, in the movement of a substituent from one position to another, this concept requires partial formation of the final bond before the initial bond is completely ruptured, steric as well as electronic conditions should be critical in determining the possibility of the shift. It has not been suggested hitherto that the ortho and para shifts proceed by different mechanisms, but this possibility is not excluded by existing evidence.