[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

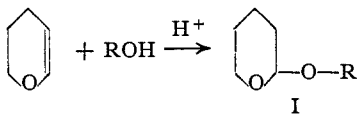
The Protection of Hydroxyl Groups

BY WILLIAM E. PARHAM AND E. L. ANDERSON[1]

It has been shown, principally by Gilman and his co-workers,[2] that metalation of phenols and phenolic ethers constitutes an important step in the synthetic route to certain organic compounds. Metalation of phenolic ethers generally yields fewer isomers than does metalation of the corresponding phenols[3]; however, the use of the ether as a protecting group has the disadvantage that the product obtained subsequent to reaction is still an ether, and conditions for its cleavage are often so vigorous that considerable loss by decomposition may result.

This paper describes the results of a search for a more suitable means of protecting the hydroxyl group (both aromatic and aliphatic) in reactions which are conducted in basic media. For this purpose, conversion of hydroxy compounds to acetals suggested itself because this grouping is not only stable under alkaline conditions, but is also readily cleaved by mild action of aqueous acids with the regeneration of the hydroxyl group.

Paul,[4] and more recently Woods and Kramer,[5] have shown that dihydropyran reacts rapidly with compounds containing the hydroxyl group in the presence of an acid catalyst to yield cyclic acetals of type I. The yields from aliphatic alcohols were

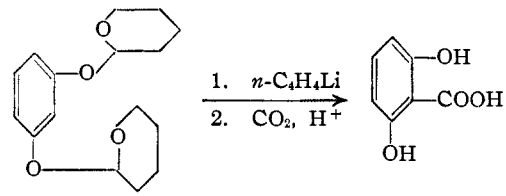


I

generally high (70–90%); however, the yield from phenol was reported to be only 37%.

We have studied the formation of acetals of type I and have found that the 2-tetrahydropyranyl ethers of phenol and *p*-bromophenol may be prepared in 77 and 83% yields, respectively. The *bis*-2-tetrahydropyranyl ethers of resorcinol, catechol and hydroquinone were prepared in yields of 86, 55 and 54%, respectively, by using an excess of dihydropyran. In the case of catechol, the mono-2-tetrahydropyranyl ether was obtained as a by-product in 30% yield.

To determine whether such acetals would serve as useful intermediates in synthetic work, the 2-tetrahydropyranyl ether of phenol and the *bis*-2-tetrahydropyranyl ethers of resorcinol, catechol and hydroquinone were metalated by action with *n*-butyllithium. Conversion of the organometallic compounds to the corresponding hydroxy acids by carbonation and subsequent acidic hydrolysis established the position at which metalation had occurred. These reactions are illustrated by the following example. The results are summarized in Table II.



The reactions of several aliphatic acetals of type I were also investigated. Acetals were prepared from trimethylene chlorohydrin, ethylene bromohydrin and pentamethylene glycol. 2-(γ-Chloro-*n*-propoxy)-tetrahydropyran (II) underwent a Williamson ether synthesis to give 2-(γ-ethoxy-*n*-propoxy)-tetrahydropyran (III). Hydrolysis of this acetal gave the mono ethyl ether of trimethylene glycol.

2-(β-Bromoethoxy)-tetrahydropyran (V) reacted to a limited extent under forced conditions with magnesium. One of the products of the reaction was ethylene, a product similarly obtained from other β-halo-ethers.[6]

Experimental[7,8]

Aliphatic Acetals.—Equimolar quantities of dihydropyran and the alcohol containing a few drops of concentrated hydrochloric acid were allowed to stand for three hours with occasional shaking. Ether was added and the solution was shaken vigorously with 10% sodium hydroxide to insure removal of all traces of acid. The solution was dried, the solvent was removed and the residue distilled under reduced pressure through a six-inch column packed with glass helices.

Aromatic Ethers.—To 2 moles of dihydropyran containing 4 drops of concentrated hydrochloric acid was slowly added 0.5 mole of dihydroxybenzene. The reaction was exothermic and required cooling to prevent charring. The mixture was allowed to stand for one hour and 200 ml. of ether was added. The solution was washed with 100 ml. of 10% sodium hydroxide to remove the catalyst and any phenolic compounds present. The ether was dried over anhydrous sodium sulfate and the ether and excess dihydropyran removed by distillation. The 2-tetrahydropyranyl ethers were purified by vacuum distillation or by crystallization.

Catechol Mono-2-tetrahydropyranyl Ether (IX).—When the alkaline washings obtained in the preparation of VIII were saturated with carbon dioxide, a cream-colored oil separated. This was extracted with ether and the solution was dried over anhydrous sodium sulfate. Removal of the ether and vacuum distillation of the residual oil gave 30 g. (30%) of catechol mono-2-tetrahydropyranyl ether, b. p. 124–126° (3 mm.). An aqueous solution of this phenol gave a deep blue color with ferric chloride.

2,3-Dihydroxybenzoic Acid from Catechol bis-2-Tetrahydropyranyl Ether.—Metalation was effected by slowly

(1) Abstracted from a thesis by E. L. Anderson presented to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science.

(2) Gilman, Swiss and Cheney, THIS JOURNAL, **62**, 1963 (1940).

(3) Gilman, *et al.*, *ibid.*, **62**, 667 (1940).

(4) Paul, *Bull. soc. chim.*, [5] **1**, 973 (1934).

(5) Woods and Kramer, THIS JOURNAL, **67**, 2122 (1947).

(6) Tallman, *ibid.*, **56**, 126 (1934).

(7) The dihydropyran was kindly furnished by E. I. du Pont de Nemours & Co.

(8) Microanalyses by R. Amidon, J. Buckley and W. Hunter.

TABLE I

ACETALS OF TYPE I

	R = 2-Tetrahydropyran	Yield	B. p., °C.	Mm.	$n^{20}D$	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
II	$ClCH_2CH_2CH_2OR$	78	103	14	1.4515	53.78	53.50	8.46	8.58
III	$C_2H_5OCH_2CH_2CH_2OR$	60	93	10	1.4364	63.78	63.40	10.71	10.71
V	$BrCH_2CH_2OR$[a]	82	94	14	1.4810	40.21	39.84	6.27	6.40
VI	$RO(CH_2)_6OH$	39[b]	120	3	1.4599	63.78	63.52	10.71	10.66
VII	$RO(CH_2)_6OR$	20[b]	149	2	1.4638	66.10	66.15	10.36	10.26
VIII	o-$C_6H_4(OR)_2$	55	170	0.65	1.5238	69.03	68.89	8.01	8.15
IX	o-$C_6H_4(OH)(OR)$	30[c]	120	3	1.5369	68.03	67.97	7.27	7.24
X	m-$C_6H_4(OR)_2$	86	197	4[d]	1.5340	69.03	69.03	8.01	7.72
XI	p-$C_6H_4(OR)_2$	54	[e]			69.03	69.05	8.01	7.97
XII	C_6H_5OR	77	103	4	1.5228	74.13	74.13	7.92	8.15
XIII	p-BrC_6H_4OR	83	109	0.26[f]		51.38	51.46	5.10	5.40

[a] Decomposes on standing. [b] Yields obtained from equimolar mixture of the glycol and dihydropyran. When an excess of the glycol was used, the yield of VI was 47% and the yield of VII was 9%. [c] Catechol mono-2-tetrahydropyranyl ether was obtained in 30% yield as a by-product when either equivalent or excess amounts of dihydropyran were used. [d] M. p. 73–76°. [e] Chloroform was used in place of ether during the preparation of XI. The product recrystallized from ethanol, m. p. 125–127°. [f] M. p. 57–57.5° (recrystallized from ethanol).

TABLE II

THE PREPARATION OF HYDROXYBENZOIC ACIDS

Product metalated R = 2-tetrahydropyran	Product isolated	Yield, %	Melting point, °C.	Melting point after purif., °C.	Conversion to the diacetate	Acid was identified by conversion to the methyl or dimethyl ester	Comparison to known acid
o-$C_6H_4(OR)_2$	2,3-Dihydroxybenzoic[a] acid	48	197–200	200–202[b]	M. p. 147–148 Lit.[11] 148–150	M. p. 77–78 Lit.[12] 76–79	M. p. and mixed M. p.[10] 200–202
m-$C_6H_4(OR)_2$	2,6-Dihydroxybenzoic acid	60	158–160	163–164[c]	.....	M. p. 68–69 Lit.[16] 67–68	Lit.[13] m. p. 167 The possible isomers melt above 210[14,15]
p-$C_6H_4(OR)_2$	2,5-Dihydroxybenzoic acid and	48	194–197	197–198[b]	M. p. 117–118 Lit.[19] m. p. 118–119	M. p. 86–87 Lit.[18] m. p. 87	Lit.[17] m. p. 199–200
	2,5-Dihydroxyterephthalic acid[d]	5	335–339 dec.			M. p. 129–130 Lit.[21] m. p. 133	
C_6H_5OR	Salicylic acid	52	155–156				Mixed m. p. 155–156

[a] The ethyl ester was prepared. *Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.46; H, 5.85. The reported[10] melting point of ethyl 2,3-dihydroxybenzoate is 130.5°. In view of our evidence for the structure of 2,3-dihydroxybenzoic acid, the melting point recorded as 130.5° must be in error. [b] Recrystallized from water. [c] Purified by sublimation. [d] This acid was further characterized by its characteristic fluorescence in water and alcohol.[20]

adding 14 g. (0.05 mole) of catechol bis-2-tetrahydropyranyl ether dissolved in 50 ml. of absolute ether to a solution of *n*-butyllithium prepared[9] from 21. g. (0.3 gram atom) of lithium and 15 g. (0.15 mole) of *n*-butyl chloride in ether. After the initial reaction had subsided (about thirty minutes), the solution was heated at the reflux temperature for twenty hours. Carbonation yielded a cream-colored solid which dissolved when 100 ml. of 15% hydrochloric acid was added. The solution was shaken vigorously for a few moments and the organic layer was separated and extracted with 150 ml. of saturated sodium bicarbonate solution. 2,3-Dihydroxybenzoic acid was obtained in 48% yield (3.7 g.), m. p. 197–200°, upon acidification and ether extraction of the alkaline solution. This acid recrystallized from water, m. p. 200–202°. Other hydroxybenzoic acids were prepared by a simple modification of the above procedure.

2-(γ-Ethoxy-*n*-propoxy)-tetrahydropyran (III).—A mixture of 25 g. of 2-(γ-chloro-*n*-propoxy)-tetrahydropyran and alcoholic potassium hydroxide was heated at the reflux temperature for three hours. After removal of the potassium chloride by filtration and evaporation of the alcohol, distillation of the residual oil yielded 16.4 g. (60% yield) of colorless liquid boiling at 99–100° (12 mm.) (see Table I).

Hydrolysis of 2-(γ-Ethoxy-*n*-propoxy)-tetrahydropyran (III).—A mixture of 6.3 g. (0.033 mole) of III was shaken with 25 ml. of 2 *N* hydrochloric acid until solution was effected (two minutes). The solution was allowed to stand at room temperature for fifteen minutes and then extracted with ether. After drying the ether over anhydrous potassium carbonate and distilling at atmospheric pressure, two fractions were obtained. The first fraction, 2.3 g. (68%), was collected at 156–164° (740 mm.), $n^{20}D$ 1.4225. These properties are in close agreement with the properties reported for the mono ethyl ether of trimethylene glycol.[22] The second fraction, 1.6 g. (25%), was collected at 195–200° and was found to be unchanged starting material.

The Reaction of 2-(β-Bromoethoxy)-tetrahydropyran (V) with Magnesium.—Under normal conditions, com-

(9) Gilman, Wright and Moore, THIS JOURNAL, **62**, 2327 (1940).

(10) Praxmarer, *Monatsh.*, **27**, 1201–1204 (1906).

(11) Rietz, U. S. Patent 1,140,716, *Chem. Abs.*, **9**, 1829 (1915).

(12) Bayer, *Chem. Centr.*, **86**, I, 180 (1915).

(13) Senhofer and Brunner, *Sitz. k. Akad. Wiss. Wien*, **80**, II, 504 (1906).

(14) Bistrzycki and v. Kostanecki, *Ber.*, **18**, 1985 (1885).

(15) Bottinger, *ibid.*, **8**, 374 (1875).

(16) Mauthner, *J. prakt. Chem.*, **124**, 322 (1930).

(17) Graebe and Marty, *Ann.*, **340**, 213 (1905).

(18) Bruner, *Monatsh.*, **34**, 916 (1913).

(19) v. Hemmelmayer, *ibid.*, **30**, 286 (1909).

(20) Herrmann, *Ann.*, **211**, 335 (1882).

(21) Hantzsch, *Ber.*, **48**, 807 (1915).

(22) Noyes, THIS JOURNAL, **19**, 767 (1897).

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°).

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

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.

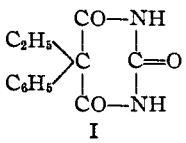
MINNEAPOLIS 14, MINNESOTA RECEIVED JULY 9, 1948

[CONTRIBUTION FROM ABBOTT LABORATORIES]

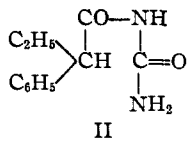
Anticonvulsant Drugs. II. Some Acylureas[1]

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.