physical constants of all but the 2-methyl and 2-ethyl derivatives have been described for the first time.

2. 2-Butylbiphenyl has been shown to exist in two distinct crystalline modifications.

CLEVELAND, OHIO RECEIVED DECEMBER 3, 1949

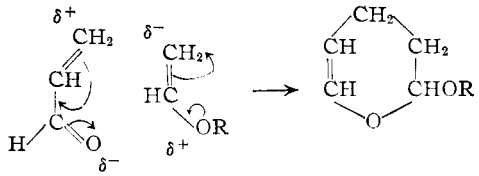
[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

The 1,4-Addition of Vinyl Ethers to α,β-Unsaturated Carbonyl Compounds

BY RAYMOND I. LONGLEY, JR., AND WILLIAM S. EMERSON

The dimerization of α,β-unsaturated carbonyl compounds such as acrolein, crotonaldehyde, methyl vinyl ketone and phenyl vinyl ketone is well known.[1] Acrolein adds acrylonitrile and methyl acrylate to the 1,4-conjugated system to give 2-cyano-3,4-dihydro-1,2-pyran and 2-carbomethoxy-3,4-dihydro-1,2-pyran, respectively.[2]

We have found that α,β-unsaturated carbonyl compounds add vinyl ethers even more readily than they dimerize.[3] This is not surprising in view of the polarization of the molecules.



Acrolein, crotonaldehyde, methacrolein, cinnamaldehyde, β-furylacrolein, methyl vinyl ketone, benzalacetone and benzalacetophenone have been found to undergo this addition. Methyl vinyl ether, ethyl vinyl ether, *n*-butyl vinyl ether, ethyl isopropenyl ether and *n*-butyl cyclohexenyl ether served as dienophiles. Fourteen 2-alkoxy-3,4-dihydro-1,2-pyrans have been synthesized in this manner in yields of 25–87% as shown in Table I.

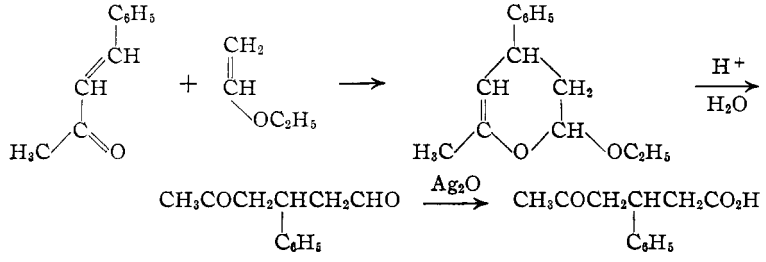
In these additions ethyl vinyl ether gave higher yields than methyl vinyl ether. Crotonaldehyde was appreciably less reactive than acrolein, since it required a 50° higher temperature for comparable yields. Methacrolein gave lower yields than most of the other α,β-unsaturated carbonyl compounds, since it dimerized far more readily.

In order to ascertain the structures of these products, 2-ethoxy-3,4-dihydro-1,2-pyran was hydrolyzed with dilute hydrochloric acid to glutaraldehyde, which was identified as its *p*-nitrophenylhydrazone. 2-Methoxy-4-methyl-3,4-dihydro-1,2-pyran and 2-methoxy-5-methyl-3,4-dihydro-1,2-pyran were hydrolyzed similarly and the resulting substituted glutaraldehydes were oxidized without isolation to the known 3-methyl- and 2-methylglutaric acids, respectively. 2-Ethoxy-6-methyl-4-phenyl-3,4-dihydro-1,2-pyran was hydrolyzed to 5-oxo-3-phenylhexanal. Oxidation yielded the known 5-oxo-3-phenylcaproic acid.

The authors are grateful to Dr. George F. Deebel and Mr. Richard Anderson for the preparation of the ethyl isopropenyl ether.

Experimental

Starting Materials.—Acrolein and methacrolein were obtained from the Shell Chemical Co. Crotonaldehyde, benzalacetone, benzalacetophenone and cinnamaldehyde were Eastman Kodak Co. "pure" products, whereas furylacrolein and methyl vinyl ketone were the "practical" grade redistilled. Methyl vinyl ether was obtained from both the Matheson Co. and Carbide and Carbon Chemicals Corp. Ethyl vinyl ether and *n*-butyl vinyl ether came from the General Aniline and Film Co. Ethyl isopropenyl ether was prepared as described in the literature.[4] *n*-Butyl cyclohexenyl ether was prepared by boiling under reflux a benzene solution of cyclohexanone and excess butanol in the presence of *p*-toluenesulfonic acid, while



the evolved water was collected in a Dean and Stark trap. The pure ether boiled at 90–91° (17 mm.), (80–81° (10 mm.)),[5] $n^{25}D$ 1.4577.

Condensations.—All of the condensations were effected by heating the α,β-unsaturated carbonyl compound and the vinyl ether in a bomb in the presence of 0.10–1.00% of hydroquinone. The conditions and yields obtained are summarized in Table I. The properties of the various 2-alkoxy-3,4-dihydro-1,2-pyrans are summarized in Table II.

Glutaraldehyde was prepared essentially by the method of Woods and Sanders.[6] A mixture of 300 cc. of water, 25 cc. of concentrated hydrochloric acid and 120 g. of 2-ethoxy-3,4-dihydro-1,2-pyran was stirred for twenty-two minutes, during which time the temperature rose to 38° and the mixture became clear. After standing one and one-

(1) See particularly Alder, Offermanns and Rüden, *Ber.*, **74**, 905, 926 (1941), and Alder and Rüden, *ibid.*, **74**, 920 (1941).

(2) Anzilotti, Fiat Final Report No. 1157, PB 85174, U. S. Department of Commerce, January 21, 1948.

(3) Since this paper was submitted, a paper on the same subject by Smith, Norton and Ballard was presented at the Philadelphia Meeting of the American Chemical Society, Division of Organic Chemistry, April 9, 1950.

(4) Dolliver, Gresham, Kistiakowsky, Smith and Vaughan, THIS JOURNAL, **60**, 440 (1938).

(5) Johannissian and Akumian, *Bull. Univ. Etat. R. S. S. Arménie*, No. 5, 245 (1930); *Chem. Zentr.*, **101**, II, 552 (1930).

(6) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946).

TABLE I

PREPARATION OF 2-ALKOXY-3,4-DIHYDRO-1,2-PYRANS

α,β-Unsaturated carbonyl compound	Vinyl ether	Moles[a]	Temp., °C.	Time, hr.	3,4-Dihydro-1,2-pyran produced	Yield, %
Acrolein	Methyl vinyl	1.35	135	12	2-Methoxy	81
Acrolein	Ethyl vinyl	1.10	140	12	2-Ethoxy	84
Acrolein	*n*-Butyl vinyl	1.16	135	12	2-*n*-Butoxy	82
Acrolein	Ethyl isopropenyl	0.46	130	16	2-Ethoxy-2-methyl	50
Acrolein	*n*-Butyl cyclohexenyl	0.36	175	17	1-*n*-Butoxy-2-oxabicyclo[4,4,0]-3-decene	40
Crotonaldehyde	Methyl vinyl	1.12	200	22	2-Methoxy-4-methyl	74
Crotonaldehyde	Ethyl vinyl	1.16	175	15	2-Ethoxy-4-methyl	87
Methacrolein	Methyl vinyl	2.00	155	19	2-Methoxy-5-methyl	25
Methacrolein	Ethyl vinyl	1.75	150	21	2-Ethoxy-5-methyl	40
Cinnamaldehyde	Ethyl vinyl	1.44	180	12	2-Ethoxy-4-phenyl	60
β-Furylacrolein	Ethyl vinyl	1.83	210	30	2-Ethoxy-4-furyl[b]	85
Methyl vinyl ketone	Ethyl vinyl	1.55	140	16	2-Ethoxy-6-methyl	50
Benzalacetone	Ethyl vinyl	1.66	200	42	2-Ethoxy-6-methyl-4-phenyl	75
Benzalacetophenone	Ethyl vinyl	6.30	180	13	2-Ethoxy-4,6-diphenyl	74

[a] Mole ratio ether to carbonyl compound. [b] Prepared by T. C. Shafer.

TABLE II

PROPERTIES OF 2-ALKOXY-3,4-DIHYDRO-1,2-PYRANS

3,4-Dihydro-1,2-pyran	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-Methoxy-	126–127	760	1.4397	0.994	63.2	63.3	8.8	8.9
2-Ethoxy-	42	16	1.4376	.966	65.6	65.6	9.4	9.2
2-*n*-Butoxy-	71–72	15	1.4404	.933	69.2	69.2	10.3	10.5
2-Ethoxy-2-methyl-	47.5	18	1.4327	.939	67.7	67.6	9.9	9.6
1-*n*-Butoxy-2-oxabicyclo-[4,4,0]3-decene	128.5	17	1.4689	.978	74.3	74.2	10.5	10.4
2-Methoxy-4-methyl-	137–140	760	1.4370	.955	65.6	65.6	9.4	9.6
2-Ethoxy-4-methyl-	110	172	1.4350	.931	67.6	67.6	9.9	10.1
2-Methoxy-5-methyl-	46.5–47.5	16	1.4435	.973	65.6	66.0	9.4	9.4
2-Ethoxy-5-methyl-	59–60	18	1.4419	.950	67.6	67.3	9.9	10.1
2-Ethoxy-4-phenyl-	139	11	1.5209	1.043	76.5	77.0	7.9	8.0
2-Ethoxy-4-furyl-	98	5	1.4885	1.083	68.1	68.3	7.2	7.2
2-Ethoxy-6-methyl-	51–52	14	1.4393	...	67.6	67.5	9.9	10.0
2-Ethoxy-6-methyl-4-phenyl	153	17	1.5180	1.025	77.1	77.2	8.3	8.1
2-Ethoxy-4,6-diphenyl	150	0.25	1.5800	1.090	81.4	81.5	7.1	7.0

half hours, the solution was neutralized with sodium bicarbonate, saturated with sodium chloride and extracted twice with ether. Distillation of the combined ether extracts yielded 55 g. (59%) of glutaraldehyde, b. p. 75–81° (15 mm.), (74–78 (16 mm.)),[7] $n^{25}D$ 1.4330.

The *p*-nitrophenylhydrazone, prepared by the method of Shriner and Fuson,[8] melted at 167–169° (157–159°) without recrystallization.

Anal. Calcd. for $C_{17}H_{18}O_4N_6$: N, 22.7. Found: N, 22.5.

3-Methylglutaric Acid.—A 10-g. sample of 2-methoxy-4-methyl-3,4-dihydro-1,2-pyran was hydrolyzed at 40° as above and then oxidized by the method of Shriner and Fuson[9] with 22 g. of potassium permanganate in 500 cc. of water. The clear solution was saturated with sodium sulfate and extracted 12 times with ether. Evaporation of the combined extracts yielded 10 g. (88%) of crude 3-methylglutaric acid. It was crystallized from chloroform–hexane to give 7 g. (61%) of pure material, m. p. 84–86° (85–86).[10]

2-Methylglutaric Acid.—A 5-g. sample of 2-methoxy-5-methyl-3,4-dihydro-1,2-pyran was hydrolyzed and oxidized as above to yield 5.5 g. (97%) of crude 2-methylglutaric acid. Recrystallization from chloroform–hexane gave 4 g. (70%) of pure material, m. p. 74–76° (77–78°).[11]

5-Oxo-3-phenylhexanal.—A mixture of 109 g. of 2-methoxy-6-methyl-4-phenyl-3,4-dihydro-1,2-pyran, 60 cc. of water, 100 cc. of acetone and 3 cc. of concentrated hydrochloric acid was heated with stirring in a nitrogen atmosphere. At 35° it became homogeneous. It was held at 40° for one hour, neutralized with sodium bicarbonate, saturated with sodium chloride and extracted with 250 cc. of hexane and 100 cc. of benzene. Distillation of the extract yielded 81 g. (85%) of 5-oxo-3-phenylhexanal, b. p. 133–139° (2 mm.). An analytical sample boiled at 137° (2 mm.), $n^{25}D$ 1.5183, d^{25}_{25} 1.063.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.3; H, 7.4.

5-Oxo-3-phenylcaproic Acid.—To a vigorously stirred mixture of 5 g. of 5-oxo-3-phenylhexanal, 10 g. of silver nitrate and 100 cc. of water held at 20° was added over a two and one-half hour period a solution of 6 g. of sodium hydroxide in 150 cc. of water. After six hours additional stirring, the mixture was filtered, extracted with 75 cc.

(7) Schöpf and Lehmann, *Ann.*, **518**, 1 (1935).

(8) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(9) Ref. 8, p. 170.

(10) Komnenos, *Ann.*, **218**, 145 (1883).

(11) v. Auwers, *ibid.*, **292**, 132 (1896).

of ether and again filtered. Acidification with concentrated hydrochloric acid precipitated an oil which solidified on cooling. It was separated by filtration and dried over phosphorus pentoxide to yield 3.2 g. (59%) of crude 5-oxo-3-phenylcaproic acid. After one crystallization from hexane it melted at 81–83° (84–85°).[12]

(12) Knoevenagel and Fries, *Ber.*, **31**, 761 (1898).

Summary

α,β-Unsaturated carbonyl compounds have been found to add vinyl ethers to the 1,4-conjugated system. Fourteen 2-alkoxy-3,4-dihydro-1,2-pyrans have been synthesized in this manner.

DAYTON, OHIO RECEIVED DECEMBER 28, 1949

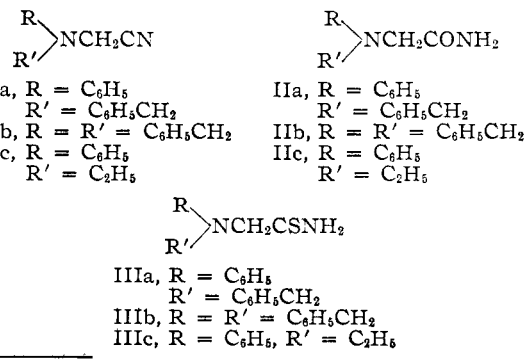
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Preparation and Derivatives of N-Substituted Glycinonitriles

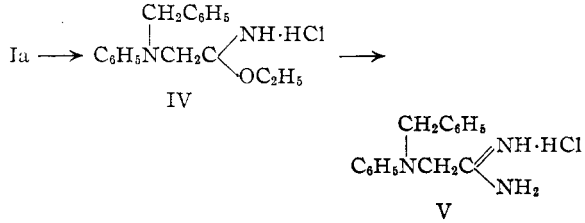
BY ROBERT A. TURNER[1a] AND CARL DJERASSI[1b]

In an earlier article[2] was described a convenient preparation of N,N-dimethylglycinonitrile from dimethylamine, formaldehyde and hydrocyanic acid. Since substituted glycinonitriles were required as starting materials for some projected syntheses, the cyanomethylation procedure was extended to several secondary amines. It was found that when secondary amines other than dimethylamine were employed, particularly aromatic amines, it was necessary to limit the amounts of formaldehyde and cyanide, else resinification became extensive; elevated temperature and a solvent also were necessary. In this manner an apparently general and simple procedure for the cyanomethylation of secondary amines was developed, and its use is illustrated in the experimental section with benzylaniline, dibenzylamine and ethylaniline.

All of the glycinonitriles (I) were readily converted into the corresponding amides (II) by treatment with concentrated sulfuric acid at low temperature, or to the thioamides (III) by reaction with ammonia and hydrogen sulfide. While the nitriles (I) were converted to the corresponding hydrochlorides in anhydrous ether, their behavior differed under other conditions. For instance, when a solution of N-benzyl-N-phenylglycinonitrile (Ia) in commercial ether was treated with hydrogen chloride gas, the only pure product isolated was benzylaniline hydrochloride. Similar results were observed with concentrated hydrochloric acid at 0°, while at a higher temperature some of the amide IIa was also formed. N-Ethyl-N-phenylglycinonitrile (Ic) yielded the nitrile hydrochloride with concentrated hydrochloric acid at 0°, but it gave chiefly the amide IIc on warming. The corresponding dibenzyl derivative Ib, on the other hand, afforded the nitrile hydrochloride under either set of conditions.



In view of the high antihistaminic activity of Antergan[3] and Antistin[4] it was of interest to convert the now readily available nitrile Ia into derivatives of potential value as histamine antagonists. Reaction of the nitrile Ia with hydrogen chloride in chloroform solution with the calculated amount of ethanol led to the corresponding imidic ester hydrochloride IV, which on treatment with ethanolic ammonia gave the hydrochloride of N-benzyl-N-phenylaminoacetamidine (V), an "open analog" of Antistin.[4] The amidine exhibited appreciable antihistaminic activity *in vitro*, but proved to be fairly unstable in aqueous solution. The antihistaminic activity is in agreement with observations made in another series,[5] where replacement of the dimethylamino group by an acetamidine moiety did not adversely affect the pharmacological properties.



Condensation of the thioamide IIIa with two N-substituted 1-bromo-4-aminobutanone-2 hydrobromides (VI)[6] very readily afforded the 4-

(1) Present locations: (a) Department of Biochemistry, Cornell University Medical College, New York, N. Y.; (b) Laboratorias Syntex, S. A., Laguna Mayran 413, Mexico City, D. F.

(2) Turner, THIS JOURNAL, **68**, 1607 (1946).

(3) N,N-Dimethyl-N′-benzyl-N′-phenylethylenediamine; *cf.* Halpern, *Arch. Internat. Pharmacodynamie*, **68**, 339 (1942).

(4) 2-(N-Benzyl-N-phenylaminomethyl)-imidazoline; *cf.* Meier and Bucher, *Schweiz. Med. Wochschr.*, **76**, 294 (1946).

(5) Djerassi and Scholz, THIS JOURNAL, **69**, 1688 (1947).

(6) Prepared by bromination of the corresponding "Mannich bases" in hydrogen bromide–acetic acid solution; *cf.* Land, Ziegler and Sprague, *ibid.*, **69**, 125 (1947).