m.p. 207–209° dec., unchanged by crystallization from hot ethanol.

Oxidation of Cyclohexene in Propionic Anhydride.—This oxidation was carried out in the ultraviolet irradiation apparatus. A solution of 197 g. (2.4 moles) of cyclohexene in 468 g. (3.9 moles) of propionic anhydride was irradiated at 50–60° for 24 hours, oxygen being passed through the solution continuously. Fractional distillation gave 28.5 g. (22% yield) of 3-oxa-4-cycloheptenyl propionate (VIb), b.p. 44–48° (0.5 mm.), $n^{20}D$ 1.4586.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.64; H, 8.34.

Treatment of VIb with acidified 2,4-dinitrophenylhydrazine gave the yellow derivative of adipaldehyde, m.p. 236–237° dec., and the red derivative of cyclopentene-1-carboxaldehyde, m.p. 206–207° dec.

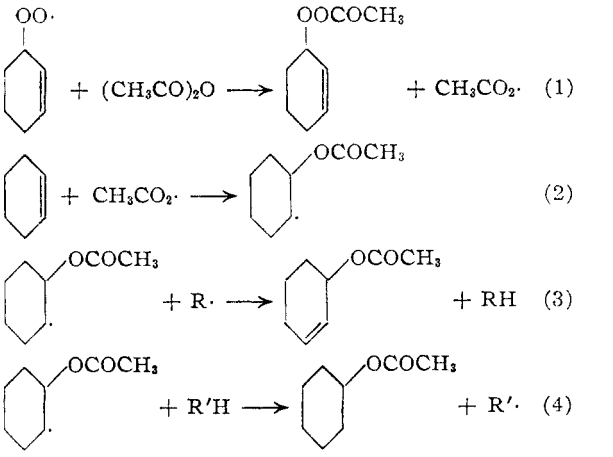
No attempt was made to isolate cyclohexyl propionate and cyclohexene-3-one in this case.

Discussion

The formation of the esters VIa and VIb may be explained by the rearrangement of the first-formed peresters of cyclohexene hydroperoxide. The formation of cyclohexene-3-one may be explained as described by Criegee[4] for α-tetralone. The formation of cyclohexyl acetate and the influence of acetic anhydride on oxygen uptake are particularly noteworthy. Kharasch and Burt[10] report that the two major products of acid-catalyzed decomposition of cyclohexene hydroperoxide in acetic acid are cyclohexenyl acetate and cyclopentene-1-carboxaldehyde. No cyclohexyl acetate was obtained. In the present work cyclohexyl acetate was a major product, while no cyclohexenyl acetate could be found; we are not certain that the latter was absent, however.

The following sequences indicate one possible reaction path, of the several under consideration, which can account for our observations.

The perester in equation 1 is free to undergo rearrangement to VIa. The cyclohexenyl peroxy radicals in equation 1 react as acetoxy radicals rather than decomposing. They account for the cyclohexyl acetate obtained and, probably, are also responsible, by hydrogen abstraction from cyclohexene, for much of the acetic acid obtained. It is believed that the apparent absence of cyclohexenyl acetate from the oxidation products is due to further oxidation of



this unsaturated ester. Work is in progress on this point. It is possible that the R'H in equation 4 is cyclohexene. Independent evidence for the validity of reactions 2, 3 and 4 has been obtained.[11]

In a later paper the extension of this oxidation to other hydrocarbons will be reported.

Acknowledgments.—The continuous encouragement and advice from Dr. P. O. Tawney during the course of this work are gratefully acknowledged. The authors also wish to thank Mr. C. H. Stiteler and Mr. K. A. Leibbrand for technical assistance. Spectrographic work was performed by Mr. R. R. Hampton, Mr. C. L. Hilton and Miss J. E. Wilson.

(10) M. S. Kharasch and J. G. Burt, *J. Org. Chem.*, **16**, 150 (1951).

(11) H. J. Shine and J. R. Slagle, unpublished work.

WAYNE, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR TROPICAL MEDICINE, CAIRO]

The Reaction of α-Ethoxymethylenecarboxylic Esters with Some Cyclic Amidines

BY H. ANTAKI

RECEIVED OCTOBER 15, 1957

The condensation of ethyl ethoxymethyleneacetoacetate and cyanoacetate with 2-aminopyridine and its 3-, 4- and 6-methyl derivatives gives the corresponding ethyl 2-pyridylaminomethyleneacetoacetates and cyanoacetates. These esters were cyclized by distillation under reduced pressure to the respective 4H-pyrido[1,2-a]pyrimidines. 2-Aminoquinoline behaves similarly. The ultraviolet absorption spectra of the compounds have been determined and are discussed in relation to their structures.

The reaction between ethyl ethoxymethylenemalonate and 2-aminopyridine and its derivatives[1–2] has been reported to proceed through the intermediate ethyl 2-pyridylaminomethylenemalonate which cyclized in diphenyl ether to ethyl 4 - ketopyrido[1,2-a]pyrimidine - 3 - carboxylate. 6-Substituted-2-aminopyridines on the other hand give 1,8-naphthyridines,[3–7] a behavior ascribed to steric hindrance coupled with activation of the 3-position through electron release by the 6-substituent. The reaction has now been extended to ethyl ethoxymethyleneacetoacetate and cyanoacetate in view of the observation that the pyrido[1,2-a]-pyrimidines previously reported[8] produced the so-

(1) G. Lappin, THIS JOURNAL, **70**, 3348 (1948).

(2) R. Adams and I. Pachter, *ibid.*, **74**, 5491 (1952).

(3) V. Petrow, E. L. Rewald and B. Sturgeon, *J. Chem. Soc.*, 1407 (1947).

(4) A. Mangini and A. Colonna, *Gazz. chim. ital.*, **72**, 183 (1942); *Chem. Zentr.*, 111 **II**, 2613 (1940).

(5) E. Ochiai and K. Miyaki, *Ber.*, **74**, 1115 (1941).

(6) R. Adams, THIS JOURNAL, **68**, 1317 (1946).

(7) O. Seide, *Ber.*, **59**, 2465 (1926).

(8) H. Antaki and V. Petrow, *J. Chem. Soc.* 551 (1951).

TABLE I

COMPOUNDS I

R_1	R_2	M.p., °C.		Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H*[a]	CH_3CO	182	$C_{15}H_{14}O_2N_4$	63.8	4.9	19.8	63.7	5.1	19.2
H	CN	133	$C_{11}H_{10}O_2N_3$	61.1	4.6	19.4	60.9	5.0	19.2
3-CH_3	CH_3CO	84	$C_{13}H_{16}O_2N_3$	62.9	6.4	11.2	63.1	5.9	10.9
3-CH_3	CN	133	$C_{12}H_{12}O_2N_3$	62.6	5.2	18.2	62.9	5.6	17.8
6-CH_3*	CH_3CO	185	$C_{17}H_{18}O_2N_3$	65.8	5.8	18.0	65.9	5.5	17.9
6-CH_3	CN	154	$C_{12}H_{12}O_2N_3$	62.6	5.2	18.2	62.1	5.2	17.9

[a] Compounds marked with an asterisk have been isolated as the respective amides and the analyses reported accordingly; solvent benzene–petroleum ether (b.p. 60–80°).

TABLE II

COMPOUNDS II

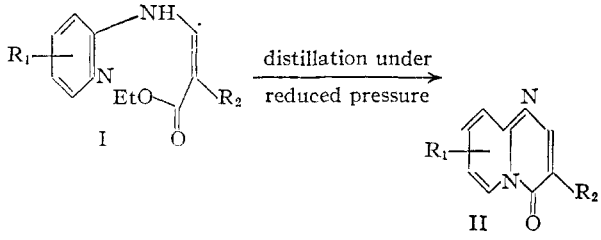
R_1	R_2	M.p., °C.		Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3CO	152	$C_{10}H_8O_2N_2$	63.9	4.2	14.8	63.9	3.8	14.4
H	CN	208	$C_9H_5ON_3$	63.2	2.9	24.5	63.4	2.9	24.1
9-CH_3	CH_3CO	164	$C_{11}H_{10}O_2N_2$	65.3	4.9	13.8	65.0	4.8	13.9
9-CH_3	CN	188	$C_{10}H_7ON_3$	64.8	3.8	22.7	64.8	3.6	23.3
6-CH_3	CH_3CO	124	$C_{11}H_{10}O_2N_2$	65.3	4.9	13.8	65.2	4.9	13.7
6-CH_3	CN	207	$C_{10}H_7ON_3$	64.8	3.8	22.7	65.0	3.8	22.7
8-CH_3	CH_3CO	170	$C_{11}H_{10}O_2N_2$	65.3	4.9	13.8	64.9	5.0	13.1

Solvent benzene–petroleum ether (b.p. 60–80°).

called hepatic shift on oral administration to Gerbels experimentally infected with *S. mansoni*.

Ethyl ethoxymethyleneacetoacetate and cyanoacetate condensed with 2-aminopyridine to give ethyl 2-pyridylaminomethyleneacetoacetate and cyanoacetate, respectively, which cyclized on distillation under reduced pressure to give 3-acetyl- and 3-cyano-4-keto-4H-pyrido[1,2-a]pyrimidine in good yield.

Structure I for these esters is evidenced by the similarity of the ultraviolet absorption spectrum of ethyl 2-pyridylaminomethylenecyanoacetate with the malonate prepared by Lappin (ref. 1) and known to be of this configuration. Compounds I and II give crystalline methosulfates and methoiodides on treatment with the corresponding quaternating agents.



The reaction was extended successfully to 3-methyl-2-aminopyridine to form the 9-methyl derivatives. Whereas ethyl ethoxymethyleneacetoacetate reacted similarly with 4-methyl-2-aminopyridine, condensation with the cyanoacetic ester was complicated by molecular rearrangement. This is summarized in the reaction scheme below.

Compound III could not be cyclized with 1:1 HCl, a procedure which yields V from IV; substance V is quite distinct from the isomeric one obtained by the condensation of 4-methyl-2-aminopyridine with EEMM according to the method described by Lappin (ref. 1). Compound VII was recovered unchanged from a similar treatment (HCl, 1:1) in accordance with its cyclic amidine structure. However, alkaline hydrolysis gave 4-methyl-2-aminopyridine. The fact that IV does not cyclize to VII on refluxing in ethanol precludes its formation from III by prior rearrangement to IV followed by cyclization. 6-Methyl-2-aminopyridine reacted with the two esters to give ethyl 6-

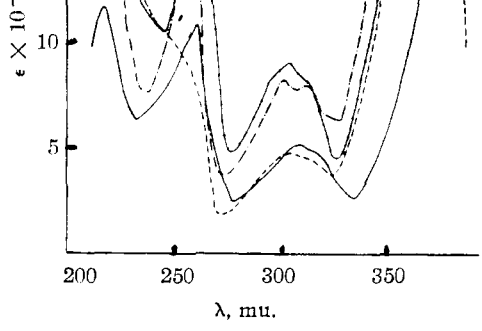
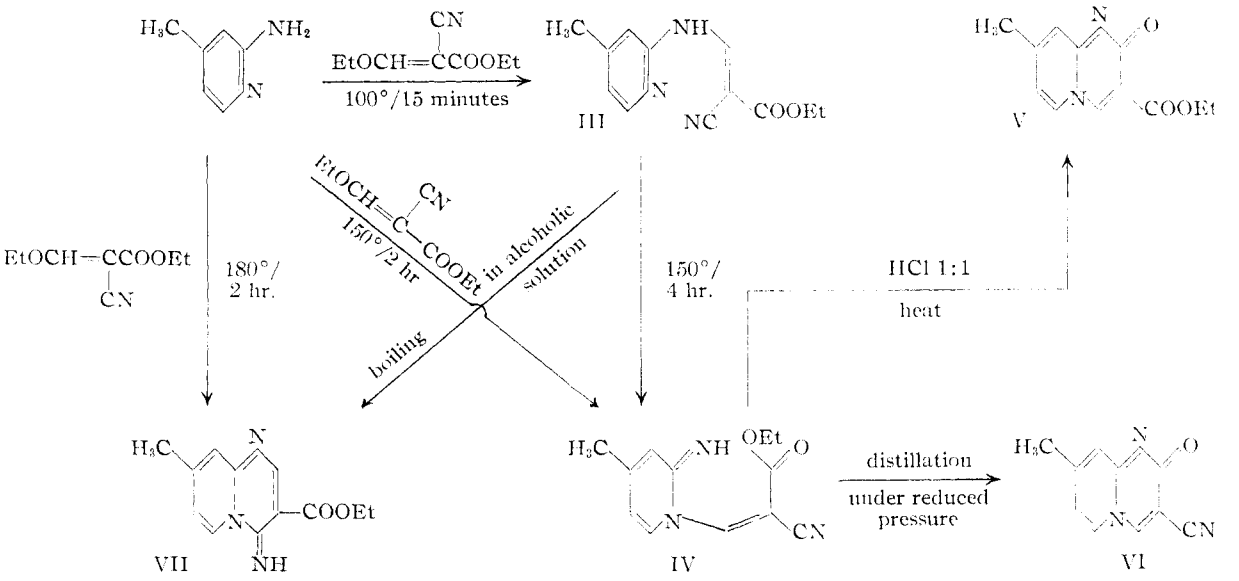


Fig. 1.—Ultraviolet light absorption of 3-acetyl-9-methyl-(++++), 3-cyano-9-methyl-(— · — ·), 3-acetyl-8-methyl-(- - - -), 3-cyano-6-methyl-(———), 4-keto-4H-pyrido-[1,2-a]pyrimidine.

methylpyridyl-2-aminomethyleneacetoacetate and cyanoacetate, respectively. Distillation under reduced pressure, however, gave unexpectedly 3-acetyl- and 3-cyano-4-keto-6-methyl-4H-pyrido-[1,2-a]pyrimidine. That ring nitrogen cyclization in these compounds has occurred is established by their identical ultraviolet absorption spectra as compared with the 9-methyl derivatives where



ring nitrogen cyclization is the only possibility. Additional evidence for this structure is obtained by alkaline hydrolysis which yields 6-methyl-2-aminopyridine. 2-Aminoquinoline gave similarly 3-cyano-4-keto-6,7-benzo-4H-pyrido-[1,2-a]pyrimidine by way of the intermediate ethyl 2-quinolyl aminomethylenecyanoacetate.

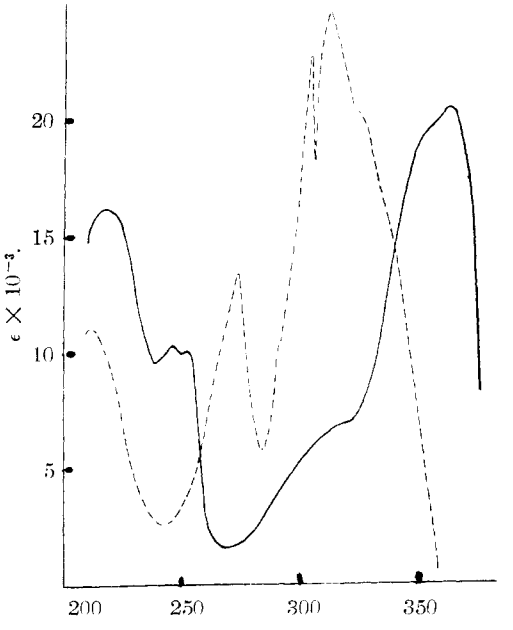
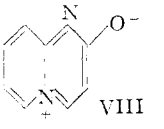


Fig. 2.—Ultraviolet light absorption of ethyl 4-imino-8-methyl-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (- - - -) and 3-cyano-2-keto-2H-pyrido[1,2-a]pyrimidine (———).

The ultraviolet absorption spectra of the compounds in absolute ethanol are illustrated in Figs. 1–3.

A constant feature in the spectra of this class of compounds is the presence of a band with intense absorption in the region 330–390 mμ. N-Substituted pyridone-2-imine has a single broad band[9] with λ_{max} at 350 mμ. The bathochromic shift coupled with a hyperchromic effect exerted on this band is due to conjugative interaction with the newly introduced β-amino-α,β-unsaturated ketone or nitrile chromophore. A band of low intensity in this region is present in the ultraviolet absorption spectrum of 2-keto-2H-pyrido[1,2-a]pyrimidine determined by Pachter and Adams (ref. 2). This may be considered as evidence for the major contribution of zwitterionic fully aromatic structures



VIII

such as VIII to the resonance state of the molecule.

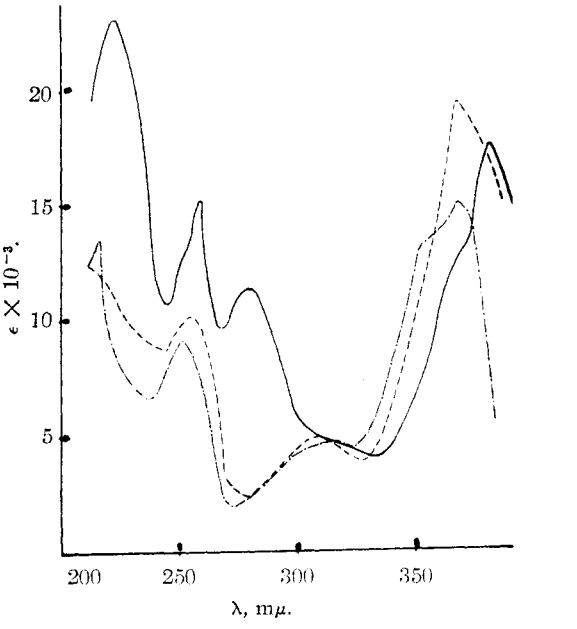


Fig. 3.—Ultraviolet light absorption of 3-cyano-6,7-benzo-(———), 3-acetyl-(- - - -), 3-cyano(— . —) 4-keto-4H-pyrido[1,2-a]pyrimidine.

(9) L. C. Anderson and N. V. Seeger, THIS JOURNAL, **71**, 340 (1949).

A new region of absorption with λ_{max} at *ca.* 308 mμ is present in the spectra of 3-cyano- and 3-acetyl-4-keto - 4H - pyrido[1,2-a]pyrimidines. Ethyl 4 - keto - 4H - pyrido[1,2-a]pyrimidine - 3 - carboxylate displays a similar band. This is corresponding with the region of absorption of the β-amino-α,β-unsaturated ketone chromophore[10] whereas the corresponding carboxylic esters absorb in an essentially similar region.[11,12]

Experimental

3-Cyano-4-keto-6,7-benzo-4H-pyrido(1,2-a)pyrimidine.—2-Aminoquinoline (1.5 g., 1 mol.) and ethyl ethoxymethylene cyanoacetate (1.7 g., 1 mol.) were heated in an oil-bath at 100° for 15 minutes. The solid reaction mass was crystallized after cooling from benzene–petroleum ether to yield white needles, m.p. 171° (Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.4; H, 4.8; N, 15.7. Found: C, 68.0; H, 4.7; N, 15.5). The ester was distilled under reduced pressure (water-pump) and the distillate crystallized from the same solvent as yellow needles, m.p. 215° (Calcd. for $C_{13}H_{17}ON_3$: C, 70.5; H, 3.1; N, 19.0. Found: C, 69.9; H, 3.2; N, 19.2).

Ethyl 4-Imino-8-methyl-4H-pyrido(1,2-a)pyrimidine-3-carboxylate.—Ethyl 4-methylpyridyl-2-aminomethylene-cyanoacetate prepared as above from 4-methyl-2-aminopyridine and ethyl ethoxymethylenecyanoacetate separated in white platelets from alcohol, m.p. 134° (Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.6; H, 5.2; N, 18.2. Found: C, 62.4; H, 5.0; N, 18.3). The ester was refluxed in alcoholic solution for 30 minutes on the water-bath. After removal of the solvent the residue was fractionally crystallized from benzene–petroleum ether. In addition to unchanged ester, ethyl 4-imino-8-methyl-4H-pyrido(1,2-a)pyrimidine-3-carboxylate was obtained as yellow needles, m.p. 152° (Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.3; H, 5.6; N, 18.1. Found: C, 61.9; H, 5.1; N, 17.8).

Ethyl N-(4-methyl-2-imino-1,2-dihydropyridyl)-methylenecyanoacetate was prepared by heating equimolecular amounts of 4-methyl-2-aminopyridine and ethyl ethoxymethylene cyanoacetate at 150° for 2 hr. or by rearranging the isomeric ester at 150° for 2 hr. **Ethyl N-(4-methyl-2-imino-1,2-dihydropyridyl)-methylenecyanoacetate** crystallized from benzene–petroleum ether in pink plates, m.p. 154° (Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.3; H, 5.6; N, 18.1. Found: C, 62.5; H, 5.5; N, 17.9). The ester was boiled for a few minutes with aqueous 1:1 hydrochloric acid, the solution cooled and neutralized with ammonia. Ethyl 2-keto-8-methyl-2H-pyrido[1,2-a]pyrimidine-3-carboxylate crystallized in yellow plates, m.p. 164° from alcohol (Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.0; H, 5.1; N, 12.0. Found: C, 61.8; H, 4.9; N, 11.8). Distillation of the ester under reduced pressure gave 3-cyano-2-keto-8-methyl-2H-pyrido(1,2-a)-pyrimidine in brown plates, m.p. 274° from alcohol (Calcd. for $C_{10}H_7ON_3$: C, 64.8; H, 3.8; N, 22.7. Found: C, 64.5; H, 3.8; N, 22.5).

CAIRO, EGYPT

(10) N. Cromwell, F. Miller, A. Johnson, R. Frank, and D. Wallace, THIS JOURNAL, **71**, 3337 (1949).
(11) S. Glickman and A. Cope, *ibid.*, **67**, 1017 (1945).
(12) V. Boekelheide and E. Agnello, *ibid.*, **72**, 5005 (1950).

[CONTRIBUTION FROM THE DEVELOPMENT DEPARTMENT, UNION CARBIDE CHEMICALS CO., DIVISION OF UNION CARBIDE CORP.]

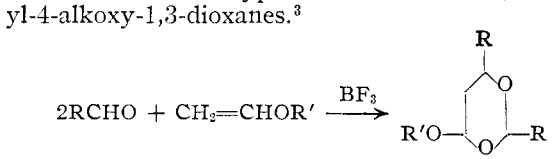
The Chemistry of α,β-Unsaturated Ethers. II. Condensation with Aldehydes

BY R. I. HOAGLIN, D. G. KUBLER AND R. E. LEECH[1]

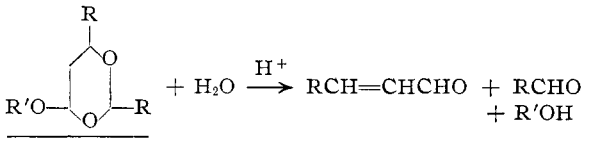
RECEIVED OCTOBER 30, 1957

A new reaction of aldehydes and α,β-unsaturated ethers, which is catalyzed by acids to form β-alkoxyaldehydes and β-alkoxyketones, is reported. These products are readily de-alcoholated to conjugated, unsaturated, carbonyl compounds. This method is of particular value for the production of pure conjugated, unsaturated aldehydes containing one, two, three or more unsaturated groups by the proper selection of the aldehyde and the α,β-unsaturated ether. A mechanism for the reaction is proposed.

A previous paper[2] from this Laboratory discussed the scope and utility of the reaction of acetals and α,β-unsaturated ethers to form 1,1,3-trialkoxyalkanes. More recently it has been found that saturated aliphatic aldehydes and vinyl ethers combine in a Prins-type reaction to form 2,6-dialkyl-4-alkoxy-1,3-dioxanes.[3]



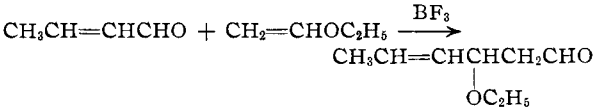
Acid-catalyzed hydrolysis of these products provides α,β-unsaturated aldehydes containing two more carbon atoms in the chain than the starting aldehyde.



(1) Presented in part before the Division of Organic Chemistry at the 132nd Meeting of the American Chemical Society at New York, N. Y., September, 1957.
(2) R. I. Hoaglin and D. H. Hirsh, THIS JOURNAL, **71**, 3468 (1949).
(3) R. I. Hoaglin and D. H. Hirsh, U. S. Patent 2,628,257 (February 10, 1953).

Copenhaver[4] has reported that aldehydes such as benzaldehyde or 2-ethylbutyraldehyde react with vinyl ethers to provide resinous acetals containing the reactants in a 1-to-1 ratio. These resinous acetals were not separated and identified, but acid-catalyzed hydrolysis of these materials provided α,β-unsaturated aldehydes containing two more carbon atoms in the chain than the starting aldehyde. For example, Copenhaver obtained cinnamaldehyde in 60% yield from the hydrolysis of the reaction product of benzaldehyde and vinyl methyl ether.

Our study of this reaction, utilizing crotonaldehyde and vinyl ethyl ether, demonstrates that aldehydes can react with α,β-unsaturated ethers in a 1-to-1 molar ratio. When catalyzed by boron trifluoride, the product was 3-ethoxy-4-hexenal instead of a resinous acetal.



The present investigation shows that the course of the reaction of aldehydes and vinyl ethers will vary depending upon the nature of the reactants

(4) J. W. Copenhaver, U. S. Patent 2,543,312 (February 27, 1951).