Dehydration Reaction of Hydroxamic Acids with Unsaturated Ethers

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In a preceding paper[1] a successful method for the conversion of hydroxamic acids into isocyanates by means of a ketene dimer has been described. It is one of the improved methods of Lossen rearrangement. In the present study, the dehydration of hydroxamic acids with organic reagents is extended to some unsaturated ethers. The dehydration by means of acetylenic ether was tried first, since acetylenic ether is hydrated to give carboxylic ester, which is unreactive with isocyanate and is known to be an effective reagent for the dehydrations of carboxylic acids, phosphoric acids[2], primary nitroparaffins[3,4] and aldoximes[4,5] into carboxylic acid anhydrides, pyrophosphoric acids, nitrile oxides and nitriles, respectively. It has also been confirmed that initially-formed addition compounds of acetylenic ether with the above-mentioned compounds are the necessary intermediate for these reactions.

It has been now established that without a catalyst benzhydroxamic acid does not react with ethoxyacetylene, but the reaction is carried out easily at about 40~50°C in the presence of a catalytic amount of boron trifluoride in tetrahydrofuran to give an addition compound. After removal of the solvent, the

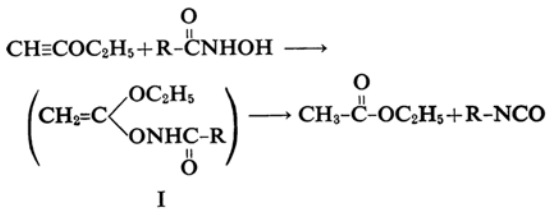
1) T. Mukaiyama and H. Nohira, *J. Org. Chem.*, **26**, 782 (1961).
2) J. F. Arens and T. Doornbos, *Rec. trav. chim.*, **74**, 79 (1955).
3) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, **82**, 5339 (1960).
4) T. Mukaiyama and T. Hata, This Bulletin, **33**, 1382 (1960).
5) T. Mukaiyama and T. Hata, ibid., **33**, 1712 (1960).

TABLE I. REACTION OF HYDROXAMIC ACIDS WITH ETHOXYACETYLENE

Hydroxamic acid R-C(=O)NHOH, R =	g.	EA* g.	Pyrolysis condition: Temp. °C	Pyrolysis condition: Pressure mmHg	Isocyanate: Distilling range °C	Isocyanate: Yield %
$C_6H_5CH_2$-	2.0	1.4	100~120	12~15	75~90	55
p-$CH_3OC_6H_4$-	2.0	1.2	85~100	0.5~1	54~57	65
p-$CH_3C_6H_4$-	2.0	1.4	80~ 90	11~12	69~72	70
p-ClC_6H_4-	1.3	0.9	100~120	1.5	43~45	60
m-$NO_2C_6H_4$-	2.0	1.1	100~120	0.5~1	71~80	50
p-$NO_2C_6H_4$-	2.0	0.95	90~110	0.5~1	80~85	45

* EA = Ethoxyacetylene

adduct is obtained as a viscous liquid which decomposes at about 90°C. When it was decomposed in a Claisen flask at a temperature between 90~110°C under reduced pressure, phenyl isocyanate was obtained in a 65% yield along with ethyl acetate.

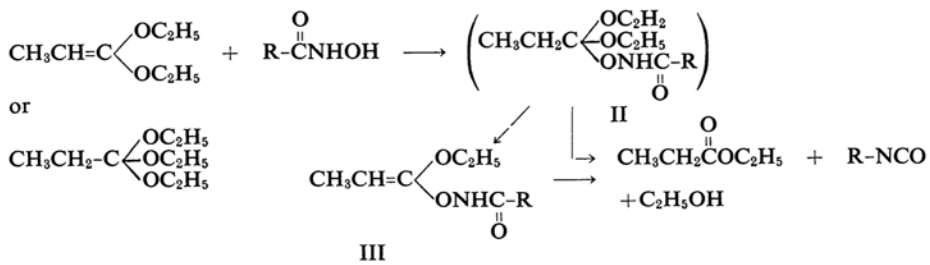


I

In order to obtain a variety of isocyanates by this process, the reactions of hydroxamic acids with acetylenic ether were examined, and successful results were obtained. The results of the experiments are summarized in Table I.

In the next place, dehydration with methylketone diethylacetal, a compound which possesses a similar dehydrating ability, was tried. In this connection, the dehydration of aldoximes with methylketone diethylacetal has been already examined, and an interesting reaction, to give isonitriles, rearranged products, has been reported[4,6]. It was found that a variety of hydroxamic acids react with methylketene diethylacetal at 30~50°C without a catalyst to give addition compounds. These adducts II are unstable, viscous liquids and could not be isolated as pure liquids or crystaline substances. However, by their decomposition at 80~100°C under reduced pressure, the corresponding isocyanates are obtained in good yields along with ethyl propionate and ethanol.

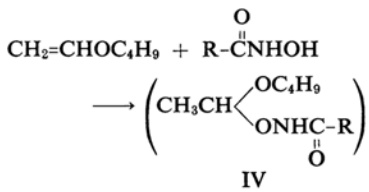
In the course of attempts to isolate the adducts II, a crystalline substance (m. p. 86~86.5°C decomp.) was obtained from the reaction mixture of *p*-nitrobenzhydroxamic acid and methylketene diethylacetal. From the results of the elementary analyses, the infrared spectra and some other examinations, the structure of this substance was concluded to be III, 1-ethoxypropenyl-1-*p*-nitrobenzhydroxamate. It decomposes into *p*-nitrophenyl isocyanate and ethyl propionate almost quantitatively. In addition, the same substance is obtained by the reaction of *p*-nitrobenzhydroxamic acid and ethyl orthopropionate; this reaction is also considered to proceed through the same intermediate II, as is shown in the following equations:



III

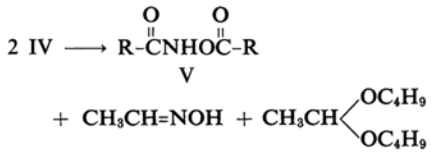
Finally, the dehydration of hydroxamic acids with vinyl ether, which has been confirmed to be an effective reagent for the dehydration of benzaldoxime into benzonitrile[5], was examined. Analogous to the reaction described above, benzhydroxamic acid reacts with *n*-butylvinyl ether in the presence of a catalytic amount of phosphoric acid to give an adduct as a viscous liquid.

6) T. Mukaiyama, K. Tonooka and K. Inoue, *J. Org. Chem.*, **26**, 2202 (1961).



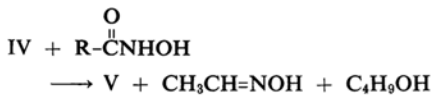
IV

This adduct could not be isolated pure, but it was confirmed to possess the structure of IV from its infrared spectrum. It decomposes, against expectation, however, at a relatively low temperature (50~70°C) into dibenzhydroxamic acid (or benzoyl benzhydroxamate) (V), acetaldoxime, acetaldehyde dibutylacetal and butanol. The formation of these products may be explained by the following two equations:



V

and

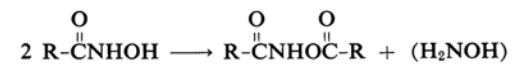


Dibenzhydroxamic acid (m. p. 163~164°C) is identified with an authentic sample, showing no depression in mixed melting points. The presence of acetaldoxime, acetaldehyde dibutylacetal and butanol is confirmed by fractional distillation and gas-chromatographic analysis.

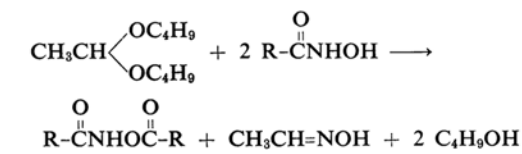
This type of reaction, to produce dihydroxamic acids from hydroxamic acids by the action of ethyl acetoacetate or potassium cyanide, has been reported by Moissan[7], wherein it was suggested that this reaction is equivalent to 1 mol. dehydroxylamination from 2 mol. of hydroxamic acids. But some points concerning the mechanism of the reaction have remained unclarified.

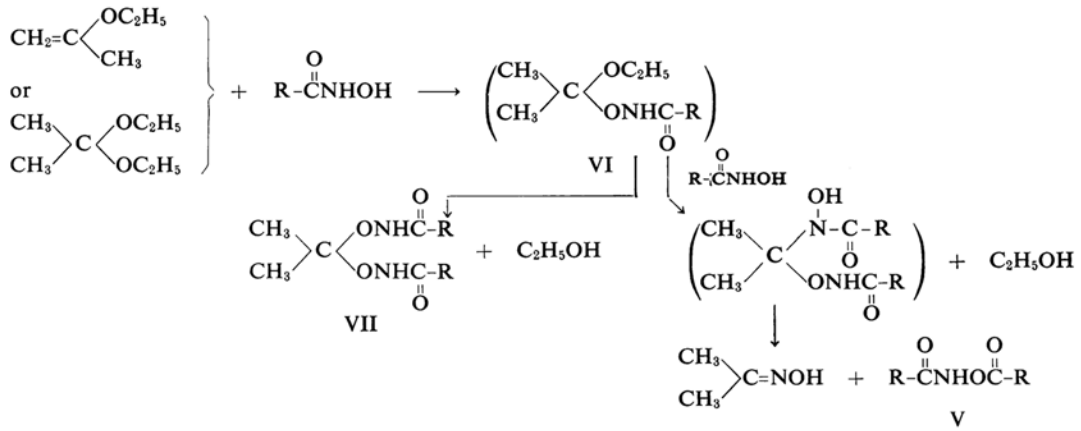
Table II. Reactions to give dihydroxamic acids

Hydroxamic acid R-CNHOH (R=)	Dehydroxylaminating reagent	Dihydroxamic acid R-CNHOC-R: Yield %	M. p. °C
$C_6H_5CH_2$-	*n*-Butyl vinyl ether	37	150~151
p-$CH_3OC_6H_4$-	*n*-Butyl vinyl ether	47	143~143.5
p-$CH_3C_6H_4$-	*n*-Butyl vinyl ether	52	156~157
p-$NO_2C_6H_4$-	*n*-Butyl vinyl ether	27	174.5
C_6H_5-	*o*-Nitrobenzaldehyde	38	163~164
C_6H_5-	Acetaldehyde di-*n*-butylacetal	77	163~164



It is now established that a variety of hydroxamic acids react with *n*-butyl vinyl ether under the same condition as has been mentioned in the case of benzhydroxamic acid to give corresponding dihydroxamic acids (Table II). Further experiments were tried in order to ascertain whether or not carbonyl compounds or their derivatives, which are able to react with hydroxylamine to give oximes, are effective in this type of reaction. Analogous to the reaction of vinyl ether, dibenzhydroxamic acid has been obtained by the reaction of benzhydroxamic acid with acetaldehyde dibutylacetal, *o*-nitrobenzaldehyde, ethylpropenyl ether or acetone diethylketal. When acetaldehyde dibutylacetal is used, for example, the reaction is shown by the following equation.





7) M. U. Moissan, *Compt. rend.*, **140**, 1398 (1905).

In this case, the reaction is thought to proceed through the intermediate IV, and this result, together with the formation of III from ethyl orthopropionate, suggests that the ethoxyl group in orthoester or acetal is easily replaced by the -ONHCO-R group. This has been further confirmed by the following evidence.

When ethyl propenyl ether or acetone diethylketal was used, a crystalline product which melts at 160~161°C was isolated along with dibenzhydroxamic acid and identified as isopropylidene bis-benzhydroxamic acid, VII. Therefore these reactions are thought to proceed via the intermediate VI, which in turn changes into V or VII.

Experimental

Reaction of Benzhydroxamic Acid with Ethoxyacetylene.—A solution of ethoxyacetylene (1.1 g., 0.016 mol.) in 7 ml. of dry tetrahydrofuran was added dropwise with stirring over a period of 10 min. into a suspension of benzhydroxamic acid (2.0 g., 0.015 mol.) and 3 drops of boron trifluoride etherate in 8 ml. of tetrahydrofuran at 40°C. After the addition was completed, the mixture was stirred for an additional hour. The solvent was subsequently removed under reduced pressure, and an adduct I ($R = C_6H_5-$) was obtained as a viscous liquid which decomposed at about 100°C. By the decomposition of this adduct in a Claisen flask at 90~100°C under reduced pressure (12~15 mmHg), 1.1 g. (65%) of phenyl isocyanate was obtained, along with 0.8 g. (60%) of ethyl acetate.

Similarly, benzyl-, *p*-anisyl-, *p*-tolyl-, *p*-chlorophenyl-, *p*-nitrophenyl and *m*-nitrophenyl isocyanate were obtained from corresponding hydroxamic acids. Their experimental conditions and yields are listed in Table I.

Reaction of Benzhydroxamic Acid with Methylketene Diethylacetal.—A mixture of benzhydroxamic acid (4.11 g., 0.03 mol.) and methylketene diethylacetal (7.8 g., 0.06 mol.) in 30 ml. of dry ether was stirred for 3 hr. at 30°C. After the mixture became homogeneous, the solvent was removed under reduced pressure, and an adduct II ($R = C_6H_5-$) was obtained as a colorless, viscous liquid. By a similar pyrolytic process, it decomposed into ethyl propionate, phenyl isocyanate and ethanol in a high yield. Phenyl isocyanate was converted into diphenylurea by the addition of aniline (2.81 g., 0.03 mol.) to the pyrolyzate, which was collected in a cooled trap; 5.28 g. (83%, m. p. 238~239°C) of sym-diphenylurea was obtained.

Similarly, benzyl- and *p*-anisyl isocyanate were obtained from corresponding hydroxamic acids in yields ranging from 50 to 85%.

Formation of 1-Ethoxyprophenyl-1-*p*-nitrobenzhydroxamate (III).—A mixture of *p*-nitrobenzhydroxamic acid (6.6 g., 0.036 mol.) and methylketene diethylacetal (8.0 g., 0.062 mol.) in 70 ml. of dry ether was stirred for 4 hr. at 30°C. After the mixture became homogeneous, the solvent was removed under reduced pressure, and 8.9 g. (92%) of III ($R = NO_2-C_6H_4-$), was obtained as pale yellow crystalline. It was recrystallized from ether, m. p. 86~86.5°C, decomp.

Found: C, 54.41; H, 5.39; N, 10.62. Calcd. for $C_{12}H_{14}N_2O_5$; C, 54.13; H, 5.30; N, 10.52%.

It was readily soluble in ether, ethanol and sparingly in benzene and carbon tetrachloride. Its hydrolysis in dilute hydrochloric acid and ethanol gave *p*-nitrobenzhydroxamic acid, which was confirmed by its characteristic color reaction with ferric chloride. The infrared absorption bands are 3060~3125 cm^{-1} m (broad), 2986m, 2930m, 1635w (shoulder), 1600s, 1520w (shoulder), 1435m, 1310m, 1235s, 1155s, 1109w, 1075s, 1030w, 972s, 943m, 870m, 857m, 810m, (Nujol or carbon tetrachloride solution, s=strong, m=medium, w=weak).

Similarly, the same substance III was obtained from the reaction of *p*-nitrobenzhydroxamic acid with ethyl orthopropionate in an 82% yield.

Decomposition of III.—The above-mentioned III (5.32 g., 0.02 mol.) was decomposed under reduced pressure (17~18 mmHg) in a 50 ml. Claisen flask heated in an oil bath (150°C). The low boiling part of the pyrolyzate was collected in a cooled trap, from which 1.54 g. (75%, b. p. 98~99°C) of ethyl propionate was obtained by distillation. Separately, 2.73 g. (91%, m. p. 53~55°C) of *p*-nitrophenyl isocyanate was obtained from the pyrolysate which remained in the flask (recrystallization from chloroform).

Reaction of Benzhydroxamic Acid with *n*-Butyl Vinyl Ether.—A mixture of benzhydroxamic acid (2.75 g., 0.02 mol.), *n*-butyl vinyl ether (2.0 g., 0.02 mol.) and 2 drops of phosphoric acid (85%) in 11 ml. of ethyl acetate was refluxed for 3 hr., cooled and filtered. The precipitate of dibenzhydroxamic acid was washed with warm water and recrystallized from ethyl acetate (yield, 1.35 g. 56%, m. p. 163~164°C). By fractional distillation of the filtrate, two fractions of A (37~42°C/12.5 mmHg, 0.62 g.) and B (65~75°C/12.5 mmHg, 0.45 g.) were obtained. The fraction A was identified as a mixture of acetaldoxime and *n*-butanol by gas-chromatographic analysis, while the B was acetaldehyde di-*n*-butylacetal.

Similarly, a variety of dibenzhydroxamic acids were obtained from the reaction of corresponding hydroxamic acids with *n*-butyl vinyl ether or some other reagents. The results of all the experiments are summarized in Table II.

Formation of the Intermediate IV.—A mixture of benzhydroxamic acid (2.75 g. 0.02 mol.), *n*-butyl vinyl ether (2.0 g., 0.02 mol.) and 2 drops of phosphoric acid was warmed without a solvent at 50°C for an hour, and an adduct IV ($R = C_6H_5-$) was obtained as a viscous liquid. The infrared absorption bands of a carbon tetrachloride solution are at 3404 cm^{-1}(w) attributed to the free N-H group and at 3225 cm^{-1}(m) (broad) to the associated N-H group. Bands due either to the O-H group of hydroxamic acid or to the $C{=}CH_2$ group of vinyl ether were not observed. This intermediate IV decomposed to give dihydroxamic acid on heating, and even at room temperature it changed slowly to give dihydroxamic acid.

Formation of Isopropylidene-bis-benzhydroxamic Acid VII.—A mixture of benzhydroxamic acid

(2.75 g., 0.02 mol.) and isopropenyl ether (1.72 g., 0.02 mol.) in 10 ml. of ethyl acetate was refluxed for an hour in the presence of *p*-toluenesulfonic acid (0.03 g.). The solvent was removed under reduced pressure, and the residue was washed with ether and subsequently with warm water. It was then dried and weighed (1.1 g., m. p. 140~146°C). By fractional crystallization from ethyl acetate, 0.5 g. of VII (R = C_6H_5–, m. p. 160~161°C) and 0.1 g. of dibenzhydroxamic acid (m. p. 163~164°C) were obtained.

Found (for VII): C, 65.02; H, 5.89; N, 9.17. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91%.

The infrared absorption bands are 3175 cm^{-1} m (broad), 2955s, 2890m, 1658s, 1592m, 1326m, 1205w, 1159m (Nujol or carbon tetrachloride solution).

Similarly, the same substance VII was obtained from the reaction of benzhydroxamic acid with acetone diethylketal in a good yield (75%), along with a trace of dibenzhydroxamic acid.

Summary

Dehydration reactions of hydroxamic acids with unsaturated ethers have been studied. The reaction of hydroxamic acids with ethoxyacetylene or methylketene diethylacetal led to the formation of corresponding isocyanates, along with ethyl acetate or ethyl propionate and ethanol, through the intermediate of addition compounds of hydroxamic acids and the dehydrating reagents.

The reaction of hydroxamic acids with *n*-butyl vinyl ether, on the other hand, led to the formation of dihydroxamic acids, along with acetaldoxime and acetaldehyde dibutylacetal. This type of reaction was further extended to the reactions of hydroxamic acids with propenyl ether, acetals and aldehydes, and the formation of dihydroxamic acids was confirmed.

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