[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

The Dehydration of Secondary and Tertiary Alcohols

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Ten secondary and two tertiary alcohols of varied length and complexity have been dehydrated by means of acid reagents, in order quantitatively to determine the identity and ratio of the resulting olefins. Much of the recorded work of this kind is unreliable or even contradictory on account of incompletely controlled reaction conditions and failure properly to separate the reaction products. To avoid these sources of error, standardized procedures of dehydration have been used and all olefins have been isolated as pure individuals, then oxidized with ozone to demonstrate their structure. Besides the products expected from straight dehydration, rearranged derivatives have been found. We have tried, without success, to reconcile our results with the theory of Goldwasser and Taylor.[1] We have found them well covered by Whitmore's theory.[2]

The customary action of an aldehyde on a Grignard reagent was used to prepare 3-hexanol, 2-methyl-3-pentanol, 4-methyl-2-pentanol, 6-methyl-3-heptanol, 2,2-dimethyl-3-hexanol and 1-phenyl-1-butanol. Other alcohols were obtained from a research project of the American Petroleum Institute directed by Dr. C. E. Boord, at this University, to include 4-methyl-2-pentanol, 2-heptanol, 5-methyl-2-heptanol, 4-octanol, 2,4-dimethyl-3-pentanol, 2-methyl-2-butanol, and 2,2,3-trimethyl-3-pentanol.

Experimental Procedure

For liquid phase dehydration, concentrated (94%) sulfuric acid of analytical grade was added to the alcohol, in 10% weight; or else concentrated (85%) phosphoric acid was used in the ratio of one mole of acid to one mole of alcohol. Dehydration was performed by heating with an electric mantle the mixture of acid and alcohol held in a glass flask sealed to a distilling column 60 cm. long and 12 mm. in internal diameter. To permit the removal of the olefins as formed, the temperature of the reaction mass was adjusted slightly above the boiling range of the dehydration products. Each experiment consumed one mole of alcohol and was completed in two hours. The experiments were repeated until enough material was on hand for separation, characterization and identification of each olefin.

For vapor-phase dehydration, the alcohols were passed at the rate of 40 ml. per hour through a column of reagent held in a Pyrex tube 135 cm. long and 20 mm. in outside diameter. The tube was electrically heated and controlled to a uniform temperature. The reagents were: (1) commercial, 8–14 mesh, alkali-free "activated alumina"; (2) "floridin," a commercial clay activated by heating at 225° in a current of air; (3) aluminum sulfate, impregnated on pumice (42 g. of the dodecahydrate on 80 g. of pea-size pumice dehydrated at 200° for two hours); (4) phosphoric acid, made up by mixing 120 g. of the commercial "solid acid" with 35 g. of pea-size pumice and dehydrating at 300° for two hours in a stream of nitrogen.

The dehydration products were washed with dilute sodium bicarbonate, rinsed, then dried by freezing out the water at −78°. Fractional distillation was performed in adiabatic distilling columns packed with $^1/_{16}$" single turn metal helices and equipped with a head of the total reflux-partial take-off type. As needed, columns were used which had a controlled efficiency of 69, 55, 50 or 45 theoretical plates, determined with a mixture of *n*-heptane and methylcyclohexane.[3] The distillate was collected at the rate of 1 to 3 ml. per hour in a water-jacketed receiver graduated in 0.1 ml. Individual fractions generally amounted to 10–12 ml. A continuous record was kept of the boiling points and prevailing pressures. Only in the few cases where two olefins boiled so close that they could not be separated by means of the 69-plate column was the mixture ozonized and the ratio of the olefin determined from the ratio of their ozonization products, as shown in the text.

For identification, solutions of 0.1 to 0.4 mole of olefin in methylene chloride were ozonized at −78°. The ozone generator used was that recently described[4]; the procedure of ozonide hydrolysis and simultaneous oxidation had been outlined previously.[5] The cleavage products were divided by means of cold, dilute sodium carbonate into an acid portion containing the oxidized aldehydes and a neutral portion containing the ketones. The ketones were isolated by fractional distillation and converted to their 2,4-dinitrophenylhydrazone or semicarbazone. The salts of the acid portion were twice extracted with ether to eliminate traces of ketones and unreacted ozonides, acidified with phosphoric acid and subjected to continuous ether extraction overnight. The ether extract was cooled to −78° to freeze out the water, and a neutral equivalent determined on an aliquot part. After removal of the ether, the acids were isolated by fractional distillation when possible, or else as their ethyl esters. Finally they were converted to their *p*-toluide or anilide. All observed melting points were confirmed by mixed melting points with known samples.

The identification of the olefins was quite convincing, as ozonization yielded crystalline derivatives of the oxidation products in amounts averaging 45%. The few compounds which were not identified as thoroughly were determined as follows.

1. The fraction marked "mixed" from the fifth alcohol in Table I gave on ozonization 30% of acetic acid + 12% of methyl butyl ketone, 22% of propionic acid + 8% of methyl propyl ketone and 20% of butyric acid + 14% of methyl ethyl ketone. Too complicated to have quantitative significance, the fraction was merely interpreted as a mixture of 3-methyl-2-heptene + 4-methyl-3-heptene + 3-methyl-3-heptene.

2. The sample of 2,3-dimethyl-1-hexene obtained from the tenth alcohol in Table I gave 40% of $CH_3COCH(CH_3)C_3H_7$. Lacking an authentic sample for comparison, we degraded this ketone to α-methylvaleric acid, whose anilide and toluide were subjected to mixed melting points with derivatives of the authentic acid.

3. The tetramethylethylene obtained from the seventh and eighth alcohols was a small fraction with acceptable boiling point and refractive index. Upon ozonization it gave an acetone test of 105%; since our best ozonization yields were not higher than 75%, this result was interpreted as an indication that two moles of acetone were made from one mole of hexene, and that tetramethylethylene *could* be present. This experimental indication is insufficient to serve as a basis for a discussion.

Experimental Results

The dehydration results are listed in Table I,

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[1] Goldwasser and Taylor, THIS JOURNAL, **61**, 1751 (1939).

[2] Whitmore, *ibid.*, **54**, 3274 (1932).

[3] Ward, U. S. Dept. of Interior. Technical paper 600 (1939).

[4] Henne and Perilstein, THIS JOURNAL, **65**, 2183 (1943).

[5] Henne and Hill, *ibid.*, **65**, 752 (1943).

TABLE I

DEHYDRATION RESULTS

Alcohol	Reagent[a] and temp., °C.	Total	Olefin yields, in mole per mole of alcohol						Residue,[d] grams per mole
			No shift		Double bond shift		Carbon shift		
CCCCCC | O | H			CCC=CCC	CC=CCCC	C=CCCCC				
	A 385	0.92	0.71	0.14	0.07				6.1
	AS 300	.92	.58	.23	.12				5.1
	Ph 250	.86	.62	.19	.06				8.7
	Ph L	.88	.62	.25	.02				8.3
	S L	.81	.61	.20	..				12.3
CCCCCCC | O | H			C=CCCCCC	CC=CCCCC	CCC=CCCC				
	A 385	1.00	0.28	0.70	0.02				2.0
	AS 300	.94	.11	.52	.31				4.3
	Ph 300	.84	.14	.28	.42				2.3
	F 385	.89	.13	.51	.26				5.6
	Ph L	.92	.08	.72	.12				7.0
	S L	.94	.08	.71	.15				1.5
CCCCCCCC | O | H			CCC=CCCCC	CCCC=CCCC					
	A 380	0.92	0.46	0.46					8.1
PhCCCC | O | H			[b] PhC=CCC [c]						
	A 390	0.96	0.36	0.60					3.0
	AS 300	.91	.68	.23					9.0
CCCCCCC C | O | H			CCCCC=CC C	CCCC=CCC C	CCC=CCCC C			‘(CC=CCCCC + CCC=CCCC + C C CCC=CCCC mixed) C	
	A 385	0.91	0.46	0.26	0.20			..	8.1
	AS 300	.92	.50	.20	.15			0.07	8.5
	Ph 250	.82	.14	.20	..			.48	15.0
	Ph L	.87	.58	.16	.11			.03	4.7
	S L	.86	.43	.28	.16			..	10.0
CCCCCCC C | O | H			CCCCCC=C C	CCCCC=CC C					
	A 385	0.97	0.36	0.61					3.4
CCCCC C | O | H			CCCC=C C	CCC=CC C	CC=CCC C	C=CCCC C	CC=CCC C	CC=CC C C	
T	A 390	0.88	0.43	0.43	0.02	..	..	..	5.6
P	A 380	.87	.44	.44	..	..	..	..	4.7
Technical	AS 300	.93	.02	.12	.60	0.06	0.12	0.02	5.3
Pure	AS 300	.94	.02	.14	.55	.11	.11	.02	5.0
T	Ph 150	.66	.03	.09	.45	.06	.03	..	33.0
T	Ph 200	.76	.02	.09	.47	.09	.09	..	23.0
T	Ph 250	.82	.02	.14	.46	.09	.09	.02	10.0
P	Ph 250	.87	.06	.12	.46	.12	.12	..	9.3
T	Ph 300	.87	.02	.11	.52	.11	.11	.02	10.0
T	Ph 350	.80	.02	.08	.54	.08	.08	.02	10.0
T	F 300	.87	.09	.09	.52	.09	.09	..	9.0
T	F 350	.90	.05	.10	.50	.10	.15	..	8.0
T	Ph L	.81	.23	.35	..	.23	..	..	10.0
T	S L	.88	.30	.49	.10	..	..	..	7.7
CCCCC C | O | H			CCC=CC C	CC=CCC C	C=CCCC C		CC=CCC C	CC=CC C C	
	A 385	0.93	0.47	0.30	0.08		..	..	3.9
	AS 300	.93	.19	.50	.12		0.12	..	4.4
	Ph 250	.89	.12	.46	.06		.15	0.09	9.1
	Ph L	.93	.23	.70	..		..	..	10.0
	S L	.86	.14	.70	.02		..	..	8.0
CCCCC C | C O | H			CC=CCC C C				CC=CCC CC		
	A 375	0.84	0.72				0.12		10.0
	A 350	.89	.76				.13		8.0

TABLE I (*Concluded*)

Alcohol	Re-agent[a] and temp., °C.	Olefin yields, in mole per mole of alcohol							Residue,[d] grams per mole
		Total	No shift		Double bond shift	Carbon shift			
C CCCCCC C | O H			[b] C CCC=CCC C	[c]		C=CCCCC CC	CC=CCCC C C	CCC=CCC CC	
	A 350	0.32	0.09	0.06		0.17	..	..	81.4
	A 375	.90	.36	.09		.40	0.05	..	14.0
	A 385	.79	.33	.14		.19	.14	..	15.6
	A 400	.89	.40	.04		.40	.04	..	16.0
	AS 300	.64	.12	..		.12	.24	0.10	39.4
	Ph 250	.89	..	..		.22	.22	.30	9.4
	Ph L	.38	..	..		.08	.25	.02	67.2
	S L	.67	.10	..		.10	.39	.10	24.6
C CCCC | O H			C=CCC ·C	CC=CC C	CCC=C C				
	A 150	0.73	0.29	0.44	..				15.3
	A 200	.86	.18	.64	0.04				3.4
	A 250	.88	.27	.53	.08				2.6
	A 300	.93	.30	.55	.09				1.3
	A 350	.93	.35	.47	.11				2.2
	A 400	.92	.22	.56	.14				2.6
CC CCCCC C | O H			CC CCC=CC C			CC C=CCCC C			
	A 260	0.51	0.21			0.31			27.0

[a] A = alumina; AS = aluminum sulfate; F = fluoridin; Ph = phosphoric acid; S = sulfuric acid; L = liquid phase. [b] = low boiling isomer. [c] = high boiling isomer. [d] Residue: in most cases, it was mainly unreacted carbinol. On phosphoric acid at 250° or higher, it was polymerized olefins mostly.

TABLE II

PHYSICAL PROPERTIES

	F. p., °C.	B. p., °C. (760 mm.)	B. p., °C.	B. p., Mm.	n^{20}_D	d^{20}_4
2,3-Dimethyl-2-hexene	Glass	122.11	121.11	737	1.4258	0.73957
2,2-Dimethyl-3-hexene (high boiling isomer)	Glass	105.75	104.80	740	1.4099	.71865
1-Phenyl-1-butene (high boiling isomer)	−43.06	198.68	197.43	738	1.5420	.90186
1-Phenyl-1-butene (low boiling isomer)	Glass	187.13	185.77	737	1.5284	.89772
3-Hexanol			87.0	109	1.4168	.8195
2-Methyl-3-pentanol			86.0	155	1.4178	.8230
2-Methyl-4-pentanol		133.0			1.4122	.8075
2-Methyl-5-heptanol		169.7			1.4254	.8220
2,2-Dimethyl-3-hexanol		156.1			1.4261	.8342
1-Phenyl-1-butanol		232.9			1.5139	.9740

which shows that in vapor phase dehydration alumina caused the least amount of rearrangement; aluminum sulfate brought about more rearrangement; solid phosphoric acid was by far the cause of the more complicated shifts.

Physical properties of compounds which were obtained in a particularly high state of purity are listed in Table II.

Discussion

Our dehydration results are explainable on the basis of Whitmore's theory.[1] The normally expected olefins are the result of the loss of an OH^- group, with creation of a carbonium at the place of loss; a subsequent proton elimination from a carbon adjacent to the carbonium permits the creation of a double bond. Whitmore has extensively studied the relative tendency of various groups to yield such a proton, by observing the ratio of the resulting olefins.[6] The olefins which correspond to one or several double bond shifts are explained by the shift onto the carbonium of an electron pair bearing a hydrogen from an adjacent carbon, prior to proton loss and creation of a double bond. The olefins with rearranged chains are similarly obtained by the shift onto the carbonium of a pair of electrons bearing a CH_3 group, prior to proton loss and double bond creation. All the compounds actually found can be so explained. It is also possible to predict compounds which were not found.

As to the intimate mechanism, Whitmore considers that the shifts occur without leaving the organic molecule. In discussion with Dr. W. G. Young, of the University of California at Los Angeles, the senior author (A. L. H.) came to pre-

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(6) Whitmore, THIS JOURNAL, **64**, 2970 (1942), and preceding papers.

fer the view that after the initial loss of the OH^- group, it is a series of transfers of protons (or $CH_3{}^+$ groups) to the catalyst with consequent formation of an olefin, followed by re-transfer of the proton from the catalyst onto the olefin. This preference is motivated by the consideration that the re-transfer should not occur at random, but preferentially onto that side of the double bond where electron density is highest. The number of probable isomers is thus cut down, and fits the experimental results closer. Addition of a proton from an acid catalyst to an olefin is by no means in contradiction with Whitmore's work.[7]

Table I shows that repeated or complex shifts are infrequent and occur only with the more acid catalysts; it also shows a marked tendency to reduce the amount of branching; methyl group shiftings from 2- to 3-position are pronounced, but rare from 3- to 4-position.

Summary

Ten secondary and two tertiary alcohols have been dehydrated by means of agents of varied acidity, and at different temperatures. The ratios of the resulting olefins have been established. Results are tabulated and shown to be in good agreement with Whitmore's theory.

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[7] Laughlin, Nash and Whitmore, THIS JOURNAL, **56**, 1395 (1934).

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Porphyrexide and Porphyrindine Analogs Derived from 1-Hydroxyaminocyclohexyl Cyanide

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Porphyrexide and porphyrindine, synthesized by Piloty and his co-workers[1,2] some forty years ago, are substances of considerable general interest. They are also of some special utility in connection with certain analytical and structural problems relating to proteins that possess substituent sulfhydryl groups.[3,4] In this Laboratory, porphyrindine has been used advantageously in studies of so-called sulfhydryl-enzymes; for example, as one of the diagnostic reagents for the differentiation in the protein-enzyme, urease, of the more "accessible" and rapidly oxidized *a* sulfhydryl fraction from the *b* category that has appeared to be more directly associated with reversible inactivations of this enzyme.[5,6]

Our present purpose has been to test the generality of the Piloty synthesis and, if possible, to make available additional useful substances of this class. A spirocyclohexyl analog of porphyrexide, here described, has been found to be non-inactivating with respect to urease.[6] This observation gains in significance, in its bearing upon certain structural relationships in urease, when it is considered that the magnitude of the potential[7] of the half-reduced dye system, E'_0, at *p*H 7, was ascertained in this work to be 0.690 volt. This is approximately the apparent potential of the iodine:iodide system (in very dilute aqueous solution) under comparable conditions; it will be recalled that urease is inactivated readily in the presence[6] of iodine plus iodide-ion under conditions that do not permit a similar drastic action by porphyrindine.

The Piloty Synthesis.—The original synthesis included a number of steps starting with the addition of the elements of hydrogen cyanide to acetoxime in the preparation of 1-hydroxyaminoisobutyronitrile. We have demonstrated[8] how this initial step may be accomplished reliably with the use of a phosphate–hydrocyanic acid buffer mixture and have found, in agreement with the experience of Kuhn and Franke, that the subsequent steps in the synthesis need occasion no difficulty, although the over-all yields may be low.[9] The essential steps in the building of a molecule of the porphyrexide type are well illustrated in the Experimental Part.

In exploratory tests with various oximes, we ascertained that our procedure for the hydrogen cyanide:ketoxime reaction gives excellent results when applied to the preparation of 1-hydroxyaminocyclohexyl cyanide from cyclohexanone oxime. This constitutes the initial step in the synthesis, recorded in the experimental part, that yields the cyclic N-hydroxy compounds, spiro-(1-cyclohexane-4')-2',5'-diimino-3'-hydroxyhydantoin A and the corresponding bis-hydrazino derivative C. These substances are oxidizable readily to compounds B and D, respectively. The oxidant, B, spiro-(1-cyclohexane-4')-2',5'-diimino-hydantoin-N-(3')-oxide, has been found to be noticeably more stable in aqueous solutions

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[1] O. Piloty and V. Schwerin, *Ber.*, **34**, 1863, 1870, 2354 (1901)

[2] O. Piloty and W. Vogel, *ibid.*, **36**, 1283 (1903).

[3] R. Kuhn and P. Desnuelle, *Z. physiol. Chem.*, **251**, 14 (1938).

[4] J. P. Greenstein, *J. Biol. Chem.*, **125**, 501 (1938).

[5] L. Hellerman, in *Cold Spring Harbor Symposia on Quantitative Biology*, **7**, 165 (1939).

[6] L. Hellerman, F. P. Chinard and V. R. Deitz, *J. Biol. Chem.*, **147**, 443 (1943).

[7] Electrode potentials are referred to the normal hydrogen electrode. See W. M. Clark, "The Determination of Hydrogen Ions," Williams and Wilkins Co., Baltimore, Md., 1928.

[8] C. C. Porter and L. Hellerman, THIS JOURNAL, **61**, 754 (1939).

[9] The preparative details have been examined also by H. A. Lillevik, R. L. Hossfeld, H. V. Lindstrom, R. T. Arnold and R. A. Gortner, *J. Org. Chem.*, **7**, 164 (1942).