The Vapor Phase Catalytic Dehydrogenation of 1,6-Hexanediol

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The dehydrogenation of 1,6-hexanediol can be directed to give predominately the lactone of 6-hydroxyhexanoic acid, 6-hydroxyhexanal, 2,3,4,5-tetrahydrooxepin, or 2-methylcyclopentanone by proper selection of reaction conditions. Possible reaction pathways are discussed.

Although the catalytic dehydrogenation of diols to lactones is a well-established reaction[1] little information was available when this study was initiated[2] on the nature of the reaction by-products or the factors that governed their formation. The reaction products obtained in a vapor phase dehydrogenation of 1,6-hexanediol (I) and some tentative reaction pathways are indicated by formulas I through XII. All compounds shown except adipaldehyde (IV) could be detected in gas chromatographs of the reaction mixtures. In most instances these compounds were isolated and characterized with the aid of mass, infrared, and n.m.r. spectra and solid derivatives.

Results

The catalytic vapor phase dehydrogenation of 1,6-hexanediol (I) is an example of a reaction in which changes in the reaction conditions can bring about a profound change in the nature of the products (Table I). By proper selection of catalyst, catalyst support, carrier gas, and reaction temperature, this reaction can be directed to give either 6-hydroxyhexanal (II),[3] the lactone of 6-hydroxyhexanoic acid (V), 2,3,4,5-tetrahydrooxepin (III), or 2-methylcyclopent-anone (IX) in high yield. Moderate amounts (5 to 20%) of cyclopentanecarboxaldehyde (VIII) and cyclopentanemethanol (XI) are produced. Trace quantities (less than 1% each) of 2-methylcyclopentenone (VI), 1-cyclopentenealdehyde (VII), 1-cyclopentenemethanol (X), and the *cis* and *trans* forms of 2-methylcyclopentanol (XII) can be detected (Scheme I).

The lactone V was always one of the main products regardless of the catalyst used. Under optimum conditions 80 to 90% of the hexanediol that reacted was converted to V (runs 7, 8 and 12). Optimum conditions included (1) use of hydrogen as the carrier gas; (2) low reaction temperatures and inert catalyst supports (pumice) to suppress competing reactions;

Scheme I
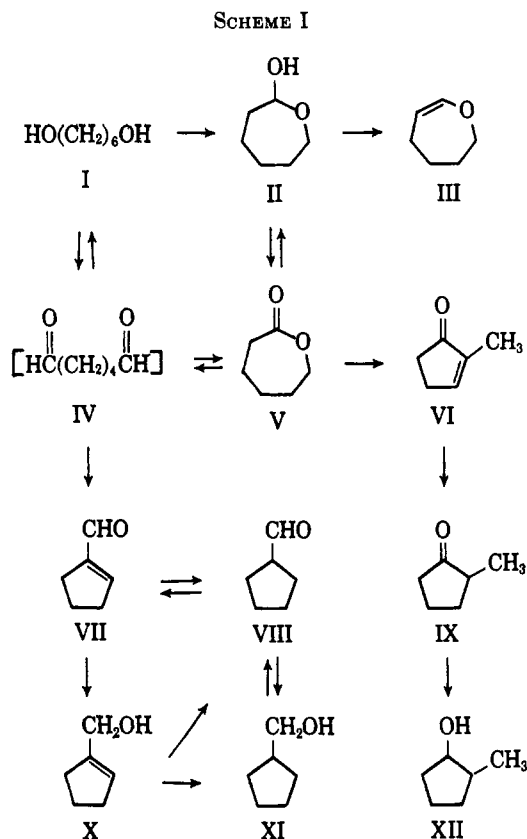
and (3) control of contact time to keep the hexanediol conversion between 50 and 75%.

Increasing the temperature can bring about a quantitative hexanediol conversion, but the main product at higher temperatures is the ketone IX along with some aldehyde VIII and alcohol XI (runs 1, 2, and 3). Active catalyst supports aid in this transformation (run 11).

When the hydrogen normally used as a carrier gas is replaced by nitrogen or by ethylene the activity of the catalyst is slowly reduced (runs 4 and 6). The formation of V, IX, and VIII is suppressed and the degree of hexanediol conversion is halved. Under these conditions, the main reaction product is the hemiacetal II.[3] If hydrogen is again used as the carrier gas, the catalyst slowly regains its original activity (run 5).

Dehydrogenation over a 15% copper–0.85% chromium on kieselguhr catalyst always gave large amounts of a compound to which structure III has been assigned. The infrared and n.m.r. spectra of this compound were similar to those of 2,3-dihydropyran. The compound III could be hydrolyzed to 6-hydroxyhexanal (II). In addition, reaction of III with acidic 2,4-dinitrophenylhydrazine gave a quantitative yield of the 2,4-dinitrophenylhydrazone of 6-hydroxyhexanal.

(1) (a) A. O. Zoss and D. L. Fuller, The Manufacture of γ-Butyrolactone at I. G. Farbenindustrie A. G., Ludwigshofen, FIAT Final Report No. 945 (PB-60902); (b) J. W. Reppe, *Chem. Ind.*, **57**, 458 (1945); (c) L. P. Kyrides and F. B. Zienty, *J. Am. Chem. Soc.*, **68**, 1385 (1946); (d) L. C. Schniepp and H. H. Geller, *ibid.*, **69**, 1545 (1947); (e) J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, N. Y., 1949, p. 152; (f) J. W. Reppe, *Ann. Chem.*, **596**, 180 (1955); (g) S. Oka, *Bull. Chem. Soc. Japan*, **34**, 12 (1961); (h) S. Oka, *ibid.*, **35**, 982 (1962).

(2) In a parallel investigation, S. Oka [*Bull. Chem. Soc. Japan*, **35**, 562 (1962)] found that vacuum distillation of 1,6-hexanediol over a copper chromite-zinc oxide catalyst gave cyclopentenecarboxaldehyde, cyclopentanecarboxaldehyde, and cyclopentanemethanol in addition to ε-caprolactone. The work of Kyrides and Zienty,[1c] indicated that 1-pentanol-4-one and 2-methyl-4,5-dihydrofuran as well as γ-valerolactone could be produced from 1,4-pentanediol. Dihydrofuran was a by-product of the manufacture of γ-butyrolactone from 1,4-butanediol.[1a,e]

(3) 6-Hydroxyhexanal (II) exists partially in the hemiacetal form in the solid. The relative amounts of the two forms in the gas phase is not known, but it is only 15% in the hemiacetal form in dilute solution in dioxane.

TABLE I

EFFECT OF REACTION CONDITIONS UPON PRODUCT COMPOSITION[a]

Run no.	Temp., °C.	Contact[b] time, sec.	Mole % diol in feed	Catalyst[c]	% conversion	Capro-lactone	6-Hydroxy-hexanal	Tetra-hydro-oxepin	Carbonyl[d]	Cyclo-pentane-methanol
1	300	1.1	3.2	I	100	26.5	0.0	0.6	48.2	18.7
2	300	2.5	6.6	I	100	10.3	0.0	1.5	60.5	20.0
3	250	2.5	6.2	I	87	46.0	0.0	0.0	31.6	13.8
4	250	2.8	6.7	II	46	22.8	53.1	0.0	6.5	0.0
5	250	0.9	3.2	II	81	63.0	7.8	0.0	21.4	5.7
6	250	1.2	3.2	II	52	18.9	78.8	0.0	1.6	0.7
7	250	1.3	3.3	III	76	83.5	0.0	0.0	13.7	1.8
8	250	1.4	5.8	III	52	92.3	0.0	0.0	3.1	4.4
9	250	1.0	2.7	IV	100	32.4	0.0	35.6	20.8	7.2
10	200	1.0	2.5	IV	79	56.2	0.0	38.2	5.6	0.0
11	250	1.3	3.5	V	100	44.4	0.0	5.1	40.4	4.9
12	250	2.0	5.0	VI	50	82.0	0.0	0.0	8.2	2.2

[a] The product composition is based on the hexanediol that reacted. The carrier gas was hydrogen except in run 4 in which it was ethylene and run 6 in which it was nitrogen. [b] Contact time is defined as volume of material at reaction conditions flowing through reactor in unit time/volume of reactor. [c] The composition of the catalysts is given in the Experimental section. [d] A mixture of 2-methylcyclopentanone and cyclopentanecarboxaldehyde with the 2-methylcyclopentanone always predominating.

TABLE II

BEHAVIOR OF VARIOUS PRODUCTS UNDER REACTION CONDITIONS[a]

Run no.	Feed	Temp., °C.	Contact[b] time, sec.	% in feed	Catalyst	% conversion	Product composition
13	Caprolactone	250	1.2	4.1	III	0.68	69% VIII + IX, 7% XI, 12% VI, 3% III
14	Caprolactone	250	0.8	2.7	III	0.20	75% VIII + IX, 25% VI
15	Caprolactone	250	3.6	10.2	III	1.03	70% VIII + IX, 10% XI, 16% VI, 2% III
16	Caprolactone	275	4.6	9.4	II	37.1	54% IX, 22% VIII, 6% VII, 3% VI, 15% XI
17	Caprolactone[c]	275	4.6	4.7	II	32	54% IX, 9% VIII, 3% VII, 5% VI, 28% XI
18	Cyclopentenemethanol	275	5.7	7.3	II	99	50% VIII, 50% XI
19	Cyclopentenemethanol	275	2.1	2.4	II	99	36% VIII, 64% XI
20	Cyclopentenemethanol[d]	275	4.6	5.0	II	99	42% VIII, 58% XI
21	Cyclopentanealdehyde	275	4.6	9.4	II	65	99% XI, 1% VII
22	Tetrahydrooxepin	250	2.0	3.2	III	0	
23	Tetrahydrooxepin	250	4.8	7.5	III	0	

[a] The carrier gas was hydrogen in all runs. [b] Contact time is defined as volume of material at reaction conditions flowing through reactor in unit time/volume of reactor. [c] The carrier gas contained 10 mole % steam. [d] The carrier gas contained 25 mole % steam.

Reaction Pathways

6-Hydroxyhexanoic Acid Lactone.—The mechanism by which the lactone V is formed from 1,6-hexanediol is not known. The hemiacetal form of 6-hydroxyhexanal (II) could be isolated as a trace component under most reaction conditions and could be an intermediate in this reaction.[4] Although adipaldehyde (IV) could not be detected in the reaction product, it also could be a transient intermediate in the formation of V via a Tischenko reaction. Although Dolgov[5] states that the dehydrogenation of ethanol to ethyl acetate involves a Tischenko reaction of acetaldehyde, Oka[1h] has presented strong evidence for a hemiacetal intermediate in the dehydrogenation of diols to lactones. Oka obtained cyclopentenecarboxaldehyde but not ε-caprolactone from adipaldehyde under reaction conditions that favored ε-caprolactone formation from 1,6-hexanediol.

The existence of the dialdehyde IV as a transient intermediate must be invoked again to explain the formation of VIII and XI. The α,β-unsaturated aldehyde VII, the product of an intramolecular aldol condensation of IV,[6] can be isolated, but all attempts to detect IV itself by gas chromatography failed.

2-Methylcyclopentanone.—It had been reported[7] that the α,β-unsaturated alcohol X underwent an oxotropic rearrangement to IX in aqueous sulfuric acid. Thus, the reaction sequence VII → X → IX represented a plausible reaction pathway. A number of runs were made in which the alcohol X was passed over catalyst II in a stream of hydrogen at 275° (Table II). In all instances an essentially quantitative conversion to a mixture of VIII and XI occurred. A similar product mixture was obtained when VIII was used as feed to the reactor (run 21, Table II).

Since the oxotropic rearrangement of X to IX would involve the addition of water to an allylic carbonium ion, several reactions were carried out with X in which steam was added to the carrier gas. This addition of steam did not change the reaction products.

A re-examination of the rearrangement of cyclopentenemethanol (X) in aqueous acid in the presence of 2,4-dinitrophenylhydrazine was undertaken in which the n.m.r. spectrum of the 2,4-dinitrophenylhydrazone of the crude reaction product was compared with those of authentic samples of the 2,4-dinitrophenylhydrazones of VIII and IX. Contrary to the report of Dreiding and Hartman,[7] in 50 vol. % sulfuric acid at room temperature the 2,4-dinitrophenylhydrazone of the aldehyde VIII was obtained in 83% yield. There was no detectable ketone IX in the isolated product,

(4) J. C. Craig and E. C. Horning, J. Org. Chem., **25**, 2098 (1960).

(5) B. N. Dolgov, M. M. Koton, and S. D. Lel'chuk, J. Chem. Ind. (USSR), **12**, 1066 (1935); Chem. Abstr., **30**, 1027 (1936); B. N. Dolgov, T. V. Nazovkina and I. M. Stroiman, J. Gen. Chem. USSR, **25**, 467 (1955).

(6) J. English, Jr., and G. W. Barber, J. Am. Chem. Soc., **71**, 3310 (1949).

(7) A. S. Dreiding and J. A. Hartman, ibid., **78**, 1216 (1956).

although traces of IX could be found in the mother liquor. Treatment of X with aqueous 50% acid for 1 hr. followed by addition of 2,4-dinitrophenylhydrazine still gave no IX.

However, lowering the acid concentration to 35 vol. % (50 wt. %) sulfuric acid gave a product containing 76% VIII and 24% IX. No reaction conditions could be found (see Experimental) that gave less than 69% of the aldehyde VIII. This indicates that double-bond migration to form the aldehyde is more rapid than oxotropic rearrangement to the ketone in five-membered ring systems.

As an alternative reaction path the conversion of the lactone V (or of an intermediate involved in the production of the lactone V from the diol I) to the ketone IX is proposed. Hexenoic acid could be such a reaction intermediate. Plattner and Pfau[8] found that a 20% conversion of undecylenic acid to 2-hexyl-2-cyclopentenone could be obtained over a silica catalyst at 350° in the vapor phase. Lactones undergo a similar reaction to yield 2-substituted cyclopentenones in the presence of phosphorus pentoxide[9] or polyphosphoric acid.[10] From this, it would appear that the ketone IX could arise from the reaction of the lactone V with catalyst support to give the unsaturated ketone VI followed by hydrogenation of the double bond. The isolation of trace amounts of VI supports this reaction scheme. When the lactone V was fed to the vapor phase reactor, IX was produced in concentrations up to 15% depending upon the catalyst and reaction conditions employed (Table II). However, the yields of IX were always less and sometimes strikingly less (runs 13–15, Table II) from V than they were from the diol I under the same conditions. This indicates that some intermediate in the dehydrogenation of the diol is easily converted into IX.

2,3,4,5-Tetrahydrooxepin.—The vinyl ether III was probably formed by the dehydration of the hemiacetal form of 6-hydroxyhexanal (II). This is analogous to the dehydration of 4-hydroxybutyraldehydes to 2,3-dihydrofurans.[3,11] This reaction occurred to a large extent on only one of twelve catalysts that were tested and is probably due to the nature of the surface in this particular kieselguhr catalyst support. Traces of nonvolatile acid on the catalyst surface are reported to accelerate this dehydration.[1c]

Wilson[12] isomerized 2,3-dihydrofuran vapor to cyclopropanecarboxaldehyde at 500° in a column containing glass beads. If III underwent a similar reaction VIII would be the product. Two runs were made in which the ether III was passed over catalyst III at 250° at long contact times (Table II). Hexanediol gives no III under these conditions with this catalyst but does give a 10 to 20% conversion to VIII and IX. The tetrahydrooxepin III was recovered unchanged which rules out the possibility of it being a precursor of VIII.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are corrected. Infrared spectra were recorded using a Perkin-

Elmer 221 spectrophotometer. Mass spectra were obtained on a Consolidated Type 21-103 instrument. N.m.r. spectra were run on a Varian A-60 n.m.r. spectrometer using tetramethylsilane as an internal standard. Both preparative and analytical gas chromatographic work was carried out with a Burrell K-2 using glass columns.

Materials.—1,6-Hexanediol from Eastern Chemical Company was fractionally distilled through a 30-tray Oldershaw column to give a middle fraction, b.p. 155° (20 mm.), f.p. 41.90°, that contained no impurities detectable with the gas chromatograph. ε-Caprolactone (99+% purity) was used as received from Union Carbide Chemicals Company. 2-Methylcyclopentanone was purchased from K and K Laboratories (Lot No. 26994). Cyclopentanecarboxaldehyde was prepared by the method of Roth and Erlenmeyer.[13] The 2-methylcyclopentanols and cyclopentanemethanol were obtained by sodium borohydride reduction of the appropriate carbonyl compounds.[14] 1-Cyclopentenecarboxylic acid was prepared from cyclopentanone cyanohydrin[15] and reduced with lithium aluminum hydride[16] to give 1-cyclopentenemethanol contaminated with 9% cyclopentanemethanol.

Methods and Equipment.—The dehydrogenation reactor was a vertical Pyrex tube (100 × 2.8 cm.) equipped with three thermocouples and wrapped with Nichrome heating tape. Any desired temperature from 150 to 300° could be maintained within ±2°. The reactor tube was packed with 500 ml. of catalyst pellets. Molten 1,6-hexanediol was pumped into a vaporizer at the bottom of the reactor tube at the rate of 40 to 60 ml./hr. The vaporizer was packed with Berl saddles and maintained at 290–310°. A stream of carrier gas (hydrogen, nitrogen, ethylene, or steam) was passed through the vaporizer and then through the reactor at the rate of 50 to 200 l./hr. The majority of the product was condensed by an air-cooled condenser. The more volatile products were caught in a trap maintained at −78°. The average run lasted 8 hr. with the reactor being lined out for 3 hr. before any product was collected. Weight accountability across the reactor was 98 to 100%.

Catalyst I.—Harshaw Cu-X-L 280A-1-3-1 T 1/8 (39.6 wt. % copper and 2.1 wt. % Chromium on kieselguhr) was heated to 100° in nitrogen until the copper salts were converted to black copper oxide. The catalyst was then heated to 230° for 4 hr. and then to 275° in a stream of hydrogen until it turned red.

Catalyst II.—Catalyst II was identical to catalyst I except that the copper oxide was reduced for 6 hr. at 150° in a stream of hydrogen. This catalyst was never heated above 250° and retained its black color and catalytic activity.

Catalyst III.—To a solution of 71.5 g. (0.29 mole) of CuSO₄·5H₂O in 400 ml. of water was added 31 g. (0.29 mole) of Na₂CO₃. The precipitate of CuCO₃·Cu(OH)₂ was washed free of sulfate ion with distilled water. The precipitate was shaken with 500 ml. of crushed 4-8-mesh pumice, 100 ml. of water, and 18 ml. of water glass until the pumice was completely coated. The wet stones were poured into the reactor and heated to 100° for 2 hr. under nitrogen and then for 4 hr. at 200° under hydrogen.

Catalyst IV.—Harshaw catalyst Cu 2801 T 1/8 (15 wt. % copper and 0.85 wt. % chromium on kieselguhr pellets) was screened to remove fines and then heated to 200° or 2 hr. in a stream of nitrogen and then for 4 hr. in a stream of hydrogen. When activated it was black.

Catalyst V.—Harshaw catalyst Cu-X-L 1996-3-1 G 3-8 consisted of 20 wt. % copper and 0.5 wt. % chromium supported on 3-8-mesh granules of wide-pore silica gel. The catalyst was calcined at 200° for 3 hr. in a stream of nitrogen and then for 4 hr. in a stream of hydrogen. The activated catalyst had a red-brown color.

Catalyst VI.—A mixture of 30 g. of CuO and 5.8 g. of UO₂(NO₃)₂·6H₂O was placed in a 70-ml. test tube wrapped with heating tape and heated to 340–355° for two 10-min. periods.[17] This reaction was run in a hood since oxides of nitrogen are given off. The CuO·CuUO₂ powder was mixed with 600 ml. of 4-8-mesh pumice, 60 ml. of water, and 22 ml. of water glass. The catalyst was dried overnight, poured into the reactor, and activated for 4 hr. at 200–240° in a stream of hydrogen.

(8) P. A. Plattner and A. S. Pfau, *Helv. Chem. Acta*, **20**, 1474 (1937).

(9) R. L. Frank, R. Armstrong, J. Kwiatek, and H. A. Price, *J. Am. Chem. Soc.*, **70**, 1379 (1948).

(10) T. M. Jacob and S. Dev, *J. Indian Chim. Soc.*, **36**, 429 (1959).

(11) E. R. Rodd, "Chemistry of Carbon Compounds," Vol. IV, Elsevier Publishing Co., New York, N. Y., 1957, p. 159.

(12) C. L. Wilson, *J. Am. Chem. Soc.*, **69**, 3002 (1947).

(13) R. Roth and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 1276 (1955).

(14) H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, **83**, 3166 (1961).

(15) O. H. Wheeler and I. Lerner, *ibid.*, **78**, 63 (1956).

(16) A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 939 (1953).

(17) G. Lammann and W. Rosenthal, *Zeit. anorg. Chem.*, **156**, 20 (1926).

Analytical Methods.—Gas chromatographic analyses were run at 190° using a 6 ft. × 0.25 in. o.d. column containing 20 wt. % Carbowax 20 M on Chromosorb. Caprolactone, hexanediol, cyclopentanecarboxaldehyde, 2-methylcyclopentanone, cyclopentanemethanol, and tetrahydrooxepin usually accounted for better than 95% of the total peak area. Sensitivities were obtained for each of these compounds. The trace components were assumed to have the same sensitivity as the closest of these compounds.

A saponification number was run on the majority of the samples. This gave a weight per cent ester of mol. wt. 114 (caprolactone) that agreed closely with the values obtained by gas chromatography.

Lactone of 6-Hydroxyhexanoic Acid (V).—The lactone, b.p. 122° (20 mm.), was isolated from the reaction product by fractional distillation and identified by comparison of its infrared spectrum with that of an authentic sample.

Composition of Low-Boiling Reaction Products.—A composite sample (435.1 g.) of low-boiling reaction products from 10 runs was carefully fractionated through a spinning-band column. Only two of ten distillation cuts represented pure compounds. The distillation cuts were subjected to a gas chromatographic examination using a 6-ft. Carbowax 20 M on Chromosorb W column at 120°. After identification of the individual compounds the following product distribution, listed in order of elution from the gas chromatograph, was found: water, 67.0 g.[18]; 2,3,4,5-tetrahydrooxepin, 6.9 g.; cyclopentanecarboxaldehyde, 79.4 g.; 2-methylcyclopentanone, 165.4 g.; cis-2-methylcyclopentanol, 2.4 g.; trans-2-methylcyclopentanol, 3.0 g.; 1-cyclopentene-carboxaldehyde, 5.3 g.; 2-methyl-2-cyclopentenone, 14.3 g.; cyclopentanemethanol, 88.8 g.; and 1-cyclopentenemethanol, 2.6 g.

Identification of Reaction Products.—When possible the mass and infrared spectra were determined with pure samples of the reaction products that were isolated by gas chromatographic trapping. Although the pairs cyclopentanecarboxaldehyde-2-methylcyclopentanone and trans-2-methylcyclopentanol-1-cyclo-pentenecarboxaldehyde were not completely resolved by the gas chromatograph the mass and infrared spectra of the crude traps still gave useful information. In each instance the spectral information agreed with the ultimate structural assignment given below. In most instances the gas chromatographic retention times were compared with those of authentic samples. For cis-2-methylcyclopentanol, trans-2-methylcyclopentanol, and 1-cyclopentenemethanol these were the only other methods of identification.

Cyclopentanecarboxaldehyde (VIII).—A gas chromatographic peak that could not be completely resolved from that of 2-methylcyclopentanone was found to have the same retention time as authentic cyclopentanecarboxaldehyde. Attempts to separate pure cyclopentanecarboxaldehyde from the reaction product by fractional distillation or by preparative gas chromatography were unsuccessful. A sample of reaction product containing 0.052 mole of cyclopentanecarboxaldehyde and 0.048 mole of 2-methylcyclopentanone was treated with 0.040 mole of a 2,4-dinitrophenylhydrazine solution.[19] The orange-yellow product, m.p. 156.2–158.2° (lit.[13] m.p. 160–162°), was identified as the 2,4-dinitrophenylhydrazone (DNP) of cyclopentanealdehyde by mixture melting point and identity of the infrared and n.m.r. spectra with those of an authentic sample.

2-Methylcyclopentanone (IX).—2-Methylcyclopentanone of 95% purity was isolated from the reaction product by fractional distillation. The following derivatives were prepared by standard procedures[19] and recrystallized from ethanol: 2,4-DNP, orange plates, m.p. 155.7–156.2° (lit.[20] m.p. 153–154°); semicarbazone, white crystals, m.p. 175.3–175.9° (lit.[21] m.p. 173–174°). Mixture melting points and comparisons of infrared spectra confirmed the identification.

1-Cyclopentenecarboxaldehyde (VII) was isolated by preparative gas chromatography [ν 2710 (weak), 1670, and 1610 cm.⁻¹]. Mass spectrum shows relatively intense parent minus one peak

(43% of parent peak) characteristic of α,β-unsaturated aldehydes. The following derivatives were prepared from gas chromatographic traps[22]: 2,4-DNP, a dark red powder after one recrystallization from ethanol, m.p. 212–214° dec. (lit.[23] m.p. 216°); semicarbazone, m.p. 205–207° dec. (lit.[24] m.p. 218°).

2-Methyl-2-cyclopentenone (VI) was isolated by preparative gas chromatography (ν 1700 and 1630 cm.⁻¹). The mass spectral parent peak is at 96. The semicarbazone, white crystals, has m.p. 215–217° dec. (lit.[24] m.p. 218°).

Cyclopentanemethanol (XI) was isolated by fractional distillation, b.p. 73–74° (20 mm.). It was characterized by its phenylurethane, m.p. 108.6–109° (lit.[16] m.p. 108–108.5°), and 1-naphthylurethane, m.p. 84.6–85.0° (lit.[25] m.p. 87.5–88°), derivatives.

2,3,4,5-Tetrahydrooxepin (III).—A chromatographically pure sample, b.p. 113–114° (760 mm.), was obtained by fractional distillation of the reaction product obtained with catalyst IV: n^{25}D 1.4545, d^{25}_{20} 0.9331.

The infrared spectrum had the following strong bands (cm.⁻¹): 2930, 2862, 1655, 1650, 1641, 1280, 1270 (sh), 1125, 1072 and 735. The mass spectrum fixed the molecular weight at 98. The n.m.r. spectrum showed a doublet centered at δ 6.32 (weight 1 proton), a quadruplet centered at 4.75 (weight 1 proton), a triplet centered at 3.95 (weight 2 protons), and multiplets centered at 2.1 (weight 2 protons), and 1.8 (weight 4 protons). This compound gave an essentially quantitative yield of the 2,4-DNP of 6-hydroxyhexanal, m.p. 101–102° (lit.[26] m.p. 104–105°), on treatment with an acidic solution of 2,4-dinitrophenylhydrazine in ethanol at room temperature.[19]

Anal. Calcd. for $C_6H_{10}O$: C, 73.4; H, 10.3. Found: C, 73.2; H, 10.3.

Hydrolysis of Tetrahydrooxepin.—A mixture of 60 ml. of water, 5 ml. of concentrated hydrochloric acid, 10 ml. of ethanol, and 20 g. of 2,3,4,5-tetrahydrooxepin was refluxed with stirring for 40 min. The reaction mixture was made neutral to phenolphthalein by titration with 1 N sodium hydroxide, saturated with sodium chloride, and extracted three times with ethyl ether. The ether extract was dried over magnesium sulfate and the ether was removed by a flash distillation. Distillation of the residue gave 3.0 g. of distillate, b.p. 112° (10 mm.), which solidified to a white, waxy solid, m.p. 54–65° (lit.[26] m.p. ranged from 57–87° and usually covered about a 10° range). The mass spectrum had its most intense peaks at 115,[27] 99, 81, and 70. The infrared spectrum had the following strong bands (cm.⁻¹): 3420, 2935, 2860, 1720, and 980–1100, and 910.

6-Hydroxyhexanal (II).—When nitrogen or ethylene were used as carrier gases in the vapor phase dehydrogenation of 1,6-hexanediol one of the main products was 6-hydroxyhexanal. Although 6-hydroxyhexanal and caprolactone were not well resolved, 6-hydroxyhexanal could be isolated by preparative gas chromatography on a Carbowax 20 M column. This material was identical in all respects with the 6-hydroxyhexanal prepared from 2,3,4,5-tetrahydrooxepin.

Adipaldehyde (IV).—An ether solution of adipaldehyde was prepared by the sodium metaperiodate oxidation of cyclohexene[28] and was used to establish the gas chromatographic retention time of adipaldehyde. No adipaldehyde was detected in any of the reaction products.

The Rearrangement of 1-Cyclopentanemethanol in the Presence of 2,4-Dinitrophenylhydrazine.[7]—When 0.505 g. of X and 0.49 g. of XI in 3 ml. of ethanol was added to 1.12 g. of 2,4-dinitrophenylhydrazine in 22 ml. of 50% (by volume) sulfuric acid there was an immediate precipitation. After 30 min. at room temperature the derivative was separated by filtration, washed with ethanol-water, and dried. The yield of crude product was 1.19 g. (83% based on X). An authentic sample of the 2,4-DNP of cyclopentanecarboxaldehyde had the following

(18) Water forms an azeotrope, b.p. 92° (760 mm.), with both cyclopentanealdehyde and 2-methylcyclopentanone.

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n.m.r. spectrum[29]: δ 1.75 (weight 8 protons), multiplet centered at 2.95 (weight 1 proton), doublet centered at 7.68 (weight 1 proton). The n.m.r. spectrum of the 2,4-DNP of 2-methyl-cyclopentanone has a sharp doublet centered at δ 1.28 (methyl protons). The n.m.r. spectrum of the crude product was identical in all respects with that of the 2,4-DNP of cyclopentane-aldehyde. There was no trace of a doublet at δ 1.28.

Repetition of this work in which the reaction mixture was allowed to stand for 24 hr. before work-up gave the same results. However, concentration of the filtrate gave unchanged 2,4-di-nitrophenylhydrazine contaminated with traces of the 2,4-DNP derivatives of VIII and IX.

If a solution of X in 50 vol. % sulfuric acid was allowed to

stand at room temperature for 1 hr. before treatment with 2,4-dinitrophenylhydrazine, the product contained an unidentified compound, probably an aldol product, in addition to the 2,4-DNP of VIII, but there was no detectable amount of the 2,4-DNP of IX.

Replacement of the 50 vol. % sulfuric acid with 50 wt. % (35 vol. %) sulfuric acid gave a crude product containing 76% VIII and 24% IX as the 2,4-DNP derivatives.

Cyclopentenemethanol did not react with the usual 2,4-dinitro-phenyl hydrazine reagent[19] (ca. 12 vol. % sulfuric acid) at room temperature, but after 45 min. on a steam bath 69% of the 2,4-DNP of VIII and 31% of the 2,4-DNP of IX were produced.

(29) The protons belonging to the 2,4-dinitrophenylhydrazine portion of the molecule are not listed.

Products from Attempted Vilsmeier–Haack Acylations of Pyrroles with Select Amides[1a,b]

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The Vilsmeier–Haack condensation of pyrroles with chloro-, oxo-, and ethoxycarbonyl-substituted amides yields the expected ketones in some cases. However, different products result in other examples, wherein the nature of the product is influenced by that of the particular pyrrole and amide. A dialkylammonium ion is considered a rational intermediate in the reaction.

The most useful general procedure for the synthesis of pyrrole aldehydes and ketones involves the application of the Vilsmeier–Haack reaction,[2–8] in which a 2- or 3-unsubstituted pyrrole is condensed usually with an N,N-disubstituted carboxamide[9] through the action of phosphorus oxychloride. At the present time, the range of application of this reaction has been incompletely explored. In this connection the possibility of self-condensation of N,N-dialkylcarboxamides[14] and of lactams,[15] the condensation of N,N-dialkylcar-boxamides with active methylene groups,[15] and replacement of alcoholic and readily enolizable keto

groups by chlorine[2] represent possible complicating features in particular cases. It is also of interest to note that, although thiophene can be converted to 2-thiophenecarboxaldehyde by condensation with N-methylformanilide without any difficulty,[16] the attempted acylation of thiophene under the conditions of the Vilsmeier–Haack reaction was reportedly[6] unsuccessful. Also, in other results related to the present discussion, ketones have been obtained in the condensation of a number of *ortho-*, *meta-*, and *para-*substituted benzanilides with dimethylaniline, whereas with the *o*-acetoxy and *o*-nitro derivatives by-product formation is dominant.[17] During the course of synthesis of pyrrole derivatives of possible biological importance, we have had occasion to investigate the application of the Vilsmeier–Haack reaction in examples which further define the scope of this reaction.

Results and Discussion

Ketones X–XVI (Table I) were readily obtained from the condensation of the appropriate pyrroles and amides. Although the optimum conditions for the synthesis of each of these was not investigated, the preparation of 2-chloroacetylpyrrole (X) was attempted a number of times using different conditions and those described in detail in the Experimental section represent the optimum found. From these results and from those obtained in the other instances where more than one trial was carried out in addition to results described in the literature,[16] it is apparent that the conditions employed in the Vilsmeier–Haack condensation can be critical. However, the yields recorded and the ease of manipulation make this method competitive

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