## CHEMISTRY OF ACETALS

COMMUNICATION 15. SELECTIVE HYDROLYSIS OF 3-ETHOXY-4-HEXENAL DIETHYL ACETAL AND SOME REACTIONS OF 3-ETHOXY-4-HEXENAL

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It has been shown previously [1] that the condensation of crotonaldehyde diethyl acetal with ethyl vinyl ether provides a convenient method for the synthesis of 3-ethoxy-4-hexenal diethyl acetal (I), which on hydrolysis with a mixture of acetic acid and sodium acetate readily gives sorbaldehyde, which is difficultly accessible by other means. It was found that the latter is able to react with ethyl (triphenylphosphoranylidene)acetate with formation of ethyl 2,4,6-octatrienoate [2]. However, attempts to bring about the condensation of sorbaldehyde with aliphatic nitro compounds have been unsuccessful; it either did not react, or was resinified.

In view of this we decided to make a more detailed study of the selective hydrolysis of 3-ethoxy-4-hexenal diethyl acetal (I) to give 3-ethoxy-4-hexenal (II) itself, which should possess the reactivity of unsaturated aldehydes and be capable of being used in the synthesis of polyenic compounds containing various functional groups. The selection of hydrolysis conditions and the estimation of the purity of the reaction products were made with the aid of gas-liquid chromatography on a 5-m column containing 1% of silicone elastomer on sodium chloride [3] in a stream of helium at 100°.

The best conditions for the selective hydrolysis of the acetal grouping were found to be obtained by stirring 3-ethoxy-4-hexenal diethyl acetal (I) with a 3% aqueous solution of phosphoric acid at  $65-70^{\circ}$  for 3 h. The resulting mixture of 3-ethoxy-4-hexenal (II) and the original acetal was readily separated by simple vacuum distillation, and the pure ethoxy aldehyde was obtained in yields of up to 78%, based on the amount of the acetal that had been hydrolyzed.



As we expected, 3-ethoxy-4-hexenal (II) was found to be an extremely reactive compound which readily underwent various condensations at the aldehyde group. We made a particularly detailed study of its condensation with nitro compounds, for this reaction could be of importance for the synthesis of nitro and amino diols of interest as physiologically active substances. It was found that 3-ethoxy-4-hexenal condenses smoothly with nitromethane, nitroethane, and 2-nitropropane with formation of the corresponding nitro diol monoethers (III), (IV), and (V). Reaction with nitrocyclohexane went equally readily, but in this case a product was formed which corresponded in elementary analysis and molecular weight to that obtained by the elimination of a molecule of ethanol. Also, the ultraviolet spectrum of this product contained no absorption bands characteristic for a diene system. We may suppose, therefore, that the product has the structure (VI). Apart from this, the infrared spectrum of the condensation product contains a weak absorption band corresponding to the presence of an unconjugated keto group, and on reaction with 2,4-dinitrophenylhydrazine it gave a small amount of a dinitrophenylhydrazone of m.p. 118-119° having the composition  $C_{20}H_{27}O_7N_5$ . These data give us grounds for supposing that the by-product of the condensation of 3-ethoxy-4-hexenal (II) with nitrocyclohexane is the nitro ketone (VII), which could be formed as a result of the oxidation of the normal reaction product.

In the exhaustive hydrogenation of the nitro diol monoethers (III) and (V) over Raney nickel 4 molecular proportions of hydrogen were absorbed and the corresponding amines (VIII) and (IX) were formed in good yields; they were characterized by some crystalline derivatives. It would have been of considerable interest to have effected the selective reduction of only the nitro group in these compounds, without affecting the double bond. It was found, however, that such methods as reduction with zinc or stannous chloride in hydrochloric acid, with lithium aluminum hydride, and with aluminum amalgam did not give the desired results. The most convenient method for this purpose is reduction with tin in acetic acid, and in the case of the nitro diol monoether (III) we succeeded in obtaining the corresponding unsaturated amine (X) by this method; it was isolated as its crystalline oxalate.

As an unsaturated aldehyde, 3-ethoxy-4-hexenal (II) readily condenses with ethyl (triphenylphosphoranylidene)acetate with formation of 5-ethoxy-2,6-octadienoic ester (XI), but we have not yet succeeded in eliminating the ethoxy group from this compound to give the corresponding trienic acid.

The hydrolysis of the acetal (I) to 3-ethoxy-4-hexenal and its further reaction at the aldehyde group do not exhaust the possibilities of the use of this compound in synthesis. Reactions at the double bond may also be of considerable interest, particularly the hydroxylation reaction, with the aid of which one may readily pass to  $C_6$  polyhydroxy aldehydes. In preliminary experiments we have shown that Wagner oxidation of the acetal (I) with potassium permanganate leads in satisfactory yield to 3-ethoxy-4,5-dihydroxyhexanal diethyl acetal (XII), which is the first synthetic member of the class of 2,6-deoxy sugars.

## EXPERIMENTAL

Hydrolysis of 3-Ethoxy-4-hexenal Diethyl Acetal (I). A mixture of 30 g of (I), 12 ml of 3% phosphoric acid, and 9 ml of alcohol was stirred in an atmosphere of nitrogen for 3.5 h at 65-70°. The mixture was cooled, ether was added, and the ether extract was washed with a little saturated sodium bicarbonate solution and dried with magnesium sulfate. Distillation gave 11.4 g of 3-ethoxy-4-hexenal, b.p. 55-58°(7 mm) and  $n_D^{18}$  1.4365, and 6.2 g of the original ether-acetal (I), b.p. 87-89° (8 mm) and  $n_D^{18}$  1.4260. The yield of the ethoxy aldehyde (II) was 78% on the ether-acetal that reacted. In thin-layer chromatography on alumina [4] the aldehyde gave one spot,  $R_f$  0.25 (8: 2 benzene-ether). Found: C67.11, 67.37; H 9.93, 10.04%. C<sub>8</sub>H<sub>14</sub>O. Calculated: C 67.57; H 9.93%.

Condensation of 3-Ethoxy-4-hexenal with Aliphatic Nitro Compounds. A mixture of 7.5 g of the ethoxy aldehyde (II), 6.4 g of nitromethane (100% excess), 0.6 g of potassium carbonate, and 12 ml of water was heated to the boil with good stirring. The reaction product was cooled, the aqueous layer was carefully extracted with ether, and the extract was dried with magnesium sulfate. Distillation gave 8.1 g (75%) of the nitro diol monoether (III), b.p. 93-94° (0.2 mm) and nD<sup>19</sup> 1.4590. Found: C 53.34, 53.33; H 8.24, 8.33; N 7.01, 7.18%. C<sub>9</sub>H<sub>17</sub>O<sub>4</sub>N. Calculated: C 53.19; H 8.43; N 6.89%.

A mixture of 7.1 g of the ethoxy aldehyde (II), 7.5 g of nitroethane (100% excess), 0.65 g of potassium carbonate, and 13 ml of water was heated to the boil with good stirring. After the above-described procedure we obtained 8.1 g (81%) of 5-ethoxy-2-nitro-6-octen-3-ol (IV), b.p. 101-103° (0.5 mm) and  $nD^{19}$  1.4608. Found: C 55.09, 55.28; H 8.86, 8.94%. C<sub>10</sub>H<sub>19</sub>O<sub>4</sub>. Calculated: C 55.28; H 8.82%.

A mixture of 10.2 g of the ethoxy aldehyde (II), 12.5 g of 2-nitropropane, 0.75 g of potassium carbonate, and 15 ml of water was boiled for 5 min with good stirring. After the above-described treatment and vacuum distillation we obtained 10.7 g (79%) of 5-ethoxy-2-methyl-2-nitro-6-octen-3-ol (V), b.p. 90-91° (0.3 mm) and  $n_D^{18}$  1.4605. Found: C 57.48, 57.30; H 9.06, 9.14; N 6.13, 6.21%. C<sub>11</sub>H<sub>21</sub>O<sub>4</sub>N. Calculated: C 57.12; H 9.15; N 6.06%.

A mixture of 6.4 g of the ethoxy aldehyde (II), 11.6 g of nitrocyclohexane, 0.75 g of potassium carbonate, and 15 ml of water was boiled for 15 min and then cooled and extracted with ether. The extract was dried with magnesium sulfate and then vacuum-fractionated. We obtained 4.6 g (52%) of a nitro compounds of b.p. 127-128° (0.2 mm) and  $n_D^{18.5}$  1.4942, which corresponded in analysis to the compound (VI). Found: C 63.45, 63.55; H 8.66, 8.45; N 6.02, 6.16%.  $C_{12}H_{19}O_3N$ . Calculated: C 63.97; H 8.50; N 6.22%. Determination of mobile hydrogen by the Chugaev-Tserevitinov method gave the following results: 1.08, 1.14. The ultraviolet spectrum contained no absorption bands in the range 220-300 mµ.

0.6 g of the reaction product was shaken with a solution of 2,4-dinitrophenylhydrazine. We obtained 0.12 g of the 2,4-dinitrophenylhydrazone of (VII), m.p. 118-119° (from ethyl acetate);  $\lambda_{max}$  365 m $\mu$ . Found: C 53.50, 53.53; H 5.83, 5.74; N 15.32, 15.40%. C<sub>20</sub>H<sub>27</sub>O<sub>7</sub>N<sub>5</sub>. Calculated: C 53.44; H 6.06; N 15.58%.

Hydrogenation of the Nitro Diol Monoethers (III) and (V). 9.9 g of (III) was hydrogenated at 20° in presence of Raney nickel prepared from 10 g of alloy. Hydrogenation stopped after the absorption of 3890 ml of hydrogen (theory requires 4250 ml). Catalyst was filtered off, alcohol was driven off, and the residue was vacuum-distilled. We obtained 5.85 g (62%) of the amine (VIII); b.p. 76-78° (0.2 mm);  $n_D^{-18}$  1.4498. Found: C 62.31, 62.36; H 12.18, 12.35; N 9.12, 8.96%. C<sub>9</sub>H<sub>21</sub>O<sub>2</sub>N. Calculated: C 61.67; H 12.08; N 9.09%.

From the amine (VIII) we prepared crystalline derivatives: Benzoyl derivative, m.p. 78-79° (from petroleum ether). Found: C 68.52; H 8.84%. C<sub>16</sub>H<sub>25</sub>O<sub>3</sub>N. Calculated: C 68.78; H 9.02%. Oxalate, m.p. 177-178° (from a mixture of alcohol and ether). Found: C 49.39, 49.36; H 8.76, 8.70%. C<sub>11</sub>H<sub>23</sub>O<sub>6</sub>N. Calculated: C 49.80; H 8.74%.

By the similar hydrogenation of 5.25 g of the nitro compound (V) we obtained 4.6 g (76%) of 2-amino-5-ethoxy-2-methyl-3-octanol (IX), b.p. 75-76° (0.25 mm). Found: C64.73, 64.64; H 12.45, 12.42; N 6.94, 7.08%.  $C_{11}H_{25}O_2N$ . Calculated: C 64.98; H 12.39; N 6.89%.

Reduction of the Nitro Diol Ether (III) with Tin in Acetic Acid. A mixture of 0.5 g of the nitro compound (III), 0.6 g of tin, and 6 ml of acetic acid was boiled until the tin dissolved, after which the mixture was cooled, made alkaline with 20% KOH solution, and extracted with ether. The ether extract was shaken with a solution of 0.3 g of oxalic acid in ether. We obtained 0.45 g of the oxalate of the amine (X), m.p. 148-149° (from a mixture of ether and alcohol). Found: C 49.85, 49.93; H 7.89, 7.94%. C<sub>11</sub>H<sub>21</sub>O<sub>6</sub>N. Calculated: C 50.18; H 8.04%.

Condensation of the Ethoxy Aldehyde (II) with Ethyl (Triphenylphosphoranylidene)acetate. A mixture of 5.7 g of the ethoxy aldehyde (II), 20 g of ethyl (triphenylphosphoranylidene)acetate, and 200 ml of dry benzene was boiled for 5 h in an atmosphere of nitrogen. Benzene was driven off, and the residue was carefully extracted with hexane; hexane was driven from the extract, and the residue was vacuum-distilled. We obtained 6.7 g (78%) of ethyl 5-ethoxy-2,6-octadienoate (XI); b.p. 72-73° (0.3 mm);  $n_D^{24}$  1.4640. Found: C 67.63, 67.81; H 9.42, 9.44%.  $C_{12}H_{20}O_3$ . Calculated: C 67.89; H 9.50%.

Oxidation of 3-Ethoxy-4-hexenal Diethyl Acetal (I) with Potassium Permanganate. A solution of 48 g of potassium permanganate in 2 liters of water was added with vigorous stirring at 0° to a suspension of 64.8 g of the etheracetal (I) in 600 ml of water. When the whole of the permanganate solution had been added the mixture was stirred for 2 h at room temperature and then left overnight. The precipitate of manganese dioxide was separated by centrifugation and filtration, and the aqueous solution was evaporated in a rotary evaporator down to low bulk. The layer of diol that formed was separated, and the aqueous layer was repeatedly extracted with ether. The combined ethereal solution of the oxidation products was dried with potassium carbonate, ether was driven off, and the residue was vacuum-distilled. We obtained 29.3 g (40%) of 3-ethoxy-4,5-dihydroxyhexanal diethyl acetal (XII); b.p. 99-101°(0.3 mm); np<sup>19</sup> 1.4430. Found: C 57.64, 57.62; H 10.27, 10.32%. C<sub>12</sub>H<sub>26</sub>O<sub>5</sub>. Calculated: C 57.57; H 10.47%.

## SUMMARY

1. A method was developed for the hydrolysis of 3-ethoxy-4-hexenal diethyl acetal to 3-ethoxy-4-hexenal.

2. A study was made of the reactions of 3-ethoxy-4-hexenal with ethyl (triphenylphosphoranylidene) acetate and primary and secondary nitro compounds, and also of the hydroxylation of 3-ethoxy-4-hexenal diethyl acetal to the corresponding ethoxy dihydroxy  $C_6$  acetal.

## LITERATURE CITED

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