Intramolecular Aldol Condensations of the Reaction Products formed from 2,4-Pentanedione and Aldehydes

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The aldol condensation products, 5-alkyl-4,6-diacetyl-3-hydroxy-3-methylcyclohexanone (R = H, CH₃, C₂H₅) and 3,5-diacetyl-2,6-heptanedione formed from 2,4-pentanedione and aldehydes underwent further reactions involving aldol condensations and dehydrations on heating with the liquid formate, TEAF, given by 5HCO₂H·2NEt₃. These reactions finally gave the two isomers of dimethylbicyclo[3.3.1]nonadienediones. In the case of the formaldehyde condensation products, formate reactions giving 4,6-diacetyl-3-methylcyclohex-2-en-1-one and 2,4-diacetyl-5-methylphenol were also realized.

Since the works of Knoevenagel in the nineteenth century, the condensation products of 2,4-pentanedione with aldehydes and their reactions have been investigated in a number of papers. In continuous study on the reactions of triethylammonium formate (TEAF), which has been known as the constant boiling liquid of bp 95° (15 mmHg) given by 5HCO₂H·2NEt₃, an investigation of the side reaction which occurred in greater extent in the previously reported reductive fission reaction of 3,5-diacetyl-2,6-heptanedione (I) has introduced that TEAF is a medium effective for aldol condensations of the material. The present paper describes our investigation on the condensation reactions of the reaction products of 2,4-pentanedione with aldehydes in TEAF medium.

The reaction of 2,4-pentanedione with formaldehyde in the presence of base was first reported in the nineteenth century. The formations of 3,5-diacetyl-2,6-heptanedione (I) and 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone (II) were later confirmed.

In the previously reported reaction of I with TEAF which was carried out by heating at 145—150° under a stream of nitrogen, the formation of the by-product, mp 64—65°, formed in greater deal in addition to the reductive fission products, 3-methyl-2,4-pentanedione and 2,4-pentanedione, remained unsolved. Further investigation has revealed that this by-product is 4,6-diacetyl-3-methylcyclohex-2-en-1-one (III). When the reaction was carried out under a stream of dry air, dehydrogenation occurred to give 2,4-diacetyl-5-methylphenol (IV). Conversion of III into IV was substantiated on heating with TEAF under a stream of oxygen. The compound (III) may correspond to the product of mp 75°, which was obtained by Knoevenagel by the reaction, in hydrogen chloride-containing chloroform, of the "liquid and solid methylenebisacetylaceton" from the reaction of 2,4-pentanedione with formaldehyde, the solid material of which was later identified as III. The compound IV has been known as the product which Knoevenagel obtained from his "methylenebisacetylaceton" by influence of acid on standing in air. Spectral data of III and IV were consistent with their

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structures. The predominant enol structures of III and IV chelating with $\beta$-carbonyl would allow the nuclear magnetic resonance (NMR) spectral assignments where signal of III at $\tau = -6.74$ was assigned to chelating enol hydroxyl and that of IV at $\tau = -2.56$ to the chelating phenol hydroxyl. It is presumed that III is a dehydration product from II. On heating with TEAF at 145°-150° under a stream of nitrogen the formation of III from II was realized.

When the compound (II) was heated with TEAF in the atmosphere, treatment of the reaction mixture gave a crystalline material of mp 151°-152° in addition to III and IV. This material was identified as 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (V) from its spectral data discussed later. The same material was also obtained by heating III with TEAF at 145°-150° under a stream of nitrogen. Consequently, the compound V is presumed to be formed by intramolecular aldol condensation where the methyl carbon of the acetyl at $C_4$ attacks the carbonyl at $C_4$. A steric isomer of this compound, 4,8-dimethylbicyclo[3.3.1]nona-3,7-diene-2,6-dione (VI), has been described by Knoevenagel$^9$ as the material of mp 125°-127° obtained by treating his "liquid methylenebisacetylaceton" with sulfuric acid. The compound (VI) corresponds to a product formed from III by aldol condensation where the methyl carbon of the acetyl at $C_4$ attacks the carbonyl at $C_4$. To obtain this isomeric compound (VI), II was treated with hydrochloric acid under a stream of nitrogen. Crystals of mp 86°-86.5° were isolated by separation from V produced together. Although showing the melting point different from that reported by Knoevenagel, this material was identified as VI. The observed NMR spectra of V and VI were well interpreted to fit their structures as shown in Table I. The two hydrogens at $C_4$ and $C_5$ are well assigned in their NMR spectra, where the symmetrical two hydrogens of VI appear as triplet at 6.97 $\tau$, whereas the unsymmetrical ones of V appear separately as two sets of triplet at 7.04 $\tau$ and 6.60 $\tau$. In comparison of the UV and IR spectra of V and VI, shown in Table I, deviation from the planarity of the conjugated system of V due to the mutual repulsion between the two carbonyls and between the two methyls leads to shifts of ultraviolet (UV) absorption maximum to blue and of infrared (IR) stretching absorption of the carbonyl to higher wave number.

The structures of the products "ethyliden- and benzylidenebisacetylaceton" first obtained by Knoevenagel$^9$ in the reactions of 2,4-pentanedione with acetaldehyde and benzal-
dehyde were discussed by several investigators\textsuperscript{4,5} and finally established mostly on the basis of their IR spectra as the cyclic structures 4,6-diacyetyl-3,5-dimethyl-3-hydroxycyclohexanone (VII) and 4,6-diacyetyl-3-hydroxy-3-methyl-5-phenylcyclohexanone (VIII) respectively. Their NMR spectra were also consistent with their structures as can be seen in Experimental.

By the same procedure as that of the foregoing TEAF reaction of I, II and III, these compounds (VII and VIII) were subjected to the reaction with TEAF by heating at 145—150\degree. In every run two kinds of crystals were obtained from the reaction mixtures; IX of mp 133—134\degree and X of mp 65—66\degree from VII, XI of mp 182—184\degree and XII of mp 145—147\degree from VIII. On the basis of their NMR, UV and IR spectra, which are well interpreted as well as those of
V and VI, as can be seen in Table I, the structures of IX-XII were established to be bicyclo-
[3.3.1]nonadienedione derivatives such as IX: 4,6,9-trimethylbicyclo[3.3.1]nona-3,6-diene-
2,8-dione, X: 4,6,9-trimethylbicyclo[3.3.1]nona-3,7-diene-2,6-dione, XI: 4,6-dimethyl-9-
phenylbicyclo[3.3.1]nona-3,6-diene-2,8-dione, XII: 4,8-dimethyl-9-phenylbicyclo[3.3.1]-
nona-3,7-diene-2,6-dione. The materials which would be identical with those (IX—XII) obtained above have been postulated in Knoevenagel’s paper, in which both products of mp 136° and mp 64°, obtained by refluxing his “ethyldienebisacetylacetonate” with hydro-
chloric acid, are described without structural determination, and the product of mp 154°,
obtained by treating his “benzylidienebisacetylacetonate” in hydrogen chloride-containing
chloroform, described to be either XI or XII.

Experimental

Aldol Condensation Products directly obtained from 2,4-Pentanediene and Aldehydes---To a solution
of 40 g (0.4 mole) of 2,4-pentanediene and 14 ml (0.2 mole) of 37% formalin dissolved in 20 ml of ethanol
a few drops of piperidine was added. The solution was allowed to stand at room temperature for 24 hr.
Usual treatment of the reaction mixture gave 3,5-diacytetyl-2,4-heptanedioin (I), mp 33—35°, which was
previously obtained by Wilson as crystals, mp 41.5—42.5°. Anal. Calcd. for C_{11}H_{14}O_{4}: C, 62.25; H, 7.60.
Found: C, 62.36; H, 7.55.

In the above run, when increased amount of piperidine was used and the reaction time was
prolonged to 3 days, further intramolecular aldol condensation proceeded to give 4,6-diacytetyl-3-hydroxy-3-
methylcyclohexanone (II), mp 83—84° (lit. mp 89—90°). Anal. Calcd. for C_{11}H_{14}O_{3}: C, 62.25; H, 7.60.
Found: C, 62.40; H, 7.78.

When acetaldehyde and benzaldehyde were used in place of formaline, 4,6-diacytetyl-3,5-dimethyl-3-
hydroxycyclohexanone (VII), mp 101—102° (lit. mp 108°) and 4,6-diacytetyl-3-hydroxy-3-methyl-5-phenyl-
cyclohexanone (VIII), mp 164—165° (lit. mp 168—169°) were obtained, respectively, by the same proce-
dure as described above for the preparation of II. Analytical and NMR spectral data of these two products
are shown in the following. 4,6-Diacytetyl-3,5-dimethyl-3-hydroxycyclohexanone (VII): Anal. Calcd. for
C_{12}H_{16}O_{3}: C, 63.70; H, 7.82. Found: C, 63.81; H, 7.94. NMR (10% solution in CDCl_3) δ: 9.05 (3H, doublt,
J = 5.5 cps, C_2=CH_2), 8.71 (3H, singlet, C_2=CH_2), 7.82 (3H, singlet, C_2=CH_2CO), 7.63 (3H, singlet, C_2=CH_2CO),
7.54 (2H, singlet, C_2-H), 7.5—7.6 (3H, multiplet, C_2-H, C_2-H and C_2-H), 5.46 (1H, singlet, C_2-OH). 4,6-
Diacytetyl-3-hydroxy-3-methyl-5-phenylcyclohexanone (VIII): Anal. Calcd. for C_{23}H_{28}O: C, 70.81; H, 6.99.
Found: C, 70.77; H, 6.96. NMR (CDCl_3) δ: 8.69 (3H, singlet, C_2=CH_2CO), 8.37 (3H, singlet, C_2=CH_2CO),
7.96 (3H, singlet, C=CH_2CO), 7.41 (2H, singlet, C_2-H), 7.6—6.6 (3H, multiplet, C_2-H, C_2-H, and C_2-H), 6.17 (1H,
singlet, C=OH), 1.22 (5H, singlet, C_5-C_H_5).

4,6-Diacetylt-3-methylcyclohex-2-en-1-one (III)---a Mixture of 10.6 g of 3,5-diacytetyl-2,4-heptanedi-
one (I) and 86.5 g of TEAF was heated at 145—150° for 1 hr with stirring under a stream of nitrogen.
The reaction solution was subjected to distillation under reduced pressure. The previous paper has reported
the isolation of 2,4-pentanediene and 3-methyl-2,4-pentanediene from the distillate obtained.
Under high reduced pressure the resulting oily residue was distilled to give 3.8 g (40%) of yellow oil, bp 117—123° (0.4
mmHg), which soon solidified on cooling. Recrystallization from ether gave yellow prisms, mp 64—66°
(lit. mp 75°). Anal. Calcd. for C_{11}H_{14}O: C, 68.02; H, 7.27. Found: C, 68.30; H, 7.42. IR ν_{max} cm⁻¹:
1708 (C=O), 1627, 1607, 1507 (C=O, C=C). UV λ_{max} μm (e): 240 (6470), 338 (6640). NMR (10% solution
in CDCl_3) δ: 8.00 (3H, doublet, J = 1.5 cps, C_2=CH_2), 7.91 (3H, singlet, C_2=CH_2CO), 7.80 (3H, singlet, C_2-
CH_2CO), 7.3—6.3 (3H, multiplet, C_2-H and C_2-H), 3.97 (1H, multiplet, C_2-H), -6.74 (1H, broad, C_2-OH).
b A mixture of 5.3 g of 4,6-diacytetyl-3-hydroxy-3-methylcyclohexanone (II) and 43.3 g of TEAF was heated
at 145—150° for 1 hr with stirring under a stream of nitrogen. After TEAF was distilled off under
reduced pressure, the resulting oily residue was distilled under reduced pressure to give 4.0 g (83%) of solid
distillate, bp 117—120° (0.3 mmHg), which was recrystallized from ligoine to give III as yellow prisms, mp
64—66°. IR spectrum of this material was well consistent with that obtained in a).

2,4-Diacetylt-5-methylphenol (IV)---a Mixture of 10.0 g of 3,5-diacytetyl-2,4-heptanediene (I) and
86.5 g of TEAF was heated at 145—150° for 5 hr with stirring in a constant stream of air. After TEAF was

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distilled off under reduced pressure, distillation of the semi-solid residue under reduced pressure gave a solid distillate, bp 90—103° (0.1 mmHg), weighing 2.0 g. When the foregoing TEAF distillate was diluted with water and partially neutralized with KOH, additional crystals of IV were precipitated and collected by filtration. Total yield of IV was 2.7 g (28%). Recrystallization from methanol gave needles, m p 104—105° (lit., 3 mp 106°). Anal. Calcd. for C₂₃H₂₃O₃: C, 68.73; H, 6.29. Found: C, 68.73; H, 6.25. IR νOH cm⁻¹: 2990 (OH), 1676, 1637 (C=O). UV λmax nm (ε): 244 (39θ600), 263 sh (11θ000), 320 (37θ80). NMR (10% solution in CDCl₃) τ: 7.45 (3H singlet, CH₃), 7.45 (3H singlet, CH₃), 7.35 (3H singlet, CH₃), 3.20 (1H singlet, C₁₁H), 1.81 (1H singlet, C₂H), —2.56 (1H singlet, C₁OH).

b) A mixture of 4.25 g of III and 43 g of TEAF was heated at 145—150° for 4 hr with stirring in a stream of oxygen. After TEAF was distilled off, the extraction of the resulting residue with methanol gave 1.6 g (33%) of IV, m p 100—102°. IR spectrum of this material was well consistent with that obtained in a.

4.6-Dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (V)—a) A mixture of 8.5 g of II and 69.2 g of TEAF was distilled off at 145—150° for 5 hr with stirring in the air. After TEAF was distilled off under reduced pressure, the residue was subjected to distillation under reduced pressure to give the following three fractions: A) 1.8 g of yellow oil, bp 103—120° (0.1 mmHg), B) 2.5 g of yellow oil, bp 120—145° (0.1 mmHg), C) 0.5 g of yellow crystals, bp 145—180° (0.1 mmHg). The fraction B was allowed to stand overnight at room temperature. The deposited yellow crystals were collected by filtration and recrystallized from ether to give 0.9 g (11%) of III, m p 64—66°. The filtrate of B was added to the fraction A and the mixture was allowed to stand for a few days. The deposited crystals were collected and washed with a little amount of methanol to give 1.1 g of IV. Dilution of the TEAF distillate with water gave additional IV. Total yield of IV was 1.3 g (17%). The fraction C was recrystallized from methanol—ether to give 0.25 g (4%) of prisms, m p 151—152°, which were identified as V. Anal. Calcd. for C₁₁H₁₀O₂: C, 74.97; H, 6.88. Found: C, 74.88; H, 7.02. Spectral data are listed in Table I.

d) A mixture of 7.8 g of III and 69.2 g of TEAF was distilled off at 145—150° for 15 hr with stirring in a stream of nitrogen. After TEAF was distilled off, the residue was distilled under reduced pressure to give the following two fractions: A) 3.7 g of yellow oil, bp 99—127° (0.2 mmHg), B) 1.2 g (17%) of yellow crystals, bp 131—148° (0.1 mmHg). The fraction A was subjected to silica gel column chromatography using benzene as an eluent to give 0.2 g of IV and 0.7 g of the starting material, III. The fraction B was recrystallized from methanol—ether to give prisms of V, m p 151—152°. IR spectrum of this material was well consistent with that obtained in a.

4.8-Dimethylbicyclo[3.3.1]nona-3,7-diene-2,6-dione (VI)—A solution of 5.3 g of II in 50 ml of concd. hydrochloric acid was heated on a water-bath for 2 hr in a stream of nitrogen. After removal of hydrochloric acid under reduced pressure, petr. ether was added to the oily residue. The resulting crystals were collected by filtration and fractionally recrystallized from ether—petr. ether to give 0.5 g of VI, m p 86—86.5°, in addition to 1 g of V. Anal. Calcd. for C₁₁H₁₀O₂: C, 74.97; H, 6.86. Found: C, 74.80; H, 7.00. Spectral data of VI are listed in Table I.

4.6,9-Trimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (X)—A mixture of 8.9 g of 4,6-diacyt-3,5-dimethyl-3-hydroxy-cyclohexanone (VII) and 69.2 g of TEAF was distilled off at 145—150° for 18 hr with stirring under a stream of nitrogen. After TEAF was distilled off, the residue was distilled under reduced pressure to give 6.0 g of a crude distillate, bp 98—113° (0.33 mmHg), which was subjected to silica gel column chromatography using ether—petr. ether (1:1) as an eluent to give two kinds of crystals. After recrystallization of crystals, obtained from earlier fractions, from ether—petr. ether, 1.3 g (17%) of prisms, m p 65—66°, were obtained and identified as X. Anal. Calcd. for C₁₃H₁₆O₂: C, 75.76; H, 7.42. Found: C, 75.74; H, 7.39. Crystals obtained from later fractions were recrystallized from methanol to give 0.5 g (7%) of plates, m p 133—134°, which was identified as IX. Anal. Calcd. for C₁₃H₁₆O₂: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.25. Spectral data of IX and X are listed in Table I.

4.6,7-Dimethyl-9-phenylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (XI) and 4.8-Dimethyl-9-phenylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (XII)—A mixture of 14.4 g of 4,6-diacyt-3-hydroxy-5-methyl-5-phenyl-cyclohexanone (VIII) and 86.5 g of TEAF was distilled off at 145—150° for 3.5 hr with stirring. After TEAF was distilled off, the resulting residue was distilled under reduced pressure to give an oily distillate, bp 160—180° (0.3 mmHg). The crystalline residue was recrystallized from methanol to give 1.4 g (11%) of prisms, m p 182—184°, which were identified as XII. Anal. Calcd. for C₁₅H₁₈O₂: C, 80.92; H, 6.39. Found: C, 80.98; H, 6.45. The foregoing oily distillate was subjected to fractional distillation under reduced pressure to give an oily distillate, bp 160—174° (0.4 mmHg) and a solid distillate, bp 175—180° (0.4 mmHg). Recrystallization of the latter from methanol gave 7.3 g (50%) of prisms, m p 145—147°, which were identified as XII. Anal. Calcd. for C₁₅H₁₆O₂: C, 80.92; H, 6.39. Found: C, 81.10; H, 6.30. Spectral data of XI and XII are listed in Table I. The former oily distillate was not further investigated.

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