INVESTIGATION OF THE REACTION PRODUCTS OF TRIACETONAMINE AND ETHYL CYANOACETATE UNDER KNOEVENAGEL REACTION CONDITIONS

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Reaction of triacetonamine with ethyl cyanoacetate and ammonium acetate gives, in addition to the normal Knoevenagel reaction product (2,2,6,6-tetramethyl-4-ethoxycarbonylcyanomethylenepiperidine), its conversion product 3-cyano-4-(β,β-dimethylvinyl)-6,6-dimethyl-Δ^3-dehydro-2-piperidone. Acid hydrolysis of the latter gives a dihydro-α-pyrone derivative. The mechanism of the formation of the new compounds is discussed, and their structures are proved by their NMR and mass spectra.

On carrying out the condensation of triacetonamine with ethyl cyanoacetate in the presence of ammonium acetate, in addition to the expected 2,2,6,6-tetramethyl-4-ethoxycarbonylcyanomethylenepiperidine (I), there was isolated a considerable amount of a colorless, crystalline material with the molecular formula $C_{12}H_{16}N_2O$. From its IR spectrum [ν, cm^{-1}: 2225 (C ≡N) and 1675 (C = O)] and molecular weight (204) as determined by mass spectrometry and cryoscopically (in phenol), this compound could be 2,2,6,6-tetramethyl-8-cyano-Δ^3-dehydro-7-quinuclidone (II). The formation of this compound could occur by intramolecular cyclization of the ester I. However, the presence of a double bond at the bridgehead (C_4) carbon atom makes this structure unacceptable for steric reasons (Bredt's rule). The NMR spectrum of the compound $C_{12}H_{16}N_2O$ shows the presence of two pairs of equivalent methyl groups (δ 1.355 ppm and a doublet at δ 1.975 ppm), an isolated methylene group (δ 2.65 ppm), and a methine group (δ 6.206 ppm), and also one proton on nitrogen (δ 7.553 ppm). This permits us to assign the structure 6,6-dimethyl-4-(β, β-dimethylvinyl)-3-cyano-Δ^3-dehydro-2-piperidone (III) to this compound, with a substantial degree of probability.

The yield of this compound increases proportionately with an increase in the duration of the boiling time of the mixture of triacetonamine, ethyl cyanoacetate, and ammonium acetate in benzene (from 1 to 10 hr),

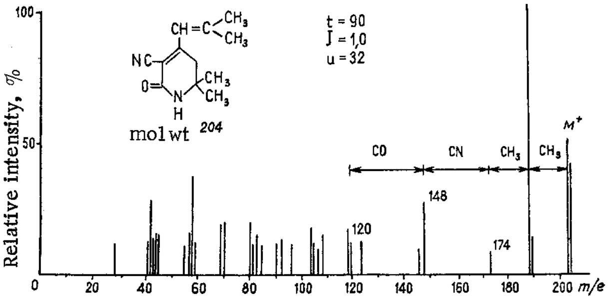

Fig. 1. Mass spectrum of 3-cyano-4-(β, β-dimethylvinyl)-6,6-dimethyl-Δ^3-dehydro-2-piperidone (III).

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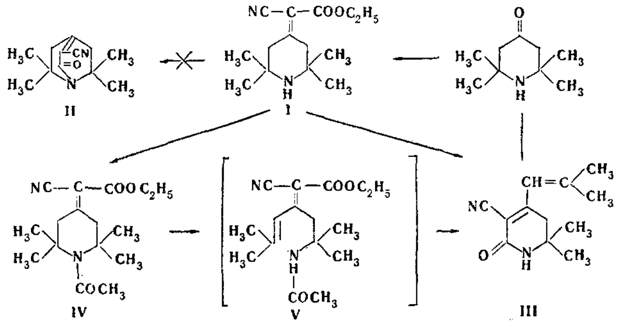
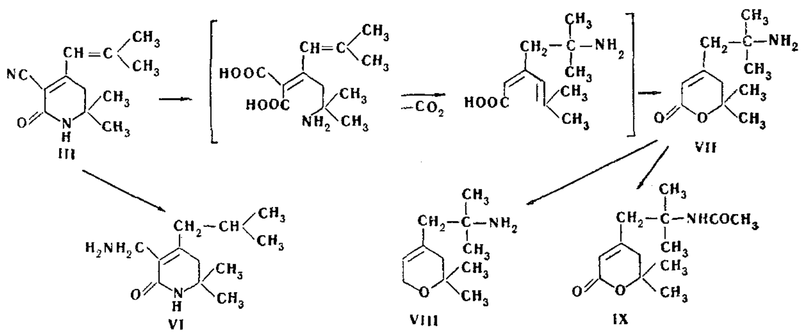
and also with an increase in the temperature of the reaction. For example, replacement of the benzene by the higher-boiling solvents toluene or xylene increases the yield of III from 12 to 39%, the yield of the ester I decreasing substantially at the same time.

It has been shown that III is formed via the acetyl derivative of I (IV), which was isolated from the reaction mixture 2 hr after the beginning of the reaction (in toluene). On heating the acetyl derivative IV above 120° C, III is invariably formed.

The ester I is also converted into the dehydropiperidone III by boiling in toluene for 3-4 hr in the presence of ammonium acetate. The formation of III from triacetonamine and ethyl cyanoacetate can apparently be explained as follows. The ester I which is first formed is acetylated by the ammonium acetate. The amide IV, in which the nitrogen atom is linked to a quaternary carbon atom, is further converted to the unsaturated intermediate compound V, which then cyclizes to the dehydropiperidone III.



The fission of the $N-C(CH_3)_2$ bond in substituted amides has been observed previously by several authors [1-3], but in all the cases described, the process occurs under conditions of acid hydrolysis.



In order to confirm the structure of III, it was subjected to a number of chemical conversions. Hydrogenation over platinum oxide gives the amine VI. Acid hydrolysis of III gives the dihydro-α-pyrone derivative (VII), which is apparently formed as a result of hydrolysis of the cyclic amide and nitrile groups, followed by partial decarboxylation and subsequent closure of the pyrone ring.

The NMR spectrum of VII possesses signals due to the protons of the two pairs of equivalent methyl groups (δ 1.190 and 1.457 ppm), two methylene (δ 2.310 and 2.566 ppm), and one methine group (δ 5.843 ppm). The dihydro-α-pyrone VII was reduced with lithium aluminum hydride to the corresponding dihydropyran VIII, and also converted to the acetyl derivative IX.

In order to confirm definitely the reactions described above, the mass spectra of these compounds were determined. The mass spectrum of III (Fig. 1) shows a strong peak due to the molecular ion with m/e 204. The major peak in the spectrum is the ion peak $(M-15)^+$ with m/e 189, which corresponds to the elimination of a methyl radical from the molecular ion. The height of this peak is apparently explained by the preferential elimination of a methyl group from the α-position of the piperidone, to give the stable ion X.

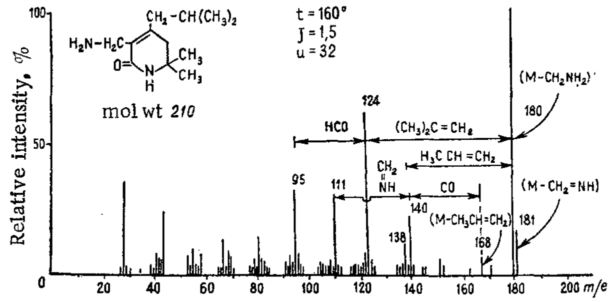


Fig. 2. Mass spectrum of 3-aminomethyl-4-(β-methylpropyl)-6,6-dimethyl-Δ^3-dehydro-2-piperidone (VI).

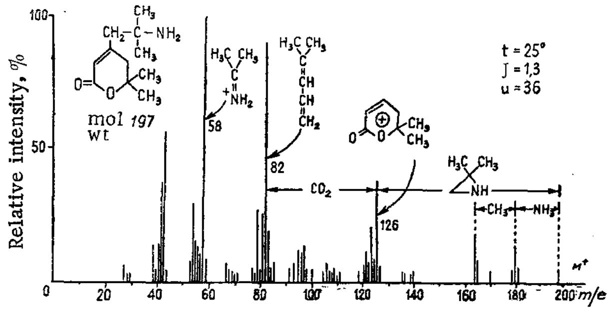
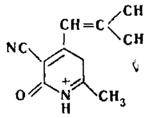


Fig. 3. Mass spectrum of 6,6-dimethyl-4-(β-methyl-β-aminopropyl)-Δ^3-dihydro-2-pyrone (VII).

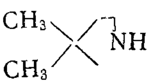


X

This, however, does not exclude the possible fission of a methyl radical from the isobutenyl group. The $(M-15)^+$ ion undergoes further elimination of a CH_3 group (ion with m/e 174), followed by a CN group (ion with m/e 148) and a CO group (ion with m/e 120).

The mass spectrum of III therefore agrees quite well with this structure.

In the mass spectrum of VI (Fig. 2), no molecular ion peak is seen. The heaviest ion, with m/e 181, is probably formed by the elimination of formaldimine ($CH_2=NH$) from the side chain (CH_2NH_2) of VI. The ion with the highest intensity is that with m/e 180, corresponding to the fission of the side chain $(M-CH_2\cdot NH_2)^+$. Further breakdown of this ion takes place by the elimination of propylene (ion with m/e 138) and butylene (ion with m/e 124). The latter ion apparently loses an HCO group to give an ion with m/e 95. The molecular ion of VI also loses propylene (ion with m/e 168), followed by a CO group (ion with m/e 140) and $CH_2=NH$ (ion with m/e 111), successively.

The mass spectrum of VII (Fig. 3) also agrees well with its structure. The molecular ion peak appears at m/e 197, the $(M-NH_3)^+$ ion with m/e 180, and the $(M-NH_3-CH_3)^+$ ion at m/e 165. The most abundant ion, however, is formed by the successive elimination of the side chain, apparently as the cyclic imine  (ion with m/e 126), and the CO_2 group (ion with m/e 82). The strongest peak in the mass spectrum is that due to the amino fragment $(CH_3)_2C{=}\overset{+}{N}H_2$ (m/e 58), the formation of which can be explained by the preferential location of the positive charge on the nitrogen atom, rather than on the oxygen atom, in the molecular ion of VII.

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil suspensions on a UR-10 recording spectrometer, and the NMR spectra were taken on a JNB-100 spectrometer in $CDCl_3$, using TMS as internal standard (we sincerely thank Yu. N. Sheinker and K. F. Turchin for the NMR spectra and for their interpretation).

The mass spectra were obtained on an MX-1303 mass spectrometer with an ionization potential of 30-40eV and a temperature of 25-160° C. Compounds III and VII were evaporated directly with the ion source close to the ionization region. Compound VI was evaporated in a glass charging vessel.

2,2,6,6-Tetramethyl-4-ethoxycarbonylcyanomethylenepiperidine (I). A 3.1-g (0.02 mole) quantity of triacetonamine, 2.26 g (0.02 mole) of ethyl cyanoacetate, and 0.62 g (20% of the weight of the ketone) of ammonium acetate were boiled in 100 ml of benzene for 1 hr, the water being removed azeotropically. The reaction mixture was cooled and treated with 20 ml of 50% potassium carbonate solution, then extracted with ether. The extracts were dried over potassium carbonate, the ether and benzene were removed, and the residue distilled in vacuo to give 2.45 g (50%) of a colorless crystalline solid with mp 57-58° C, bp 128-130° C (1.5 mm). Found, %: C 67.23; H 8.76; N 11.01. Calculated for $C_{14}H_{22}N_2O_2$, %: C 67.16; H 8.85; N 11.19. Hydrochloride, colorless crystalline solid, mp 204-206° C. Found, %: C 58.40; H 7.82; Cl 12.34; N 9.99. Calculated for $C_{14}H_{22}N_2O_2 \cdot HCl$, %: C 58.62; H 8.08; Cl 12.33; N 9.77.

1-Acetyl-2,2,6,6-tetramethyl-4-ethoxycarbonylcyanomethylenepiperidine (IV). A) A 3.1-g (0.02 mole) quantity of triacetonamine, 2.26 g (0.02 mole) of ethyl cyanoacetate, and 0.62 g of ammonium acetate were boiled in 100 ml of benzene with azeotropic removal of water for 3-4 hr. The reaction mixture was cooled, when 1.58 g (28%) of a colorless, finely crystalline solid separated, mp 115-117° C. Recrystallization from ethanol left the mp unchanged. IR spectrum, ν, cm^{-1}: 2225 ($C \equiv N$); 1740, 1635 ($C = O$). Found, %: C 65.41; H 8.11; N 9.8. Calculated for $C_{16}H_{24}N_2O_3$, %: C 65.72; H 8.27; N 9.58.

B) A 5-g (0.02 mole) quantity of I was dissolved in 25 ml of acetic anhydride, and kept at room temperature for 8-10 hr. The precipitate which separated was filtered off and washed with ether to give 3.82 g (66%) of a colorless, finely crystalline solid, mp 115-117° C which gave no mp depression on admixture with the material obtained as in A) above. On dissolving IV in a 2-3% alcoholic solution of HCl in the cold, hydrolysis of the acetyl group took place, giving the hydrochloride of I, mp 204-206° C.

3-Cyano-4-(β,β-dimethylvinyl)-6,6-dimethyl-Δ^3-dehydro-2-piperidone (III). A) A 3.1-g (0.02 mole) quantity of triacetonamine, 2.26 g (0.02 mole) of ethyl cyanoacetate, and 0.62 g of ammonium acetate were boiled in 40 ml of toluene with azeotropic removal of water for 4-5 hr. The reaction mixture was cooled, and the crystalline product was filtered off, washed with ether, and dried to give 1.58 g (38.6%) of a colorless crystalline solid, mp 183-184° C (from alcohol). Found, %: C 70.73; H 7.90; N 13.80. Calculated for $C_{12}H_{16}N_2O$, %: C 70.58; H 7.89; N 13.77.

B) A 14.6-g (0.05 mole) quantity of IV was placed in a flask and heated in an oil bath, the temperature of the reaction mixture being kept below 130° C. After cooling, the reaction mixture was triturated with 50 ml of ether, and the resulting solid was filtered off and washed with ether to give 7.6 g (75%) of a colorless, crystalline solid with mp 183-184° C (from alcohol). A mixed mp with material obtained by method A) gave no depression.

C) A 5-g (0.02 mole) quantity of I and 1.54 g (0.02 mole) of ammonium acetate were boiled in 40 ml of toluene with azeotropic removal of water for 4 hr. The reaction mixture was cooled, and the solid which separated was filtered off and washed with ether to give 2.06 g (50.6%) of a colorless, crystalline solid, mp 183-184° C (from alcohol). A mixed mp with the material obtained by method A) gave no depression.

3-Aminomethyl-4-(β-methylpropyl)-6,6-dimethyl-Δ^3-dehydro-2-piperidone Hydrochloride (VI). A 5-g (0.0245 mole) quantity of III was reduced in absolute alcohol (100 ml) over 0.1 g of platinum catalyst, at room temperature and a pressure of 20-30 mm of water. The hydrogenation was discontinued after the absorption of 3 moles of hydrogen, giving 3.5 g (58%) of V as a colorless, crystalline solid, mp 232-233° C (from alcohol). Found, %: C 58.00; H 9.68; Cl 14.56; N 11.37. Calculated for $C_{12}H_{22}N_2O \cdot HCl$, %: C 58.40; H 9.39; Cl 14.36; N 11.35.

6,6-Dimethyl-4-(β-methyl-β-aminopropyl)-Δ^3-dihydro-2-pyrone (VII). A 10.2-g (0.05 mole) quantity of III was boiled with a mixture of 100 ml of acetic acid and 50 ml of HCl for 20 hr. After cooling, the acid mixture was evaporated in vacuo, and the residue was treated with potassium carbonate solution until alkaline, then extracted with chloroform. The chloroform was removed and the residue was distilled in vacuo, the fraction with bp 128-130° C (0.5 mm) being collected. There was obtained 4.6 g (47.1%) of a viscous oil, which crystallized on standing to give colorless needles, mp 32-34° C. IR spectrum, ν, cm^{-1}: 3300-3370 (N−H) and 1715 (C=O). Found, %: C 66.90; H 9.32; N 6.93. Calculated for $C_{11}H_{19}NO_2$, %: C 67.00; H 9.64; N 7.1. Hydrochloride, colorless crystalline solid, mp 194-195° C (from alcohol). Found, %: Cl 15.19; N 5.94. Calculated for $C_{11}H_{19}NO_2 \cdot HCl$,%: Cl 15.17; N 5.99.

6,6-Dimethyl-4-(β-methyl-β-aminopropyl)-Δ^3-dihydropyran (VIII). A 7.9-g (0.04 mole) quantity of VII was reduced with lithium aluminum hydride in ether for 20 hr, giving 4.71 g (64.5%) of yellow caramel-like material, mp 137-140° C (0.9 mm). NMR spectrum, δ, ppm: 1.095; 1.310 (CH_3); 2.385 and 2.530 (CH_2); and 5.912 (CH). Found, %: C 71.76; H 11.46; N 7.62. Calculated for $C_{11}H_{21}NO$, %: C 72.07; H 11.54; N 7.64.

6,6-Dimethyl-4-(β-methyl-β-acetylaminopropyl)-Δ^3-dihydro-2-pyrone (IX). A 1.97-g (0.01 mole) quantity of VII was heated to boiling with 20 ml of acetic anhydride for 9 hr. The solution was evaporated, and the residue triturated with dry ether to give 2.3 g (95%) of a colorless, crystalline solid, mp 118-119° C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3280 (N−H), 1710 and 1650 (C=O). Found, %: C 65.07; H 8.85; N 5.82. Calculated for $C_{13}H_{21}NO_3$, %: C 65.24; H 8.84; N 5.85.

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