SYNTHESES OF DI- AND TETRAHYDROPYRROLES

II. Synthesis of 3-Ethoxycarbonyl-4-Ethoxycarbonylmethyl-2, 4-dimethyl-1-pyrroline*

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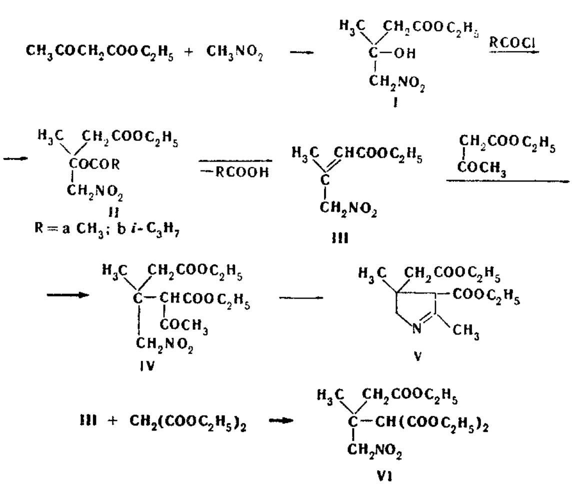
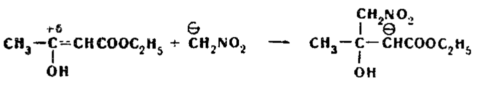
Ethyl β-hydroxy-β-methyl-γ-nitrobutyrate has been synthesized by the reaction of sodioacetoacetic ester with nitromethane, and from this 3-ethoxycarbonyl-4-ethoxycarbonylmethyl-2,4-dimethyl-1-pyrroline has been obtained in four stages.

We have previously shown that 1-pyrrolines similar to ring C of the corrin system of vitamin B_{12} can be obtained by the reductive cyclization of γ-nitro carbonyl compounds containing the required substituents. In the present work, we studied the possibility of synthesizeng in a similar manner 1-pyrrolines similar to ring B of the corrin system which contains a methyl group and an acetamide residue in position 4 and a propionamide residue in position 3. We obtained 3-ethoxycarbonyl–4-ethoxycarbonylmethyl-2, 4-dimethyl-1-pyrroline (V) by the reductive cyclization of diethyl α-acetyl-β-methyl-β-nitromethylglutarate (IV). The latter, in its turn, was synthesized in four stages from acetoacetic ester and nitromethane.



When the condensation of acetoacetic ester with nitromethane was carried out under the conditions that are generally best for ketones [3], i.e., in methanol in the presence of a catalytic amount of sodium ethoxide, we were unable to obtain good and constant yields of ethyl β-hydroxy-β-methyl-γ-nitrobutyrate (I) (the yields varied from 3 to 19%). However, acetoacetic ester can apparently condense with nitromethane by the mechanism of the Michael reaction.



$$CH_3-\overset{+\delta}{\underset{OH}{C}}=CHCOOC_2H_5 + \overset{\ominus}{C}H_2NO_2 \longrightarrow CH_3-\overset{CH_2NO_2}{\underset{OH}{C}}-\overset{\ominus}{C}HCOOC_2H_5$$

In this case, the acetoacetic ester plays the part of acceptor and its conversion into the sodium derivative must favor the reaction. Furthermore, we abandoned the use of ethanol and its alkoxide as competitors for the nitromethane. By carrying out the condensation of 2 moles of sodioacetoacetic ester and 1 mole of nitromethane in an excess of acetoacetic ester as solvent, we obtained the nitro alcohol I with a yield of 45%. The structure of the nitro alcohol obtained was confirmed by its IR spectrum and the positive reaction for a tertiary hydroxyl with mercury sulfate [5].

The dehydration of the nitro alcohol I was carried out by first converting it into the ester II with subsequent splitting out of a molecule of acid. When the nitro alcohol I was acylated with a mixture of acetyl chloride and acetic anhydride, we obtained ethyl β-acetyl-β-methyl-γ-nitrobutyrate (IIa) with a yield of 37%, but the substance has a boiling point close to that of the initial nitro alcohol I which greatly complicates their separation. A considerably better result was obtained when the nitro alcohol I was acylated with isobutyryl chloride; the yield of β-isobutyryl-β-methyl-γ-nitrobutyrate (IIb) was 85%. The splitting out of a molecule of the acid from the esters II led to ethyl β-methyl-γ-nitrocrotonic acid (III). The best yield of III (77%) was given by the isobutyrate IIb. The acetate IIa gave III with a yield of 52%. The structure of the unsaturated nitro ester III is confirmed unambiguously by its IR spectrum. Absorption at 1720 cm^{-1} corresponds to the frequency of the ester oxygen (1740 cm^{-1}) reduced by 20 cm^{-1} through the conjugation of the ethoxycarbonyl group with the double bond. According to the literature [6, 7], the absorption bands of α, β-unsaturated esters are located at 1718–1721 cm^{-1} and are 20 cm^{-1} lower than those of the corresponding saturated compounds. The stretching vibrations of the $C—NO_2$ group are located in the 1383 cm^{-1} region (symmetrical) and 1555–1565 cm^{-1} region (unsymmetrical), which corresponds to a nonconjugated nitro compound [7] (conjugation of the nitro group with the double bond would lead to a decrease in both frequencies by 30–50 cm^{-1}).

Thus, the unsaturated nitro ester III has a structure of the type of β,β-dimethylacrylic acid, the reactivity of which in the Michael condensation is low [4]. Nevertheless, we succeeded in performing the condensation of the unsaturated nitro ester III with acetoacetic and malonic esters, obtaining the diethyl ester IV and diethyl α-ethoxycarbonyl-β-methyl-β-nitro

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*For part I, see [1].

nitroglutarate (VI). The reductive cyclization of the γ-nitro ketone (IV) gave the pyrroline V, the structure of which was confirmed by its IR spectrum. A determination of the composition of the diastereoisomers in the IV and V obtained requires additional investigations.

EXPERIMENTAL

The IR spectra of the substances were recorded on a UR-10 spectrophotometer. The samples were used in the form of thin films (layer thickness 10 μ). To identify the compounds obtained, we used variants of chromatography in a thin nonfixed layer of type KSK silica gel in the benzene—chloroform (1:2) system (system 1) and on acidic alumina (activity grade III in the hexane—ethyl acetate (13:3) system (system 2), and also in a thin fixed layer of silica gel with 5% of gypsum, using isopropanol as solvent (system 3). The sorbents and the plates were prepared as described by Akhrem and Kuznetsova [8]. The layer thickness of the sorbent was about 1 mm. The substances were detected in UV light and in iodine vapor.

Ethyl β-hydroxy-β-methyl-γ-nitrobutyrate (I). 2.3 g (0.1 g-atom) of metallic sodium was dissolved in 52 g (0.4 mole) of nitromethane was then added and the mixture was heated in the water bath to 50° C for a few minutes (to obtain a homogeneous solution) and then left to stand at 18–20° C for 90 hr. Then it was neutralized with 5.75 ml of glacial acetic acid, treated with 25 ml of water, and extracted with ether. The combined ethereal extracts were washed with water, dried with $MgSO_4$, and distilled in vacuum to give 4.3 g (45%) of the ethyl ester I with bp 86–88° C (0.5 mm); R_f 0.78 (system 3); d_4^{20} 1.2010; n_D^{20} 1.4563. Found, %: C 43.62; 43.75; H 6.64; 6.89; N 7.07; 6.98%; MR_D 43.27. Calculated for $C_7H_{13}NO_5$, %: C 43.98; H 6.90; N 7.33%; MR_D 43.22. IR spectrum, ν, cm^{-1}: 1385, 1565 (NO_2), 1210 (C—O of an ester), 1735 (C=O of an ester), 3510 (OH). When the substance obtained was boiled with Deniges' reagent, a yellow precipitate was produced (reaction for a tertiary hydroxyl) [5].

Ethyl β-acetyl-β-methyl-γ-nitrobutyrate (IIa). A mixture of 25.1 g (0.131 mole) of I, 10.3 g (0.131 mole) of acetyl chloride, and 10.2 g (0.1 mole) of acetic anhydride was heated at 70–80° C for 3 hr, the unchanged acetyl chloride and acetic anhydride were distilled off, and the residue was vacuum distilled twice to give 11.6 g (37.5%) of **IIa** with bp 112–114° C (2 mm); d_4^{20} 1.1930; n_D^{20} 1.4485. Found, %: C 45.92; 46.17; H 6.44; 6.35; N 6.30; 6.34%; MR_D 52.36. Calculated for $C_9H_{15}NO_6$, %: C 46.34; H 6.48; N 6.01%; MR_D 52.69. IR spectrum, ν, cm^{-1}: 1390, 1575 (NO_2), 1250 (C—O of an ester), 1755 (C=O of an ester).

Ethyl β-isobutyryloxy-β-methyl-γ-nitrobutyrate (IIb). A mixture of 80.5 g (0.422 mole) of I and 45.5 g of isobutyryl chloride was heated at 80–90° C for 10 hr, and then air was passed through the mixture to eliminate hydrogen chloride and it was distilled in vacuum. Yield 93.9 g (85%), bp 115–117° C (0.7 mm), R_f 0.70 (system 3); d_4^{20} 1.1320; n_D^{20} 1.1320; n_D^{20} 1.4460. Found, %: C 49.97; 50.10; H 6.99; 7.16%: MR_D 61.45. Calculated for $C_{11}H_{19}NO_6$, %: C 50.58; H 7.33%; MR_D 61.93.

Ethyl-β-methyl-γ-nitrocrotonate (III); A mixture of 7.53 g (0.029 mole) of IIb and 0.5 g of anhydrous sodium acetate was heated at 105°C in vacuum 1 mm) until isobutyric acid ceased to distill over. Then the reaction mixture was dissolved in ether, the solution was washed with 5% aqueous sodium carbonate and with water and dried with $MgSO_4$, the ether was distilled off, and the residue was distilled in vacuum. Yield 3.85 g (77%), bp 92–94° C (2 mm); d_4^{20} 1.150; n_D^{20} 1.4685; R_f 0.70 (system 3). Found, %: C 48,00; 48.28; H 6.18; 6.24; N 8.23 8.25%; MR_D 41.91. Calculated for $C_7H_{11}NO_4$, %: C 48.55; H 6.39; N 8.09%; MR_D 42.31. IR spectrum, ν, cm^{-1}: 1385, 1560 (NO_2), 1220 (C—O of an ester), 1720 (C=O of an ester), 1659 (C=C). On being boiled with the Deniges' reagent, the substance formed a yellow precipitate (reaction for a double bond) [5].

Diethyl α-ethoxycarbonyl-β-methyl-β-nitromethylglutarate (VI). 2.23 g (0.01 g-atom) of metallic sodium was dissolved in 29.5 g (0.184 mole) of malonic ester, 3.18 g (0.018 mole) of III was added, and the mixture was heated at 70–80° C for 3 hr and was left at 18–20° C for 60 hr. Then it was acidified with 0.7 g (calculated amount) of glacial acetic acids treated with 20 ml of water, and extracted with ether. The combined extracts were washed with 5% sodium bicarbonate solution and with water, dried with $MgSO_4$, and distilled in vacuum. Yield 1.42 g (23%), bp 108–110° C (0.025 mm), R_f 0.53 (system 2); d_4^{20} 1.1710; n_D^{20} 1.4570. Found, %: C 50.46; 50.75; H 6.77; 6.75; N 4.35; 4.23%; MR_D 77.50. Calculated for $C_{14}H_{23}NO_3$, %: C 50.55; H 6.95; N 4.20%; MR_D 77.43.

Diethyl α-acetyl-β-methyl-β-nitromethylglutarate (IV). With stirring, 0.1 g (0.004 g-atom) of metallic sodium and 5 ml of anhydrous dimethyl sulfoxide were added to a mixture of 2.64 g (0.015 mole) of III and 3.97 g (0.03 mole) of acetoacetic ester. The resulting mixture was left at 18–20° C for 50 hr. Then it was acidified with glacial acetic acid to pH 5 and the dimethyl sulfoxide was distilled off in vacuum (8 mm). A solution of the residue in a mixture of ether and benzene (1:2) was washed with water. The solvent was then distilled off and the residue was distilled in vacuum. Yield 1.0 g (21.6%). mp 111–112° C (0.05 mm), R_f 0.39 (system 1); d_4^{20} 1.1640, n_D^{20} 1.4753. Found, %: C 52.39; 52.41; H 6.66; 6.66; N 4.65; 4.78%; MR_D 73.40. Calculated for $C_{13}H_{21}NO_7$, %: C 51.48; H 6.98; N 4.62%; MR_D 71.32. IR spectrum, ν, cm^{-1}: 1380, 1550 (NO_2), 1730 (C=O in nonenolic β-keto esters).

When the reaction was carried out in dry ether in the presence of sodium ethoxide, the yield of compound IV was 17% and in ethanol it was 20%.

3-Ethoxycarbonyl-4-ethoxycarbonylmethyl-2,4-dimethyl-1-pyrroline (V). In a hydrogenation apparatus, 5.5 g of compound IV in 35 ml of anhydrous ethanol and 5 g of Raney nickel catalyst were shaken in a current of hydrogen at 20° C until the absorption of hydrogen ceased (1.77 *l*). The catalyst was filtered off and washed on the filter with anhydrous ethanol, the solvent was driven off, and the residue was distilled in vacuum. Yield 2.54 g (54.2%), bp 122–124° C (0.08 mm); R_f 0.49 (system 1); d_4^{20} 1.1045; n_D^{20} 1.5033. Found, %: C 60.72; 60.91; H 8.06; 8.13; N 5.30; 5.48%; MR_D 68.36. Calculated for $C_{13}H_{21}NO_4$, %: C 61.16; H 8.29; N 5.48%; MR_D 68.80.

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