SYNTHESES OF DI- AND TETRAHYDROPYRROLES

IV. Synthesis of Substituted 4-Isopropyl-2-methyl- and 2,4,4-Trimethyl-Δ^1-pyrrolines*

V. M. Berezovskii, V. B. Spiro, L. Ya. Denisova, and B. M. Sheiman

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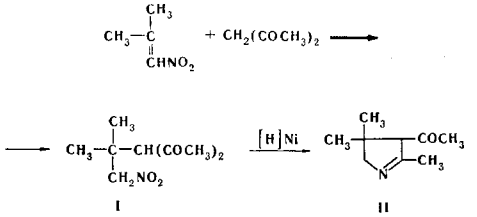
By the Michael's condensation of 3-methyl-1-nitro-1-butene with esters of α-acetoglutaric and acetosuccinic acids and of 2-methyl-1-nitropropene with acetylacetone we have synthesized the corresponding γ-nitrocarbonyl compounds, which have been converted by reductive cyclization into 3-ethoxycarbonyl-4-isopropyl-3-methoxycarbonylethyl-2-methyl-Δ^1-pyrroline, 3-ethoxycarbonyl-3-ethoxycarbonylmethyl-4-isopropyl-2-methyl-Δ^1-pyrroline, and 3-acetyl-2,4,4-trimethyl-Δ^1-pyrroline, respectively.

Our previous investigations were devoted to the synthesis of Δ^1-pyrrolines structurally similar to rings B and C of the corrin system of vitamin B_{12} [1,2].

Previously [1,3], we introduced propionic acid residues (contained in the form of amides in all the corrin rings) by the successive construction of a molecule of a γ-nitrocarbonyl compound: first on α, β-unsaturated compound was condensed with acetoacetic or malonic ester and then the methoxycarbonylethyl group was introduced by reaction with methyl acrylate. In the present work, we have investigated the possibility of carrying out the Michael's condensation of α,β-unsaturated nitro compounds with acetoacetic esters containing ethoxycarbonylmethyl and methoxycarbonylethyl groups as substituents.

Among activated olefins with a single electron-accepting group, the α,β-unsaturated nitro compounds are some of the most reactive. It is known that the reactivity of acceptors in the Michael's reaction rapidly falls with an increase in the number of alkyl groups attached to the double bond [4]. In spite of this, 2-methyl-1-nitropropene (which has two methyl groups in the β-position) readily condenses with compounds containing a methylene group such as acetoacetic [5] and malonic [6] esters. In the present work we have shown that 2-methyl-1-nitropropene also readily condenses with acetylacetone, giving an 85% yield of 3-acetyl-2,2-dimethyl-1-nitro-4-pentanone (I), the structure of which was confirmed by its conversion on reductive cyclization into the corresponding Δ^1-pyrroline (3-acetyl-2,4,4-trimethyl-Δ^1-pyrroline (II)):



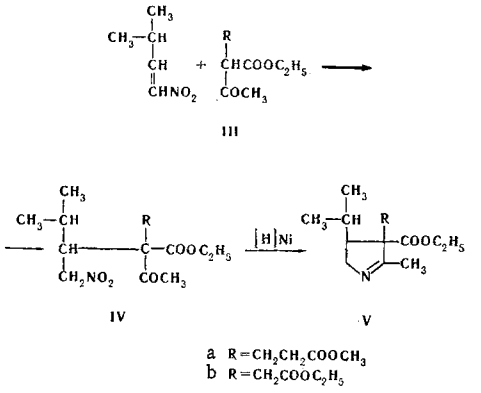
I II

*For parts I-III, see [1-3].

The structure of the latter was shown by its IR spectrum.

However, all our attempts to carry out the condensation of 2-methyl-1-nitropropene with monoalkyl derivatives of acetoacetic ester containing ethyl, ethoxycarbonylmethyl, and methoxycarbonylethyl groups as substituents have proved unsuccessful.

Various ways of performing the Michael's reaction were tried: sodium methoxide and metallic sodium were used as catalyst, alcohols and dimethyl sulfoxide were used as solvents, and the temperature and time of the process were varied; however, in no case did these reactions take place, due to the steric screening (as a result of the condensation a new C—C bond should be formed between two tertiary carbon atoms). This assumption is confirmed by the fact that the same donors, namely methyl γ-acetyl-γ-ethoxycarbonylbutyrate and diethyl acetylsuccinate (IIIa, b) condense with 3-methyl-1-nitro-1-butene, in which the β-position has only one alkyl (isopropyl) group. The structure of the methyl 4-acetyl-4-ethoxycarbonyl-5-isopropyl-6-nitrocaproic acid (IVa) obtained was confirmed by its IR spectrum.



III

IV V

a $R=CH_2CH_2COOCH_3$
b $R=CH_2COOC_2H_5$

The γ-nitro compounds IVa and b were converted by reductive cyclization into the corresponding Δ^1-pyrrolines: 3-ethoxycarbonyl-3-methoxycarbonylethyl-4-isopropyl-2-methyl-Δ^1-pyrroline (Va), and 3-ethoxycarbonyl-3-ethoxycarbonylmethyl-4-isopropyl-2-methyl-Δ^1-pyrroline (Vb). The structure of the Δ^1-pyrrolines Va and b was confirmed by their IR spectra: absorption at 1650-1670 cm^{-1} corresponds to the stretching vibrations of the C=N bond, and absorption at 1700 cm^{-1} and 1730-1735 cm^{-1} corresponds to the ketone group and the carbonyl group in esters, respectively [7-8].

EXPERIMENTAL

The IR spectra of the substances were recorded on a UR-10 spectrophotometer.

3-Acetyl-2, 2-dimethyl-1-nitro-4-pentanone-3 (I). First 0.16 g (0.007 g-at) of metallic sodium was dissolved in a solution of 5.18 g (0.052 mole) of acetylacetone in 15 ml of dry ether, 3.5 g (0.035 mole) of 2-methyl-1-nitropropene was added and the mixture was allowed to stand at 18°–20°C for 50 hr. Then it was acidified with glacial acetic acid to pH 5, the ethereal layer was washed with 5% sodium bicarbonate solution and with water and was dried with Na_2SO_4, the ether was evaporated, and the residue was distilled in vaccum. Yield 6.0 g (85.7%). Bp 114°–115°C (1 mm), d_4^{20} 1.1263; n_D^{20} 1.4672. Found, %: C 53.82, 53.57; H 7.41, 7.38; N 7.05, 6.88; MR_D 49.60. Calculated for $C_9H_{15}NO_4$, %: C 53.72; H 7.51; N 6.96; MR_D 49.40.

2, 4-Dinitrophenylhydrazone. Mp 147°–147.8°C (from ethanol). Found, %: C 47.45, 47.77; H 4.91, 4.97; N 18.48, 18.28. Calculated for $C_{15}H_{19}N_5O_7$, %: C 47.24; H 5.02; N 18.37.

Methyl 4-aceto-4-ethoxycarbonyl-5-isopropyl-6-nitrocaproate (IVa). Similarly, 8.31 g (0.038 mole) of **IIIa**, 4.0 g (0.035 mole) of 3-methyl-1-nitro-1-butene, and 0.12 g of sodium gave 3.07 g (26.6%) of IVa. Bp 138°–140°C (0.05 mm). When the reaction mixture was left in the refrigerator, white crystals deposited which, after being washed with ether, had mp 93°–95°C. Found, %: C 53.65, 53.58; H 7.35, 7.26; N 4.51, 4.23. Calculated for $C_{15}H_{25}NO_7$, %: C 54.37; H 7.61; N 4.23. IR spectrum, ν cm^{-1}: 1375, 1555 (NO_2); 1700 (C=O); 1725 (C=O in esters).

Ethyl 3-acetyl-3-ethoxycarbonyl-4-isopropyl-5-nitrovalerate (IVb). Similarly, 16.68 g (0.077 mole) of **IIIb**, 6.6 g (0.057 mole) of 3-methyl-1-nitro-1-butene, and 0.1 g of sodium (6 hr at 40°–45°C and 70 hr at 20°C) gave 4.1 g (21.6%) of **IVb**. Bp 141°–142° C (0.08mm). Found, %: N 3.81, 3.79. Calculated for $C_{15}H_{25}NO_7$, %; N 4.22.

3-Ethoxycarbonyl-3-methoxycarbonylethyl-4-isopropyl-2-methyl-Δ^1-pyrroline Va. In a hydrogenation apparatus, 0.9 g of IVa in 25 ml of anhydrous ethanol was shaken in a current of hydrogen at 20°C with 5 g of Raney nickel catalyst until the absorption of hydrogen ceased. 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 0.28 g (31%). Bp 96°C (0.02 mm); n_D^{20} 1.4580. Found, %: C 60.14, 60.17; H 8.70, 8.82; Calculated for $C_{15}H_{25}NO_4 \cdot 0.895\ H_2O$, %: C 60.17; H 9.02. IR spectrum, ν cm^{-1}: 1650 (C=N): 1735 (C=O of an ester); 1205 (C O of an ester).

3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-4-isopropyl-2-methyl-Δ^1-pyrroline (Vb). Similarly, 2.95 g of IVb gave 1.26 g (49.9 %) of Vb. Bp 85°–85.5°C (0.016 mm); d_4^{20} 1.0458, n_D^{20} 1.4600. Found, %: C 63.32, 63.00; H 9.01, 8.78; N 5.03, 4.92; MR_D 74.22. Calculated for $C_{15}H_{25}NO_4$, %: C 63.65; H 8.89; N 4.94; MR_D 75.24. IR spectrum, ν cm^{-1}: 1660 (C=N); 1730 (C=O in an ester); 1205 (C—O of an ester).

3-Acetyl-2, 4, 4-trimethyl-Δ^1-pyrroline (II). Similarly, by sublimation, 4.5 g of I yielded the corresponding Δ^1-pyrroline. Yield 2.28 g (60.9%). Mp 114.5°–115°C (petroleum ether–benzene, 2:1). Found, %: C 63.51, 63.41; H 9.41, 9.36; N 7.82, 7.89. Calculated for $C_9H_{15}NO \cdot H_2O$, %: C 63.13; H 10.01; N 8.18. IR spectrum, ν cm^{-1}: 1650 (C=N); 1700 (C=O).

Picrate—mp 141.4°–141.7°C (ethanol—ether, 3:1). Found %: C 44.74, 44.55; H 4.94, 4.90; N 14.5, 14.0. Calculated for $C_9H_{15}NO \cdot C_6H_3N_3O_7 \cdot H_2O$, %: C 45.0; H 5.04; N 14.0.

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All-Union Scientific-Research Vitamin Institute, Moscow