SYNTHESES OF DI- AND TETRAHYDROPYRROLES

I. Synthesis of Substituted 1-Pyrrolines from γ-Nitro Ketones

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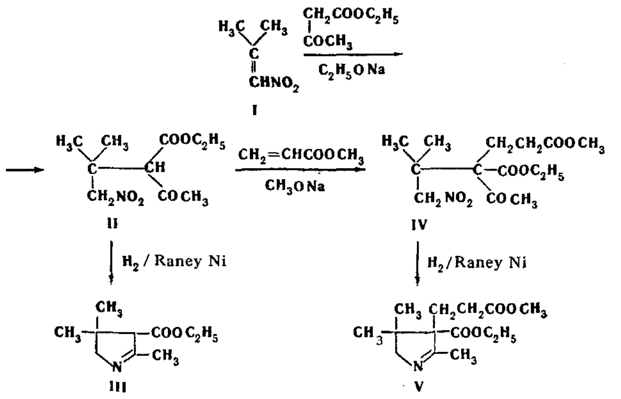
The cyclization of γ-nitro carbonyl compounds containing all the required substituents has been used to obtain polysubstituted 1-pyrrolines. Ethyl α-acetyl-β,β-dimethyl-γ-nitrobutyrate and methyl 4-acetyl-4-ethoxycarbonyl-5, 5-dimethyl-6-nitrocaproate have given respectively, 3-ethoxycarbonyl-2, 4, 4-trimethyl- and 3-ethoxycarbonyl-3-methoxycarbonylethyl-2, 4, 4-trimethyl-1-pyrrolines.

The corrin system of vitamin B_{12} consists of three 1-pyrrolines and one pyrrolidine specifically connected to one another through the α, α' positions and containing methyl groups and acetamide and propionamide residues in the β, β' positions [1]. At the present time, only the synthesis of the corrin ring containing five methyl groups as substituents has been effected [2]. Consequently, it is of interest to study methods for the synthesis of 1-pyrrolines with substituents analogous to those contained in the corrin system of vitamin B_{12} and to investigate possible methods for combining them into a tetracyclic system.

In the present work we have studied the possibility of obtaining 1-pyrrolines similar to ring C of the corrin system (which contains two methyl groups in position 4 and a propionamide residue in position 3) by the reductive cyclization of γ-nitro carbonyl compounds [2] already containing the required substituents. For the synthesis of the latter we have subjected 2-methyl-1-nitro-1-propene (I) to the Michael condensation with acetoacetic ester* to form ethyl α-acetyl-β,β-dimethyl-γ-nitrobutyrate (II) (yield 85%), with the subsequent introduction of a propionic ester residue.



The hydrogenation of II on a Raney nickel catalyst at 18°–20° C yielded 3-ethoxycarbonyl-2,4,4-trimethyl-1-pyrroline (III), a colorless very hygroscopic liquid which rapidly adds a molecule of water on standing in the air, forming a crystalline hydrate. It is interesting that the latter compound does not lose the molecule of water under the conditions of gas-liquid chromatography (136° C) and gives a single peak the retention time of which is greater than that of the anhydrous pyrroline (III) (see figure). We followed the gradual conversion of the anhydrous pyrroline III into its hydrate by means of gas-liquid chromatography (from the decrease in peak 1 and the increase in peak 2). The anhydrous pyrroline III and its hydrate form an anhydrous picrate and a picrate containing a molecule of water, respectively. The structure of the 1-pyrroline (III) was confirmed by its IR spectrum. Absorption at 1670 cm^{-1} corresponds to the stretching vibrations of a C=N bond, and absorption at 1750 cm^{-1} to the stretching vibrations of a carbonyl group in an ester [3, 5].

The reaction of II with methyl acrylate in the presence of sodium methoside led to methyl 4-acetyl-4-ethoxycarbonyl-5,5-dimethyl-6-nitrocaproate (IV). The fact that II adds to methyl acrylate by the Michael reaction through its α-carbon atom was shown by the negative reaction for an enolic grouping and the presence in the NMR spectrum of the two protons of a $-CH_2NO_2$ group (in the 4.6 ppm* region). The resonance signal of the $-CH_2NO_2$ group proved to be split into four peaks (complex spin-spin interaction of a AB system), which shows the nonequivalence of the protons in this group.

Since, on being distilled in vaccum, IV undergoes partial cleavage (for the thermal cleavage of γ-nitrocarbonyl compounds, see, for example, [6, 7], it was subjected without isolation in the pure state to reductive cyclization into 3-ethoxycarbonyl-3-methoxycarbonylethyl-2, 4, 4-trimethyl-1-pyrroline (V).

The IR spectrum of the pyrroline V is similar to that of the pyrroline III: there is absorption in the 1655 cm^{-1} region (C=N group) and in the 1735 cm^{-1} region (carbonyl group in an ester). On gas-liquid chromatography, the pyrroline V gave a peak the re-

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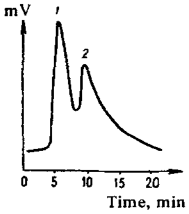
*This condensation has been described in a patent, but only the boiling point is given for compound II.

*In the NMR spectra of model compounds it was shown that the singlet from the protons of the $-CH_2NO_2$ group is located in the 4.6 ppm region. The question of the direction of the addition of methyl acrylate to the adducts I with malonic and acetoacetic esters will be discussed in detail in paper III of this series (KhGS [Chemistry of Heterocyclic Compounds], in press).

tentation time which was the same as that of the anhydrous pyrroline III.

The authors express their thanks to M. Ts. Yanotovskii for recording the gas-liquid chromatograms.



Chromatogram of a mixture of the hydrated and unhydrated forms of 3-ethoxycarbonyl-2, 4, 4-trimethyl-1-pyrroline: 1) anhydrous form 2) hydrated form.

EXPERIMENTAL

The IR spectra of the substances were recorded on a UR-10 spectrophotometer. The thin-layer chromatography was carried out on alumina of activity III in the n-heptane–ethyl acetate–chloroform (1:2:2) system (system 1) and the methyl ethyl ketone–water (30:1) system (system 2). The substances were detected in UV light and in iodine vapor. The gas-liquid chromatography of the 1-pyrrolines was carried out on a "Pye" argon chromatograph with a column length of 1.2 m using 10% poly(propylene glycol adipate) on Chromosorb W 60/100 mesh as stationary phase with a rate of flow of argon of 75 ml/min at a temperature of 136° C. The NMR spectrum was taken on a "Hitachi H 60" apparatus in CCl_4 solution with HMDS (hexamethyldisiloxane) as the internal standard.

2-Methyl-1-nitro-1-propene (I) was obtained from acetone and nitromethane via the acetate of the nitro-tert-butyl alcohol formed by a modification of the method of Lambert and Lowe, in which the acylation was carried out with a mixture of acetic anhydride and acetyl chloride (1.3:1) and not with acetic anhydride alone. Yield 92%.

Ethyl α-acetyl-β,β-dimethyl-γ-nitrobutyrate (II). A solution of sodium ethoxide (from 0.46 g of sodium and 10 ml of anhydrous ethanol) was added to a solution of 23.55 g (0.181 mole) of acetoacetic ester in 45 ml of dry ether and then, with cooling to 10–12° C, the mixture was treated with a solution of 9.15 g (0.091 mole) of I in 7 ml of dry ether, after which it was stirred at 18–20° C for 5 hr and was left to stand for 16 hr. After the reaction mixture had been neutralized to pH 5.0 with acetic acid, it was washed with sodium bicarbonate solution and with water, and dried with sodium sulfate. After the ether had been distilled off, it was distilled in vacuum. Yield 17.81 g (85.0%). Bp 126.5–127° C (1 mm) [according to the literature [4], bp 119° C (2-1 mm)]; d_4^{20} 1.1257; n_D^{20} 1.4540; R_f 0.82 (system 1). Found, %: C 51.73; 52.00; H 7.57; 7.60; N 6.13; 6.03%; MR_D 55.63. Calculated for $C_{10}H_{17}NO_5$, %: C 51.95; H 7.41; N 6.06%; MR_D 55.65. IR spectrum, ν, cm^{-1}: 1370, 1550 (NO_2), 1710–1740 (C=O).

2,4-Dinitrophenylhydrazone, mp 79.5–80° C (from ethanol). Found, %: C 46.54; 46.68; H 5.12; 5.17; N 17.22; 17.27%. Calculated for $C_{16}H_{21}N_5O_8$, %: C 46.71; H 5.15; N 17.03%.

3-Ethoxycarbonyl-2,4,4-trimethyl-1-pyrroline (III). In a hydrogenation apparatus, 10 g of II in 50 ml of anhydrous methanol containing 8 g of Raney nickel catalyst was shaken in a current of hydrogen at 20° C until the absorption of hydrogen ceased (2.66 *l* was absorbed). The catalyst was filtered off and washed on the filter with anhydrous methanol, the solvent was evaporated off, and the residue was distilled. Mp 66–67° C (0.24 mm). Yield 4.95 g (62.5%). Found, %: C 65.20; 65.22; H 9.44; 9.49; N 7.51; 7.75%. Calculated for $C_{10}H_{17}NO_2$, %: C 65.54; H 9.35; N 7.64%.

Picrate, mp 134.5–135° C (from a 3:1 mixture of petroleum ether and ethanol). Found, %: C 46.43; 46.75; H 4.69; 4.96; N 13.13; 13.38%. Calculated for $C_{10}H_{17}NO_2 \cdot C_6H_3N_3O_7$, %: C 46.35; H 4.87; N 13.56%.

On standing in the air, the pyrroline III added a molecule of water, forming colorless crystals with mp 117–118° C (from a 5:2 mixture of petroleum ether and benzene). R_f 0.83 (system 2). Found, %: C 59.85; 59.91; H 8.72; 8.89; N 6.85; 7.12%. Calculated for $C_{10}H_{17}NO_2 \cdot H_2O$, %: C 59.68; H 9.46; N 6.96%.

Picrate, mp 151–151.3° C (from a 3:1 mixture of ethanol and ether). Found, %: C 44.54; 44.65; H 4.86; 5.10; N 13.00; 13.39%. Calculated for $C_{10}H_{17}NO_2 \cdot C_6H_3N_3O_7 \cdot H_2O$, %: C 44.65; H 5.15; N 13.02%.

Methyl 4-acetyl-4-ethoxycarbonyl-5,5-dimethyl-6-nitrocaproate (IV). With stirring, to 10 g (0.0433 mole) of II were added a solution of sodium methoxide (from 0.1 g of sodium and 28 ml of methanol) was added to 10 g (0.0433 mole) of II. Then, with cooling to 5–7° C, 3.73 g (0.0433 mole) of methyl acrylate was added, and the mixture was heated at 80° C for 2 1/2 hr. Then it was acidified with acetic acid to pH 5, poured into 20 ml of water, and extracted with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution and with water and were dried over sodium sulfate. The ether was driven off and the substance was distilled. This gave 5.03 g (36.5%) of IV with bp 118–121° C (0.037 mm). R_f 0.86 (system 1). In aqueous ethanolic solution, the substance gave a negative reaction for an enol grouping with ferric chloride.

3-Ethoxycarbonyl-3-methoxycarbonylethyl-2,4,4-trimethyl-1-pyrroline (V). Under the conditions described for the pyrroline III, 5 g of IV was hydrogenated in 50 ml of anhydrous methanol in the presence of 8 g of Raney nickel catalyst. Yield 0.68 g (16%). Bp 58°–60° C (0.03 mm); n_D^{20} 1.4782. Found, %: C 61.32; 61.48; H 8.88; 9.08; N 4.99; 5.25%. Calculated for $C_{14}H_{23}NO_4 \cdot 1/4\ H_2O$, %: C 61.40; H 8.56; N 5.12%.

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