SYNTHESES OF DI- AND TETRAHYDROPYRROLES

III. Reaction of Methyl α-Methoxycarbonyl-β, β-dimethyl-γ-nitrobutyrate with Methyl Acrylate Under the Conditions of the Michael Reaction*

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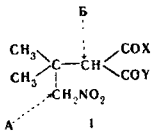
Methyl α-methoxycarbonyl-β, β-dimethyl-γ-nitrobutyrate adds to methyl acrylate by the Michael's reaction at its γ-carbon atom, in contrast to ethyl α-acetyl-β, β-dimethyl-γ-nitrobutyrate which, in the analogous reaction, adds at the α-carbon atom. The structure of the compounds obtained has been established on the basis of their NMR spectra.

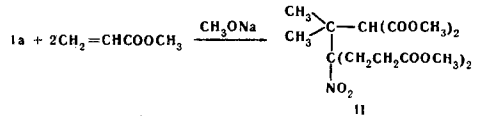
In preceding investigations we have studied the synthesis of Δ^1-pyrrolines, which are structurally similar to individual fragments—rings B and C—of the corrin system of vitamin B_{12} [1-2]. Recently, it has been established that 2-pyrrolidones can be used as the starting materials in the synthesis of corrins [3]. In the present work, studying the possibility of synthesizing 2-pyrrolidones containing the substituents corresponding to ring C of the corrin system of vitamin B_{12} [4] we have investigated the direction of addition of methyl α-methoxycarbonyl-β, β-dimethyl-γ-nitrobutyrate (**Ia**) to methyl acrylate under the conditions of the Michael's reaction. In this case, the attack of acrylic acid esters can take place at the two reaction centers of the compounds of type I that are shown by arrows.



I

a **X=Y=OCH$_3$**
b **X=Y=OC$_2$H$_5$**
c **X=CH$_3$, Y=OC$_2$H$_5$**

We have established that the nitro ester **Ia** adds to methyl acrylate by its γ-carbon atom. The initial γ-nitro ester **Ia** was synthesized by condensing equimolar amounts of 2-methyl-1-nitropropene, diethyl malonate, and sodium methoxide (the reaction takes place with the simultaneous transesterification of the ester groups). In the condensation of equimolar amounts of Ia with methyl acrylate in the presence of a catalytic amount of sodium methoxide, we obtained methyl α-methoxycarbonyl-γ-methoxycarbonylethyl-β, β-dimethyl-γ-nitropimelic acid (II) (i.e., under these conditions two methoxycarbonylethyl groups enter the γ-position).



II

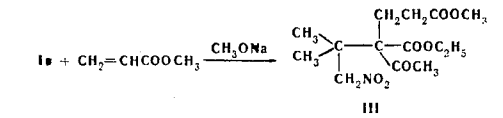
The condensation of ethyl α-ethoxycarbonyl-β, β-dimethyl-γ-nitrobutyrate (**Ib**) with methyl acrylate in the presence of a catalytic amount of sodium ethoxide took place similarly.

The structure of II was shown unambiguously by its NMR spectrum. As model structure, we took the NMR spectrum of **Ia**. It follows from a comparison of the spectra of **Ia** and II (see figure) that the resonance signal from the methyl group at 3.45 ppm in Ia is also present in II, where it is at 3.3 ppm. The singlet from the protons of the CH_2NO_2 group are displaced by screening to a weaker field—4.6 ppm. This signal is present in **Ia** and practically absent in II (the very weak signal at 4.6 ppm in II shows the presence of a small amount of a compound having $-CH_2NO_2$ or $>CHNO_2$ group).

A resonance signal from the protons of the $(CH_3)_2C<$ at 1.1 ppm is seen in compound **Ia**, and in compound II there are two singlet signals from these protons (probably because of the hindrance of the free rotation of one of the methyl groups in the β-position owing to the steric hindrance created by the two methoxycarbonylethyl groups in the γ-position in the molecule of (II). The signals from the $COOCH_3$ groups are in the 3.6-3.7 ppm region. The complex spin-spin interaction of the $>C-CH_2-CH_2-$ group (in II) belongs to an A_2B_2 system and appears in the 2.2 ppm region.

When ethyl α-ethoxycarbonyl-β-methyl-γ-nitrobutyrate is condensed with ethyl acrylate in the presence of Triton B, according to Leonard and Felley [5], the addition of one molecule of ethyl acrylate takes place, just as in our case, to the γ-carbon atom.

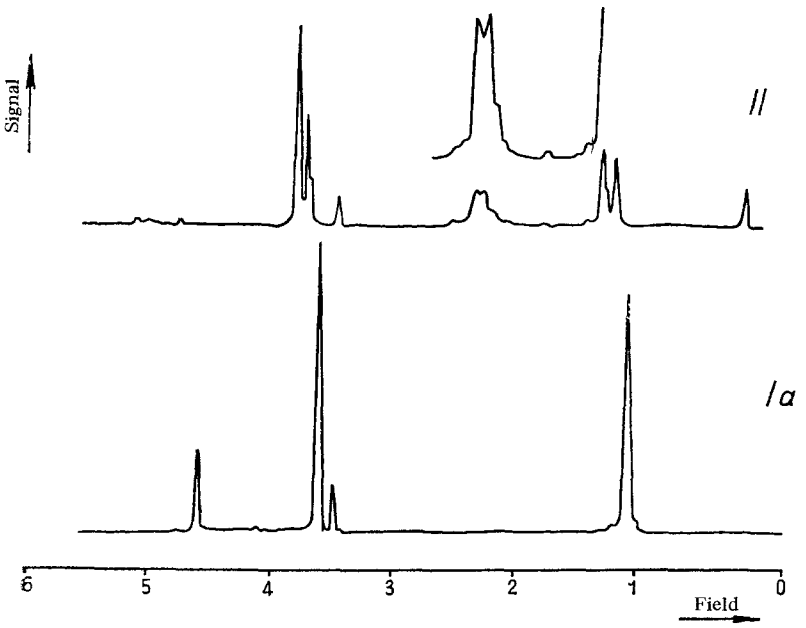
We have previously [1] shown that ethyl α-acetyl-β, β-dimethyl-γ-nitrobutyrate (**Ic**) adds to methyl acrylate in the presence of sodium methoxide by the α-carbon atom:



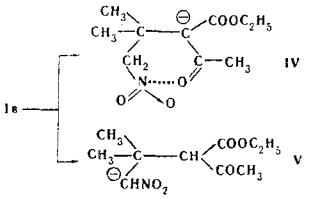
III

The change in the direction of addition to methyl acrylate of compounds of type I in dependence on their structure can be explained in the following way. The direction of the Michael's reaction in this case will be determined by what carbanion is formed from I under the action of the base. In the case of Ic the formation of two carbanions IV and V under the action of an alkaline catalyst is possible:

*For part II, see [1].



NMR spectra of compounds **Ia** and III.



as could be judged from the dissociation constants of the unsaturated pseudoacids, i.e. acetoacetic ester and nitromethane, respectively (see, for example, [6, 7]). On comparing these constants (pK_a 10.68 and 10.21, respectively [8, 9]), it would be possible to assume that the formation of the carbanions IV and V is approximately equiprobable. However, in this case, apparently, additional stabilization of the carbanion of the acetoacetic type IV is possible through interaction of the donor-acceptor type between the dipole of the nitro group and the negatively charged oxygen [10, 11]. Such interaction can raise considerably the dissociation constant of the acetoacetic part of the molecule and, consequently, favor the formation of the carbanion IV.

In the cases of **Ia** and **b**, because of the lower electron-accepting properties of the ethoxycarbonyl group the dissociation constants of the malonic ester and the nitromethane (pK_a 13.3 and 10.21, respectively) already differ strongly and (even though the donor-acceptor interaction mentioned exists in this case) a carbanion of the nitromethane type is formed. Consequently, the attack of methyl acrylate on **Ia** is directed by route **A**, which is also favored by the lower degree of steric screening of this carbanion center.

EXPERIMENTAL

The NMR spectra were taken on a "Hitachi H 60" instrument in CCl_4 solution with HMDS (hexamethyldisiloxane) as internal standard.

Methyl α-methoxycarbonyl-β, β-dimethyl-γ-nitrobutyrate (Ia). To a solution of sodium methoxide (obtained from 4.05 g of sodium and 87 ml of methanol 27 g (0.175 mole) of malonic ester in 53 ml of anhydrous methanol were added followed by 17.69 g (0.175 mole) of 2-methyl-1-nitro-1-propene in 52 ml of anhydrous methanol, and the mixture was left to stand at room temperature for a day. Then it was acidified with acetic acid to pH 5. the precipitate was filtered off, and the methanol was distilled off in vacuum. The residue was treated with water and extracted with ether, and the combined ethereal extracts were washed with sodium bicarbonate solution and with water and were dried with $MgSO_4$. The ether was evaported off and the residue was distilled in vacuum. Yield 28.5 g (70%). Bp 119°-121°C (2.5 mm); d_4^{20} 1.1980; n_D^{20} 1.4564. Found, %: C 46.89, 47.15; H 6.56, 6.76; N 6.15, 5.99; MR_D 52.99. Calculated for $C_9H_{15}NO_6$, %: C 46.38; H 6.84; N 6.00; MR_D 52.68.

The alkaline hydrolysis (20% aqueous KOH, 4 hr) of **Ia** gave an 80% yield of α-carboxy-β, β-dimethyl-γ-nitrobutyric acid (I, X = = Y = OH). Mp 160°-161°C (benzene–chloroform). Found, %: C 40.76, 40.82; H 5.39, 5.62; N 6.53, 6.44. Calculated for $C_7H_{11}NO_2$, %: C 40.98; H 5.40; N 6.83.

Dimethyl α-methoxycarbonyl-γ-methoxycarbonylethyl-β, β-dimethyl-γ-nitropimelate (II). A solution of sodium methoxide (prepared from 0.16 g of sodium and 0.5 ml of methanol) and 4.3 g (0.05 mole) of methyl acrylate was added to 13.7 g (0.05 mole) of Ia, and the mixture was allowed to stand at room temperature for 12 hr. After the reaction mixture had been washed with water, the further treatment was analogous to that described above.. Yield 7 g (63%). Bp 135°-137°C (0.06 mm); d_4^{20} 1.2100; n_D^{20} 1.4624. Found, %: C 50.04, 50.17; H 6.60, 6.86; N 3.40, 3.64; MR_D 92.17 : Calculated for $C_{17}H_{27}NO_{10}$ %. C 50.36; H 6.72; N 3.84; MR_D 92.84.

Diethyl α-ethoxycarbonyl-γ-methoxycarbonylethyl-β, β-dimethyl-γ-nitropimelate. A solution of 0.003 mole of sodium ethoxide (prepared from 0.07 g of sodium and 20 ml of ethanol) and 2.68 g (0.031 mole) of methyl acrylate was added to 8.12 g (0.031 mole) of **Ib**. The reaction mixture was boiled for 6 hr, left to stand at 20°-22°C for 30 days, and treated as described above. Yield 4.01 g (29%). Bp 123°-124°C (0.015 mm); d_4^{20} 1.1410; n_D^{20} 1.4560. Found, %: C 53.91, 53.97; H 6.96, 7.30; N 2.83, 3.06; MR_D 106.55. Calculated for $C_{20}H_{33}NO_{10}$, %: C 53.68; H 7.43; N 3.13; MR_D 106.50.

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