SYNTHESIS AND SOME CHEMICAL TRANSFORMATIONS OF NITRO- AND NITRAZA-DICARBOXYLIC ACIDS

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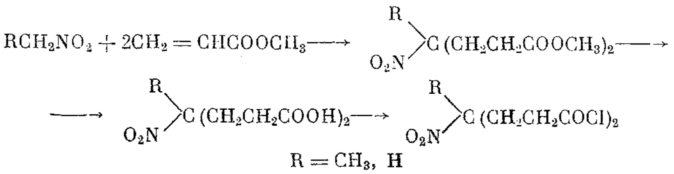
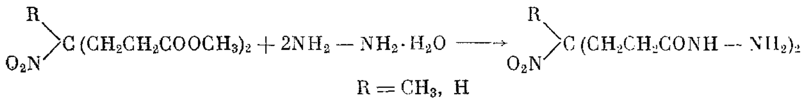
While studying the chemical transformations of nitrodicarboxylic acids [1], we synthesized the γ-nitro- and γ-nitro-γ-methylpimelic acids from nitromethane (or nitroethane) and methyl acrylate, followed by saponification of the obtained esters to the corresponding acids.



$$RCH_2NO_2 + 2CH_2{=}CHCOOCH_3 \longrightarrow (R)(O_2N)C(CH_2CH_2COOCH_3)_2 \longrightarrow (R)(O_2N)C(CH_2CH_2COOH)_2 \longrightarrow (R)(O_2N)C(CH_2CH_2COCl)_2$$

$$R = CH_3,\ H$$

From the literature, it is known [2, 3] that the dihydrazide of pimelic acid possesses antitubercular activity. The hydrazides of the substituted pimelic acid derivatives could have an analogous effect. We prepared the dihydrazides of the γ-nitro- and γ-nitro-γ-methylpimelic acids.



$$(R)(O_2N)C(CH_2CH_2COOCH_3)_2 + 2NH_2-NH_2\cdot H_2O \longrightarrow (R)(O_2N)C(CH_2CH_2CONH-NH_2)_2$$

$$R = CH_3,\ H$$

The obtained γ-nitropimelic acids, representing while crystalline compounds, react with thionyl chloride to yield the corresponding dichlorides.

The thermal stability of the nitropimelic acids and 3-nitraza-1,5-pentanedicarboxylic acid was determined. It was found that introducing a nitro group in the γ-position of pimelic acid lowers the thermal stability of the acids. This is especially noticeable when one nitro group is introduced, which can probably be explained by the presence of active hydrogen at the carbon atom bearing the nitro group. It is known that the strength of acids depends to a large degree on the substituents, and this can be clearly seen when the dissociation constants of the chloro-substituted acetic acids are compared [4].

In this paper, we studied the effect of another electronegative substituent – the nitro group – on the strength of acids. As study subjects we took the nitropimelic acids, the dissociation constants of which were compared with those for pimelic acid. The dissociation constants of these acids were determined by the potentiometric titration method using an LP-58 pH-meter equipped with calomel and glass electrodes. The concentration of the taken pimelic acids was 0.01 M, with neutralization to the extent of $^3/_4$ using 0.1 N KOH solution. The dissociation constants were calculated using the Albert–Serjeant method [4]. The results of the measurements are given in Table 1.

An examination of the dissociation constants of the pimelic acids investigated by us (see Table 1) reveals that introducing a nitro group into the acid molecule increases the strength considerably. An even greater increase in the dissociation constants is observed when two nitro groups are introduced in the γ-position of pimelic acid. This change in the dissociation constants is apparently explained mainly by the decrease in the electron density at the α-carbon atoms due to the induction effect. Replacing one nitro

TABLE 1

Formula	Dissociation constants		Temperaature, °C
	$K_I \cdot 10^{-5}$	$K_{II} \cdot 10^{-5}$	
$CH_2(CH_2CH_2COOH)_2$	3.49	0.26	25
$O_2NCH(CH_2CH_2COOH)_2$	10.0	0.575	21
$O_2NC(CH_3)(CH_2CH_2COOH)_2$......	12.6	0.347	21
$(O_2N)_2C(CH_2CH_2COOH)_2$........	30.2	1.09	21
$O_2N{-}N(CH_2CH_2COOH)_2$	16.6	0.955	21

group in γ,γ-dinitropimelic acid by the electropositive methyl group leads to a decrease in the induction effect (due to the difference in the induction effects of the methyl and nitro groups). Replacing the γ-methylene group in pimelic acid by the nitraza grouping ($N{-}NO_2$) leads to an increase in the strength of the acid. Thus, 3-nitraza-1,5-pentanedicarboxylic acid in its strength approaches that of γ,γ-dinitropimelic acid. As a result, in their strength all of the pimelic acids can be arranged in the following order of increasing strength: pimelic < γ-nitro-γ-methylpimelic<γ-nitropimelic<3-nitraza-1,5-pentanedicarboxylic<γ,γ-dinitropimelic.

EXPERIMENTAL

Dimethyl Ester of γ-Nitropimelic Acid (I). Into a four-necked flask, fitted with a mechanical stirrer, thermometer and a dropping funnel, were charged 61 g of nitromethane and freshly prepared Rodionov catalyst in an amount of 1-8% (for the preparation we took 8 g of the salt and 0.62 g of metallic Na in ethanol). With good stirring, 86 g of methyl acrylate was added gradually at 35-40°. After adding all of the methyl acrylate the mixture was stirred for another 5 h at 25-30°. Then the reaction mixture was acidified with dilute hydrochloride acid, and the obtained oil was separated, while the aqueous layer was extracted with dichloroethane. The extracts were combined with the oil, and the whole was washed with water and then dried over fused magnesium sulfate. The dichloroethane was distilled using the vacuum of a water-jet pump, while the residue was vacuum-distilled using an oil pump. We obtained 49 g (42%) of (I) as a pale yellow-green oil with b.p. 155-160° (1 mm). Literature data [5]: b.p. 160-170° (1mm); n_D^{21} 1.453. Found %: C 46.57, 46.62; H 6.60, 6.77. $C_9H_{15}O_6N$. Calculated %: C 46.35; H 6.48.

In a similar manner from 86 g of methyl acrylate and 37.5 g of nitroethane we obtained 89 g of the dimethyl ester of γ-nitro-γ-methylpimelic acid (II) as a nearly colorless oil with b.p. 143-145° (0.5 mm); n_D^{19} 1.4619. Literature data [5]: b.p. 153-155° (1 mm); n_D^{25} 1.4589. Found %: C 49.26, 49.51; H 7.09, 7.04. $C_{10}H_{17}O_6N$. Calculated %: C 48.58; H 6.93.

γ-Nitropimelic Acid (III). A mixture of 10.3 g of (I) and 100 ml of 18% hydrochloric acid solution was heated under reflux on the steam bath until all of the precipitate had dissolved, after which it was evaporated to dryness using the vacuum of a water-jet pump. The residue weighed 9.38 g. Recrystallization from dichloroethane gave acid (III) as white crystals with m.p. 83-84°. Found %: C 40.67, 40.74; H 5.21, 5.14; N 6.87, 7.13. $C_7H_{11}O_6N$. Calculated %: C 40.98; H 5.40; N 6.83.

In a similar manner from 23.7 g of (II) by treatment with 200 ml of 18% hydrochloric acid solution we obtained 20.1 g (95.5%) of γ-nitro-γ-methylpimelic acid (IV) with m.p. 114° (from water). Found %: C 43.94, 44.13; H 6.27, 6.08; N 6.61, 6.68. $C_8H_{13}O_6N$. Calculated %: C 43.83; H 5.48; N 6.39.

γ-Nitropimeloyl Chloride (V). A mixture of 10 g of (III) and 25 ml of thionyl chloride was heated on the steam bath. When the evolution of hydrogen chloride had ceased (2.5 h) the excess thionyl chloride was distilled off. The residual pale yellow oil weighed 11.4 g (85.5%) and after recrystallization from dry CCl_4 it gave white crystals of (V) with m.p. 15°. Found %: C 34.94, 35.11; H 4.04, 3.97. $C_7H_9O_4NCl_2$. Calculated %: C 34.66; H 3.75.

In a similar manner from 15.5 g of (IV) we obtained 16.3 g (89.9%) of γ-nitro-γ-methylpimeloyl chloride (VI), which after recrystallization from dry CCl_4 was obtained as crystals with m.p. 41°.

γ-Nitropimelic Acid Hydrazide (VII). A mixture of 6.33 g of (I) and 3.15 g of hydrazine hydrate was heated on the steam bath until the layers became miscible (1 h), and then for another hour. The hot solution was poured on a watch glass, and the oil crystallized on cooling. We obtained 4.0 g (63.2%) of (VII) with m.p. 151-152° (after recrystallization from ethanol). Found %: C 36.80, 36.64; H 6.57, 6.61; N 29.20, 29.40. $C_7H_{15}O_4N$. Calculated %: C 36.04; H 6.48; N 30.04.

γ-Nitro-γ-methylpimelic Acid Hydrazide (VIII). A mixture of 2.47 g of (II) and 1.25 g of hydrazine hydrate was heated on the steam bath for 3 h, and then allowed to stand overnight. The reaction mixture crystallized when rubbed with a rod. We obtained 1.18 g (47.8%) of (VIII) with m.p. 121 to 123°. Found %: N 28.16, 28.14. $C_8H_{17}O_4N$. Calculated %: N 28.32.

CONCLUSIONS

1. The γ-nitro- and γ-nitro-γ-methylpimelic acids and some of their derivatives were synthesized.

2. The dissociation constants of the nitro acids were determined by potentiometric titration. The introduction of either one or two nitro groups in the γ-position of pimelic acid increases the strength of the acids.

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