β-AMINO DERIVATIVES OF α-NITROALKYL ESTERS

COMMUNICATION 1. PRODUCTION AND HYDROLYTIC DECOMPOSITION

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This work is a continuation of investigations devoted to a study of the possibility of using nitroacetic ester as the starting material for the synthesis of amino acids. We established [1, 2] that the reaction of nitroacetic ester with the ester of orthoformic acid proceeds through an intermediate step of formation of acetals of formylnitroacetic ester and is reversible at all stages

$$O_2N{-}CH_2COOCH_3 + (RO)_3CH \rightleftarrows (RO)_2CH{-}\underset{\underset{NO_2}{|}}{CH}{-}COOCH_3 + ROH \rightleftarrows RO{-}CH{=}\underset{\underset{NO_2}{|}}{C}{-}COOCH_3 + 2ROH \quad (R{=}CH_3,\ C_2H_5)$$

When a mixture of the esters of nitroacetic and orthoformic acids is heated at 80°, only acetals are formed. Conducting this reaction by distilling off the alcohol or in the presence of acetic anhydride leads to a shift of the reaction equilibrium to the right. The esters of α-nitro-β-alkoxyacrylic acids formed are extremely reactive; they react smoothly with indole [1], ammonia, and hydrazine [3]. The latter reaction is common to primary and secondary amines, both aliphatic and aromatic (methylamine, dimethylamine, morpholine, piperidine, aniline, p-toluidine, p-chloroaniline, p-nitroaniline, p-aminophenol, N-ethyl aniline, α-naphthylamine)

$$R{-}\underset{\underset{R'}{|}}{NH} + AlkO{-}CH{=}\underset{\underset{NO_2}{|}}{C}{-}COOCH_3 \rightarrow R{-}\underset{\underset{R'}{|}}{N}{-}CH{=}\underset{\underset{NO_2}{|}}{C}{-}COOCH_3 + AlkOH$$

Esters of β-amino derivatives of α-nitroacrylic acid are also formed when acetals of formylnitroacetaldehyde are heated with the corresponding amines (morpholine, aniline)

$$R{-}\underset{\underset{R'}{|}}{NH} + (C_2H_5O)_2CH{-}\underset{\underset{NO_2}{|}}{CH}{-}COOCH_3 \rightarrow R{-}\underset{\underset{R'}{|}}{N}{-}CH{=}\underset{\underset{NO_2}{|}}{C}{-}COOCH_3 + 2C_2H_5OH$$

In the case of weakly basic aromatic amines, on the other hand, as well as urea and its derivatives [4], the corresponding α-nitro-β-aminoacrylic esters are formed directly from nitroacetic ester, the amine, and ester of orthoformic acid

$$C_6H_5NH_2 + O_2N{-}CH_2COOCH_3 + (C_2H_5O)_3CH \rightarrow C_6H_5{-}NH{-}CH{=}\underset{\underset{NO_2}{|}}{C}{-}COOCH_3 + 3C_2H_5OH$$

The replacement of weakly basic amines by morpholine (pK_b 5.6) leads to the formation of a morpholinium salt of nitroacetic ester, which does not react further with orthoformic ester.

All the α-nitro-β-aminoacrylic esters obtained (Table 1) are crystalline substances. Their solubility increases with increasing dielectric constant of the organic solvent. The solubility of compounds entirely substituted at the amino group is substantially greater. The chemical properties of β-amino derivatives of α-nitroacrylic esters are close to the properties of β-aminonitroalkenes. Thus, they are incapable of alkylation; derivatives of primary amines are not acylated [5]. As for the ester of α-nitro-β-aminoacrylic acid, acylation proceeds under the action of acetic anhydride in the presence of an anhydrous sodium

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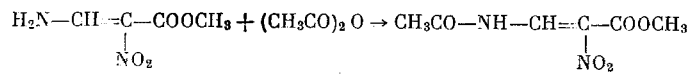
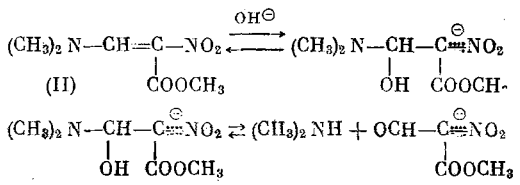
acetate



Under the action of aqueous bases, α-nitro-β-aminoacrylic esters, just like β-aminonitroalkenes [6], are cleaved at the C – N amino bond. Thus, the methyl ester of α-nitro-β-dimethylaminoacrylic acid (II) decomposes quantitatively to dimethylamine (isolated in the form of its benzenesulfonyl derivative) and the potassium salt of formylnitroacetic ester under the action of an aqueous solution of potassium hydroxide. The following scheme of hydrolytic decomposition can be proposed. The first step in this process is addition of the hydroxyl ion to α-nitro-β-dimethylaminoacrylic ester. The second step is decomposition of the anion of the nitroalcohol formed



The reaction is reversible. In the reaction of aniline hydrochloride with the potassium salt of formylnitroacetic ester, the methyl ester of α-nitro-β-anilinoacrylic acid (V) is formed in 84% yield

The tautomeric equilibrium (imine – enamine) is entirely shifted in the direction of the enamine, which is evident from the IR spectrum of this compound. The same enamine is also obtained under the action of anhydrous HCl on the potassium salt $[C_6H_5NCHC(NO_2)COOCH_3]K$, produced from (V) under the action of potassium methylate.

In contrast to α-nitro-β-dimethylaminoacrylic ester, the hydrolytic decomposition of its methylamine and aniline analogs does not proceed so smoothly. The yield of the potassium salt of formylnitroacetic ester from α-nitro-β-methylaminoacrylic ester (I) does not exceed 58%. Under the action of an aqueous solution of KOH on the methyl ester of α-nitro-β-anilinoacrylic acid, on the other hand, the yield of aniline (in the form of the benzenesulfanilide) is only 50%. This difference in the properties of β-amino derivatives of α-nitroacrylic esters may be associated with the degree of substitution of the hydrogens of the amino group, and it is most clearly manifested in the stability of these compounds during storage.

All the compounds with an entirely substituted amino group decompose during storage, being converted to a colored liquid. On the contrary, compounds containing at least one hydrogen in the amino group can be stored unchanged for several years.

EXPERIMENTAL

Production of Methyl Esters of α-Nitro-β-methylamino- (I) and α-Nitro-β-dimethylaminoacrylic (II) Acids. A 5 g portion of the methyl ester of α-nitro-β-ethoxyacrylic acid [1] was saturated for 40 min with a stream of gaseous CH_3NH_2 while cooling with ice water. The reaction mass soon crystallized. The crystals were washed on the filter with benzene. Yield of (I) 3.2 g (70% of the theoretical), mp 126-126.5° (from benzene).

The reaction with dimethylamine also proceeds analogously. When gaseous dimethylamine was passed into a flask with 5 g of the methyl ester of α-nitro-β-ethoxyacrylic acid, the reaction mass crystallized. The yellow crystals were washed with a small amount of alcohol and crystallized from the same solvent. We obtained 2.47 g (50%) (II), mp 84.5-85.5°.

Reaction of the Methyl Ester of α-Nitro-β-ethoxyacrylic Acid with Other Amines. An equimolar amount of the amine was added drop-wise to the methyl ester of α-nitro-β-ethoxyacrylic acid. The reaction mass was cooled with ice water during the addition of the amine, maintaining a temperature of 25-30°. A crystalline precipitate of the corresponding β-substituted methyl ester of α-nitro-β-aminoacrylic acid was soon isolated. The results of the experiments are presented in Table 1.

Production of β-Aminoderivatives of α-Nitroacrylic Esters by Heating Acetals of Formylnitroacetic Ester with Amines. A mixture of 28.7 g of the diethyl acetal of formylnitroacetic ester [1] and 12.5 g of aniline was heated on a boiling water bath in a flask equipped with a mixer and condenser. At the end of the distillation of the alcohol (1 h) the mixture crystallized. The yield of the methyl ester of α-nitro-β-anilinoacrylic acid (V) was 20.1 g (70%), mp 114-114.5° (from methanol).

The reaction with morpholine proceeded analogously. From 3 g of the diethyl acetal of formylnitroacetic ester and 1 g morpholine we obtained 2.02 g (65.0%) of the methyl ester of α-nitro-β-morpholinoacrylic acid (IV), mp 136-137° (from $CHCl_3$).

Reaction of the Methyl Ester of Nitroacetic Acid and Ethyl Orthoformate with Amines. Heating a mixture of 10 g of the methyl ester of nitroacetic acid, 13.5 g ethyl orthoformate, and 7.8 g freshly redistilled aniline on a boiling water bath, distilling off the alcohol formed, yielded 15.7 g (84.5%) (V), mp 114.0-114.5°.

The addition of 7.4 g morpholine to a solution of 10 g of the methyl ester of nitroacetic acid in 13.5 g ethyl orthoformate yielded a crystalline precipitate of the morpholine salt of nitroacetic ester, yield 13.4 g (78%), mp 118-119° (from methanol). Found: C 40.49; H 6.63; N 13.8%. $C_7H_{13}O_5N_2$. Calculated: C 40.90; H 6.83; N 13.65%.

Acylation of the Methyl Ester of α-Nitro-β-aminoacrylic Acid. To a solution of 2.3 g of the methyl ester of α-nitro-β-aminoacrylic acid [3] in 25 ml of acetic anhydride we added 2.0 g anhydrous sodium acetate and heated the mixture for 1.5 h at 80°. After the excess acetic anhydride was distilled off, the residue was treated with 20 ml of ethyl acetate and filtered to remove the reacted amino compound. The solution was evaporated to dryness and the crystals recrystallized from isopropanol. We obtained 1.22 g of the methyl ester of α-nitro-β-acetaminoacrylic acid, mp 54-55°. Found: N 14.96; 15.08%. $C_6H_8O_5N_2$. Calculated: N 14.89%.

Hydrolytic Decomposition of the Methyl Ester of α-Nitro-β-dimethylaminoacrylic Acid. We added 0.65 g (II) in portions to 15 ml of a 10% solution of KOH. The yellow solution, smelling of dimethylamine, was shaken for 2 h on a mechanical shaker with 0.6 ml of benzenesulfonyl chloride. The heavy oil was extracted with ether, the extract dried over Na_2SO_4, and evaporated. We obtained 0.68 g (quantitative yield) of benzenesulfodimethylamide, mp 48-48.5°. According to the data of [7]: mp 47-48°.

The solution obtained under the action of 5 ml of a 10% solution of KOH on 1.74 g (II) was cooled on an ice bath, the white precipitate of the potassium salt of formylnitroacetic ester liberated was filtered off, and washed with cold methanol. Yield of the dry salt 1.7 g (92%) t. dec. 231-232°. The salt was purified by precipitation from aqueous solution with methanol. Found: K 21.54; 21.30%. $C_4H_4NO_5K$. Calculated: K 21.13%. IR spectrum (suspension in liquid petrolatum) (ν, cm^{-1}): 1695 (COOR), 1625 (CHO).

Reaction of the Potassium Salt of Formylnitroacetic Ester with Aniline. A suspension of 1.11 g of the potassium salt of formylnitroacetic ester and 1.3 g aniline hydrochloride in 15 ml dioxane was heated to 70° and diluted with 5 ml of water. The yellow solution obtained was evaporated on a rotary evaporator to dryness, the crystalline precipitate mixed with 30 ml of water and filtered. We obtained 1.12 g (84%) of the methyl ester of α-nitro-β-anilinoacrylic acid, mp 114-114.5° (from methanol). A mixed sample of this compound with the methyl ester of α-nitro-β-anilinoacrylic acid (VI), produced above, gave no depression of the melting point.

Hydrolytic Decomposition of the Methyl Ester of α-Nitro-β-methylaminoacrylic Acid. We added 1 g (I) in portions to 5 ml of a 10% solution of KOH. After 10-15 min, a white precipitate began to separate from the solution, and liberation of methylamine was observed. The mixture was diluted with 10 ml of methanol, and the precipitate of the potassium salt of formylnitroacetic ester filtered off. An additional amount of the salt was obtained from the filtrate by evaporation. The total amount of the salt was obtained from the filtrate by evaporation. The total yield of the potassium salt of formylnitroacetic ester was 6.7 g (57.8%), t. dec. 230-232°. Found: K 21.54; 21.70%. $C_4H_4NO_5K$. Calculated: K 21.13%. IR spectrum (suspension in liquid petrolatum) (ν, cm^{-1}): 1695 (COOR), 1625 (CHO).

Hydrolytic Decomposition of the Methyl Ester of α-Nitro-β-anilinoacrylic Acid. The solution obtained by the action of 15 ml of 10% KOH on 0.83 g (V) was shaken for 2 h on a mechanical mixer with 0.9 ml of benzenesulfanilide, mp 110.5-111°. According to the data of [7]: mp 109°.

TABLE 1. Ester of Derivatives of α-Nitro-β-Aminoacrylic Acid R'RN – CH = $C(NO_2)COOCH_3$

Compound number	NRR'	Method of production*	Yield, %	Mp., °C	Empirical formula	Found, %			Calculated, %		
						C	H	N	C	H	N
I	CH_3NH	A	70,0	126—126,7	$C_5H_8NO_4$	37,49 37,34	4,99 4,82	17,51 17,50	37,50	5,04	17,50
II	$(CH_3)_2N$	A	50,0	84,5—85,5	$C_6H_{10}N_2O_4$	41,77 41,46	5,91 5,86	15,99 16,13	41,38	5,19	16,09
III		A	37,5	80—81	$C_9H_{14}N_3O_4$	50,36 50,08	6,57 6,58	13,26 13,25	50,02	6,96	13,05
IV		A B	73,0 65,0	136—137	$C_8H_{12}N_3O_5$	44,12 44,33	5,51 5,54	13,10 12,91	44,44	5,60	12,96
V		A B C	78,6 70,0 84,5	114—114,5	$C_{10}H_{10}N_2O_4$	54,22 54,04	4,45 4,59	12,57 12,61	54,02	4,54	12,61
VI		A	86,5	137—138	$C_{10}H_9N_2O_4$	46,71 46,72	3,62 3,47	11,22 11,10	46,71	3,54	10,91
VII		A	50,5	208—210	$C_{10}H_9N_3O_6$	45,00 45,24	3,37 3,44	15,33 15,56	44,95	3,40	15,73
VIII		A	75,5	96—96,5	$C_{11}H_{11}N_2O_4$	—	—	12,16 12,12	56,16	4,67	11,91
IX		A	75,5	203—204	$C_{10}H_{10}N_2O_5$	50,60 50,36	4,28 4,36	11,95 12,00	50,42	4,23	11,76
X		A	54,6	68,5—70	$C_{12}H_{15}N_2O_4$	57,20 57,09	5,42 5,50	10,94 10,83	57,59	5,64	11,20
XI	α-Naphthylamino-	A	77,8	156—157	$C_{14}H_{22}N_2O_4$	62,08 61,80	4,50 4,44	10,40 10,39	61,76	4,44	10,29

*A) By the reaction of amines with α-nitro-β-ethoxyacrylic ester. B) In the reaction of amines with the diethyl acetal of formylnitroacetic ester. C) By the reaction of aniline with esters of nitroacetic and orthoformic acids.

Action of Potassium Methylate on the Methyl Ester of α-Nitro-β-anilinoacrylic Acid. To a solution of 2.2 g (V) in 50 ml abs. methanol we added 6 ml of a solution of CH_3OK, produced from 0.08 g K. The precipitate of a yellow salt formed was filtered off and dried in air, yield 2.51 g (96.5%), t. dec. 257-258° (from methanol). Found: K 14.81; 15.04%. $C_{10}H_9O_4N_2K$. Calculated: K 15.02%.

The IR spectrum of this salt (suspension in liquid petrolatum) does not contain the bands of the valence vibrations ν_{NH} and of the nitro-group. The passage of anhydrous HCl into a suspension of the salt obtained in abs. ether yielded 0.31 g (73%) of the methyl ester of α-nitro-β-anilinoacrylic acid, mp 113.5-114.5° (from methanol). The IR spectrum of this compound (suspension in liquid petrolatum) was entirely identical with the spectrum of the initial acrylic ester (VI) (ν_{NH} 3260 cm^{-1}).

CONCLUSIONS

1. A general method of synthesizing β-amino derivatives of α-nitroacrylic esters by the interaction of amino compounds with esters of α-nitro-β-alkoxyacrylic acids or with acetals of formylnitroacetic ester was developed.

2. In the case of weakly basic amines, the corresponding esters of α-nitro-β-aminoacrylic acids are formed directly from nitroacetic ester, the amine, and orthoformic ester.

3. Hydrolytic decomposition of β-substituted α-nitro-β-aminoacrylic esters occurs at the $C-N_{amino}$ bond and depends on the degree of substitution of the hydrogens of the amino group.

LITERATURE CITED

1. K. K. Babievskii, V. M. Belikov, and N. A. Tikhonova, The Chemistry of Heterocyclic Compounds, Collection I. Nitrogen-Containing Heterocycles [in Russian], Zinatne (1967), p. 46.
2. N. A. Tikhonova, K. K. Babievskii, and V. M. Belikov, Izv. Akad. Nauk SSSR, Ser. Khim., 877 (1967).
3. M. Kamlet, J. Organ. Chem., 24, 714 (1959).

4. M. Prystas and J. Gut, Collect. Czechoslov. Chem. Commun., 28, 2501 (1963).
5. J. Freeman and W. Emmons, J. Amer. Chem. Soc., 78, 3405 (1956).
6. C. Hurd and L. Sherwood, J. Organ. Chem., 13, 471 (1948).
7. A. Ginzberg, Ber., 36, 2706 (1903).