2-AMINO-4,4-DISUBSTITUTED-5-CARBOXYMETHYL-Δ^2-1,3,4-OXADIAZOLIN-4-IUM CHLORIDES AND THEIR RECYCLIZATION IN ACETIC ANHYDRIDE

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2-Methylamino-4,4-disubstituted-5-carboethoxymethyl-Δ^2-1,3,4-oxadiazolin-4-ium chlorides were obtained from the reaction of 1,1-disubstituted-4-methylsemicarbazides with ethyl propiolate in the presence of hydrochloric acid. After hydrolysis of the ester these chlorides recyclize in acetic anhydride to 1-substituted-3-acetoxy-1H-pyrazoles. The difference in the direction of ring opening with acetic anhydride in the betaines of 1,3,4-oxadiazolin-5-acetic acids and their thia-analogs has been demonstrated.

Because of their low reactivity, the addition of substituted semicarbazides to acetylenemonocarboxylic acid and its esters has seldom been used for the synthesis of heterocyclic carboxylic acids. Since thiosemicarbazides gave 2-amino-Δ^2-1,3,4-thiadiazolin-4-io-5-acetates in this reaction [1], an attempt was made to prepare their oxa-analogs.

We found that 1,1-disubstituted semicarbazides do not react with propiolic acid or ethyl propiolate even on prolonged (12 h) boiling of ethanolic solutions of the reagents. However when an ethanolic solution of 1,1-dimethyl-4-phenylsemicarbazide and ethyl propiolate was kept at 20°C for 60 days *cis*-addition of two molecules of ethyl propiolate occurred at atoms $N_{(2)}$ and $N_{(4)}$ of the semicarbazide.

Propiolic acid is not sufficiently strong for induced addition of $N_{(1)}$ protonated semicarbazides at the triple bond. It is therefore necessary to add hydrochloric acid to an ethanolic solution of the semicarbazides IIIa,b and ethyl propiolate. The 2-methyl-4,4-disubstituted-5-carboethoxymethyl-Δ^2-1,3,4-oxadiazolin-4-ium chlorides IVa,b, which differ little in their physico-chemical properties from their thia-analogs [1], were successfully obtained in this way.

The esters IVa,b were hydrolyzed to the corresponding acids Va,b in acid media.

The thia-analogs of compounds IVa,b recyclize in the betaine form to 1,3-thiazinones [2] with acetic anhydride. When acids Va,b were heated with acetic anhydride, the products obtained differed in their physico-chemical properties from the expected 1,3-oxazinones. Elemental analysis coupled with ^{1}H NMR spectroscopy showed that the pyrazoles VIIa,b were formed. The previously described 1-methyl-3-hydroxy-1-pyrazole VIII [3] was obtained by hydrolysis of the acetyl derivative VIIa. Since the oxadiazolines Va,b recyclized as the chlorides rather than the betaines it may be assumed that the oxazole ring opened at the $O-C_{(5)}$ bond and not at the $N_{(4)}-C_{(5)}$ bond which is characteristic of the thiadiazolines. The chlorides Va,b were treated with aqueous ammonia to prepare the betaines. The solutions were evaporated in vacuum at 30°C to avoid the possibility of decomposing the betaine structure. The products were dried in vacuum and immediately treated with acetic anhydride. Pyrazoles VIIa and XI were obtained after heating the reaction mixture for 4 h. Thus cleavage of the $O-C_{(5)}$ is characteristic for both the oxadiazolines IVa,b and Va,b. (See scheme on following page.)

Since the oxadiazoline ring is retained when chlorides Va,b are treated with aqueous ammonia, the betaine VIa was isolated and its ^{1}H NMR spectrum was obtained. It appears that compound VIa exists in the aminimide zwitterionic form rather than as the amino acid betaine [1]. In the ^{1}H NMR spectrum of compound VIa, the protons of the exocyclic N-methyl group appear as a singlet at 2.72 ppm, while the carboxyl proton is observed as a broad singlet at 11.7 ppm. There is a characteristic

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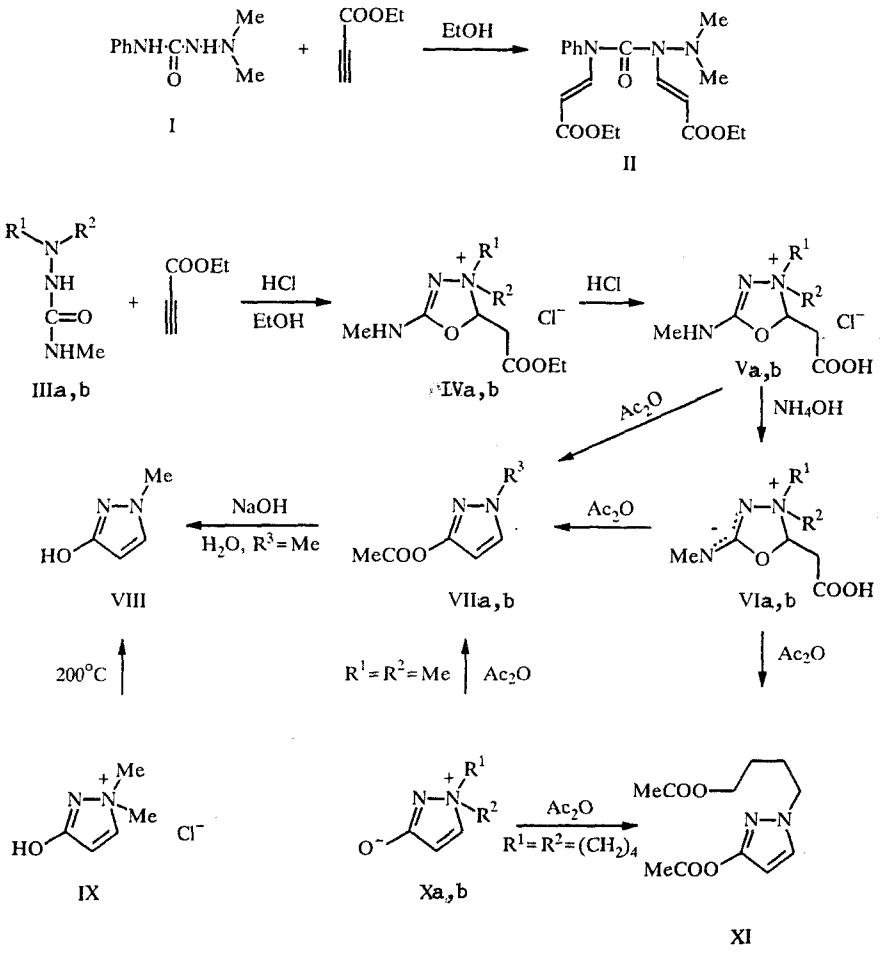

III—VI, Xa, b a $R^1 = R^2 = Me$, b $R^1, R^2 = (CH_2)_4$; VIIa, b a $R^3 = Me$, b $R^3 = (CH_2)_4Cl$

0.4 ppm decrease in the chemical shifts of the CH_X proton in the betaines in contrast to the chlorides IVa,b and Va. Analogous behavior was observed for the thia–analogs [1].

In view of this it may be proposed that the existence of the oxadiazolines of type VI in the aminimide form is the reason for the different route of ring opening in comparison with the thia–analogs.

The observed N–dealkylation of the oxadiazolines Va,b and VIa,b in acetic anhydride has been described previously [3,4]. This dealkylation of Va,b recalls the well studied pyrolysis of the pyrazoles IX and X [5,6]. For example, the analog of pyrazole VIIb, 1–(5–chloropentyl)–3–hydroxy–1H–pyrazole, was obtained from the pyrolysis of compounds of type X (R^1,R^2 = $(CH_2)_5$) [6].

By using acetic anhydride as both solvent and reagent we found a direct synthesis of the pyrazoles VIIa and XI from pyrazolium betaines Xa,b.

We note that cleavage of the $CH_3NH–C–O$ fragment during the conversion of Va,b and VIa,b into the pyrazoles VIIa,b and XI with acetic anhydride occurs analogously to the recyclization of 1,3,4–oxadiazolium salts in acetic anhydride [4].

EXPERIMENTAL

^1H NMR spectra were recorded with a Bruker WH 90/DC (90 MHz) instrument in DMSO–d_6 or $CDCl_3$ solutions with TMS as internal standard. The course of reactions and the purity of compounds was monitored by TLC on Silufol UV–254 strips with ethyl acetate or 8:6:1 chloroform–methanol–water as eluents. The semicarbazides starting materials were synthesized from the corresponding hydrazines and isocyanates by a known method [7].

Reaction of 1,1–dimethyl–4–phenylsemicarbazide with Ethyl Propiolate. Semicarbazide I (79 g, 10 mmol) was dissolved in ethanol (40 ml) and ethyl propiolate (1.0 g, 10 mmol) was added. The solution was kept for 60 d at 20°C, then

cooled to 0°C and the colorless crystals were filtered off and washed with cold isopropanol to give **1,1-dimethyl-2,4-di-(*trans*-carboethoxyvinyl)-4-phenylsemicarbazide (II, $C_{19}H_{25}N_3O_5$)** (0.9 g, 48% based on ethyl propiolate), m.p. 83-84°C. ^{1}H NMR spectrum ($CDCl_3$): 1.24 (6H, s, $2CH_3C$), 2.52 (6H, s, $N(CH_3)_2$, 4.12 and 4.14 (2H, q, CH_2O), 4.89 and 5.49 (1H, d, J = 14 Hz, =CHCO), 7.0-7.5 (5H, m, C_6H_5), 7.57 and 8.22 ppm (1H, d, J = 14 Hz, =CHN).

Reactions of the Semicarbazides IIIa,b with Ethyl Propiolate in the Presence of Hydrochloric Acid. 2-Methylamino-5-carboethoxymethyl-4,4-(1',4'-tetramethylene)-Δ^2-1,3,4-oxadiazolin-4-ium Chloride (IVb, $C_{11}H_{20}N_3O_3Cl$). Ethanol (50 ml) and conc. hydrochloric acid (2 ml) were added to semicarbazide IIIb (2.86 g, 20 mmol). After solution was complete ethyl propiolate (2.45 g, 25 mmol) was added and the mixture was boiled for 24 h. The reaction mixture was evaporated and the residue crystallized from acetonitrile to give the chloride IVb (4.2 g, 75%),m.p. 188-190°C. ^{1}H NMR spectrum (DMSO-d_6): 1.23 (3H, t, CH_3C), 1.9-2.3 (4H, m, CH_2CH_2), 2.67 (3H, d, $NHCH_3$), 3.26 (1H, dd, J = 9 and 16 Hz, CH_A), 3.72 (1H, dd, J = 3 and 16 Hz, CH_B), 3.35-4.05 (4H, br m, CH_2NCH_2), 4.18 (2H, q, CH_2O), 6.29 (1H, dd, J = 3 and 9 Hz, CH_X), 8.36 ppm (1H, br q, NH).

2-Methylamino-4,4-dimethyl-5-carboethoxymethyl-Δ^2-1,3,4-oxadiazolin-4-ium chloride (IVa, $C_9H_{18}N_3O_3Cl$) was obtained analogously from semicarbazide IIIa and ethyl propiolate after 10 h heating. M.p. 175°C (dec.). ^{1}H NMR spectrum (DMSO-D_6): 1.20 (3H, t, CH_3C), 2.62 (3H, d, $NHCH_3$), 3.18 and 3.44 (3H, s, $N(CH_3)_2$), 3.26 (1H, dd, J = 9 and 16 Hz, CH_A), 3.82 (1H, dd, J = 2.5 and 16 Hz, CH_B), 4.13 (2H, q, CH_2O), 5.98 (1H, dd, J = 2.5 and 9 Hz, CH_X), 8.40 (1H, q, NH).

Acid Hydrolysis of Esters IVa,b. 2-Methylamino-4,4-dimethyl-5-carboxymethyl-Δ^2-1,3,4-oxadiazolin-4-ium Chloride Hydrate (Va, $C_7H_{14}N_3O_3Cl\cdot H_2O$). Conc. hydrochloric acid (20 ml) was added to ester IVa (2.5 g, 10 mmol) and the mixture was boiled for 1 h, after which the solution was evaporated at low pressure. The residue was triturated with acetonitrile, filtered and dried in a vacuum dessicator to give acid Va (2.2 g, 90%), m.p. 203-204°C (dec.). ^{1}H NMR spectrum (DMSO-D_6): 2.64 (3H, d, CH_3NH), 3.15 (1H, dd, J = 9.5 and 16.5 Hz, CH_A), 3.20 and 3.46 (3H, s, $N(CH_3)_2$), 3.72 (1H, dd, J = 2.5 and 16.5 Hz, CH_B), 5.95 (1H, dd, J = 2.5 and 9.5 Hz, CH_X), 8.4 ppm (1H, q, NH).

Acid Vb, which was used after drying in reactions with acetic anhydride, was obtained analogously.

Recyclization of the Oxadiazoliniumacetic Acids Va,b. Acetic anhydride (20 ml) was added to acid Va (2.42 g, 10 mmol) and the mixture was boiled for 6 h. The anhydride was evaporated at low pressure, the residue was dissolved in ethyl acetate, boiled with activated charcoal, cooled and filtered through silica gel. The solvent was evaporated to give **1-methyl-3-acetoxy-1H-pyrazole (VIIa, $C_6H_8N_2O_2$)** (0.7 g, 50%) as a colorless oil. ^{1}H NMR spectrum ($CDCl_3$): 2.22 (3H, s, CH_3CO), 3.76 (3H, s, NCH_3), 6.05 and 7.27 ppm (1H, d, J = *2.35 Hz*, =*CHCO* and =CHN). The pyrazole (0.7 g, 5 mmol) was dissolved in sodium hydroxide solution (10 ml, 5%), the mixture was evaporated, the residue treated with acetonitrile, filtered, and the acetonitrile evaporated from the filtrate to give **1-methyl-3-hydroxy-1H-pyrazole (VIII)** (0,3 g, 61%) the physico-chemical characteristics of which agreed with literature data [5].

Pyrazole VIIa was also obtained from betaine Xa [5] by an analogous recyclization of acid Va in acetic anhydride (67% yield).

An analogous recyclization of oxadiazoline Vb gave **1-(4-chlorobutyl)-3-acetoxy-1H-pyrazole (VIIb, $C_9H_{13}N_2O_2Cl$)** as a colorless oil (83% yield). ^{1}H NMR spectrum ($CDCl_3$): 1.85 (4H, m CH_2CH_2), 2.24 (3H, s, CH_3CO), 3.51 (2H, t, CH_2Cl), 4.03 (2H, t, CH_2N), 6.07 (1H, d, J = 2.3 Hz, =CHCO), 7.26 ppm (1H, d, J = 2.3 Hz, =CHN).

Recyclization of the Betaines VIa,b. Acid Va (2.42 g, 10 mmol) was dissolved in 20 ml water and 25% aqueous ammonia was added dropwise with stirring to a pH of 8-9. Stirring was continued for 5 min, and then the mixture was evaporated at reduced pressure with a temperature no greater than 30°C. Alcohol (25 ml) was added, evaporation was repeated several times under the same conditions, and the residue was finally dried over P_2O_5 in a vacuum dessicator. ^{1}H NMR spectrum of betaine VIa (DMSO-D_6): 2.72 (3H, s, NCH_3, 3.05 (1H, dd, J = 7.5 and 16 Hz, CH_A), 3.43 and 3.55 (3H, s, $N(CH_3)_2$), 3.55 (1H, dd, J = 4 and 16 Hz, CH_B), 5.50 (1H, dd, J = 4 and 7.5 Hz, CH_X), 11.7 ppm (1H, br s, COOH). Acetic anhydride (25 ml) was added to the dried product and the mixture was boiled for 6 h. The acetic anhydride was distilled off at reduced pressure, the residue was dissolved in ethyl acetate, boiled with activated charcoal, cooled, and filtered through silica gel. The ethyl acetate was evaporated to give **1-methyl-3-acetoxy-1H-pyrazole (VIIa)** (0.5 g, 36%). The substance was identical to the product obtained from the recyclization of acid Va.

1-(4-Acetoxybutyl)-3-acetoxy-1H-pyrazole (XI, $C_{11}H_{16}N_2O_4$) (56%) was obtained analogously as a colorless oil from betaine VIb.^{1}H NMR spectrum ($CDCl_3$): 1.45-2.1 (4H, m, CH_2CH_2) , 2.06 (3H, s, CH_3COOCH_2), 2.25 (3H, s,

CH_3COOCN), 4.01 and 4.03 (2H, t, OCH_2 and NCH_2), 6.06 and 7.20 ppm (1H, d, J = 2.3 Hz, =CHCO and CHN).

1,1-(1′,4′-Tetramethylene)-1H-pyrazolio-1-oxide-3 (Xb, $C_7H_{10}N_2O$). N-Aminopyrrolidine (1.72 g, 20 mmol) was dissolved in a 1:1 methanol-water mixture (25 ml), cooled to 0°C and added dropwise at 0°C to a solution of ethyl propiolate (2 g, 20 mmol) 1:1 methanol-water (30 ml). The mixture was stirred at this temperature for 40 min and then at 20°C for an hour. The solvent was evaporated and the residue crystallized from acetonitrile on cooling to give betaine Xb (1.0 g, 37%), m.p. 185°C (dec). ^{1}H NMR spectrum (D_2O): 2.30 (4H, m, CH_2CH_2), 3.43 (2H, m, CH_2N), 3.78 (2H, m CH_2N), 6.39 and 7.68 ppm (1H, d, J = 3.5 Hz, =CHCO and =CHN).

Reaction of Betaine Xb with Acetic Anhydride. Acetic anhydride (15 ml) was added to betaine Xb (0.69 g, 5 mmol) and the mixture boiled for 4 h. Further treatment and isolation was as for the recyclization of Va,b. The physico-chemical characteristics of the product were identical to those of the product from betaine VIb.

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