PREPARATION OF 1-SUBSTITUTED HYDRAZINOACETIC ACIDS

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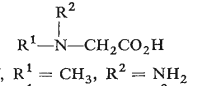
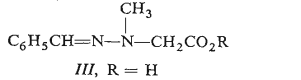
1-Methylhydrazinoacetic acid (*I*) and 1-benzylhydrazinoacetic acid (*II*) were prepared by reaction of sodium chloroacetate with the corresponding substituted hydrazine in the presence of sodium carbonate as well as by electrochemical reduction of N-nitrososarcosine (*V*) and N-nitroso-N-benzylglycine (*VI*).

In connection with syntheses of some heterocyclic systems, 1-methylhydrazinoacetic acid (*I*) and 1-benzylhydrazinoacetic acid (*II*) were required as the starting material. Only the preparation of the acid *I* has been mentioned in the literature[1]; the acid *I* has also been recently reported as the component of the antibiotic negamycin[2]. The preparative procedure[1] consists in reaction of methylhydrazine with chloroacetic acid, but a great excess of methylhydrazine must be used and the isolation of the acid *I* is rather time-consuming. The drawbacks of the earlier process have been now circumvented by the present modification. Hydrogen chloride set free by the reaction is in the modified procedure neutralised by the addition of sodium carbonate and the reaction time is shortened by the use of higher temperatures; the product is isolated in the form of sodium 2-benzylidene-1-methylhydrazinoacetate of good crystallisation properties. In this manner, the resulting product is separated not only from the starting compounds, but also from the isomeric 2-methylhydrazinoacetic acid. On acidification, the sodium salt is converted to the free 2-benzylidene-1-methylhydrazinoacetic acid (*III*) which is decomposed to benzaldehyde and the acid *I* by steam-distillation. The isolation of the product in this modified procedure is somewhat easier, but notwithstanding, the over-all yield is only 20%. A similar yield (16%) of the acid *I* is obtained when the isolation is effected with Dowex 50 (H^+) ion exchange resin. The synthesis of the acid *II* was performed with the use of benzyl-



I, $R^1 = CH_3$, $R^2 = NH_2$
II, $R^1 = C_6H_5CH_2$, $R^2 = NH_2$
V, $R^1 = CH_3$, $R^2 = NO$
VI, $R^1 = C_6H_5CH_2$, $R^2 = NO$



III, R = H
IV, $R = CH_3$

hydrazine[3] which is preferably obtained by acid-catalysed hydrolysis of 1-acetyl--2-benzylhydrazine[4]. Reaction of sodium chloroacetate with benzylhydrazine and isolation with the use of Dowex 50 (H^+) ion exchange resin afforded the acid *II* in 22% yield.

Owing to unsatisfactory yields of reactions between sodium chloroacetate and substituted hydrazines, the acids *I* and *II* were finally prepared by electrochemical reduction analogously to the preparation of 1,1-disubstituted hydrazines from the corresponding N-nitrosoamines[5,6]. Of the 1-substituted hydrazinoacetic acids, only 1-phenylhydrazinoacetic acid[6] has been hitherto prepared by this route. Electrochemical reduction of N-nitrososarcosine (*V*) on mercury electrode in the medium of 0·5M-HCl in 50% aqueous methanol afforded the acid *I* in 52% yield. The acid *II* was prepared in 64% yield by the electrochemical reduction of N-nitroso-N-benzylglycine[7] (*VI*).

As it may be seen from the above examples, the condensation of chloroacetic acid with substituted hydrazines proceeds in relatively low yields and the preparative application is limited by the accessibility of the starting substituted hydrazine. On the other hand in view of fair yields and ready accessibility of the starting N-substituted glycine derivatives, the electrochemical reduction may be regarded as a general method of preparing the 1-substituted hydrazinoacetic acids.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried for 8 h at 20°C/0·1 Torr unless stated otherwise. IR spectra were taken on a double-beam Zeiss (Jena) UR 10 spectrophotometer. Descending chromatography was performed on paper Whatman No 1 in solvent systems S_1, 1-butanol–acetic acid–water (50 : 25 : 25), and S_2, 2-propanol–concentrated aqueous-ammonia–water (7 : 1 : 2). Electrophoresis was performed on paper Whatman No 1 (40 V/cm, 1 h) in buffer solutions E_1, 0·05M-$Na_2B_4O_7$ (pH 9·2), and E_2, 1M-CH_3COOH. Spots were detected by spraying with 0·1% aqueous potassium permanganate.

2-Benzylidene-1-methylhydrazinoacetic Acid (*III*)

Methylhydrazine sulfate[8] (28·8 g; 0·2 mol) was added portionwise under stirring to a solution of sodium hydroxide (16·0 g; 0·4 mol) in water (36 ml) and the stirring continued until the solid dissolved. The solution was diluted with ethanol (150 ml) and kept at room temperature for one hour to deposit sodium sulfate which was filtered off and washed with ethanol (100 ml). The filtrate and washings were added to a mixture prepared from anhydrous sodium carbonate (21·19 g; 0·2 mol), water (350 ml), and chloroacetic acid (18·9 g; 0·2 mol), the whole refluxed for 3 h, evaporated under diminished pressure, and the residue codistilled with two 150 ml portions of water. The final residue was dissolved in water (30 ml), the solution treated with benzaldehyde (21·2 g; 0·2 mol), stirred for 1 h, kept overnight, the salt (13·9 g) collected with suction and washed with ether. Work-up of mother liquors afforded additional 8·25 g of the salt. Over-all yield, 22·15 g (47·7%) of sodium 2-benzylidene-1-methylhydrazineacetate, m.p. 207–208°C (ethyl acetate). For $C_{10}H_{11}N_2NaO_2.H_2O$ (232·2) calculated: 51·72% C, 5·64% H, 12·07% N; found: 52·48% C, 6·28% H, 11·90% N. A solution of the sodium salt (11·61 g; 50 mmol) in water (70 ml) was acidified with 5M-HCl under cooling, and the precipitate collected with suction. Yield, 7·0 g (72%) of the acid *III*, m.p. 62–65°C (benzene–light petroleum)). For $C_{10}H_{12}N_2O_2$ (192·2) calculated: 62·49% C, 6·29% H, 14·57% N; found: 61·59% C, 6·30% H, 14·53% N.

Methyl 2-Benzylidene-1-methylhydrazinoacetate (*IV*)

Esterification of the acid *III* (200 mg) with ethereal diazomethane afforded the ester *IV* as an oil, b.p. 120—130°C (bath temperature) at 0·08 Torr, n_D^{25} 1·5762. For $C_{11}H_{14}N_2O_2$ (206·2) calculated: 64·06% C, 6·84% H, 13·58% N; found: 64·58% C, 7·08% H, 13·67% N.

1-Methylhydrazinoacetic Acid (*I*)

A. A mixture of the acid *III* (1·92 g; 1 mmol) and water (60 ml) was steam-distilled to remove the benzaldehyde. The residual aqueous solution was filtered with active charcoal, the filtrate evaporated under diminished pressure, and the residue crystallised from ethanol to afford (5°C) 0·55 g (52·5%) of the acid *I*, m.p. 158—162°C (decomp.); reported[1], m.p. 153—154°C.

B. Reaction of chloroacetic acid (37·8 g; 0·4 mol) with methylhydrazine (prepared from 57·6 g *i.e.* 0·4 mol 1-methylhydrazine sulfate[8]) was performed according to the above mentioned procedure, the reaction mixture evaporated under diminished pressure to one third of the original volume, and the concentrate neutralised by additions of Dowex 50 (H^+) ion exchange resin until the evolution of carbon dioxide ceased. The mixture was then applied without filtration to a 4·5 × 30.0 cm column of the same resin, the column washed with water (1 500 ml), and the product eluted with 5% aqueous ammonia (1 000 ml). The eluate was evaporated under diminished pressure, the residue coevaporated with ethanol (100 ml), and finally dissolved in 150 ml of ethanol. The solution was kept at 5°C overnight to deposit 7·18 g of the acid *I*, m.p. 145—150°C. An additional crop (3·55 g) of the same melting point was obtained by evaporation of the mother liquor. The crops were combined and recrystallised from 80% aqueous ethanol to afford 6·65 g (15·7%) of the acid *I*, m.p. 159—161°C. R_F value 0·45 in the solvent system S_1 and 0·45 in S_2. Electrophoretical mobility: 10·3 cm in the buffer solution E_1 and 3·9 cm in E_2.

1-Benzylhydrazinoacetic Acid (*II*)

Benzylhydrazine (6·1 g; 0·05 mol) in ethanol (35 ml) was added to a solution prepared from chloroacetic acid (4·7 g; 0·05 mol), sodium carbonate (5·3 g; 0.05 mol) and water (85 ml). The whole mixture was refluxed for 3 h, concentrated under diminished pressure to the volume of about 50 ml, and the concentrate treated portionwise with Dowex 50 (H^+) ion exchange resin until the evolution of carbon dioxide ceased. The mixture was then without filtration applied to a 2·5 × 35·0 cm column of the same resin, the column washed with water (750 ml), and the product eluted with 5% aqueous ammonia (500 ml). The eluate was evaporated under diminished pressure, the residue dissolved in ethanol (50 ml), and the solution allowed to crystallize at 5°C. Crystallisation of the crude product (2·73 g) from methanol afforded 1·98 g (22%) of the acid *II*, m.p. 159—162°C (decomp.). IR spectrum (in KBr): 1 554 cm^{-1} (COO^-), 1 631 cm^{-1} (NH_2), 1 397 cm^{-1} (NH^+), 2 600—2 700 cm^{-1} (NH), 2 180 cm^{-1}. R_F value: 0·78 in the solvent system S_1 and 0·63 in S_2. Electrophoretical mobility: 7·4 cm in the buffer solution E_1 and 3·6 cm in E_2. For $C_9H_{12}N_2O_2$ (180·2) calculated: 59·98% C, 6·71% H, 15·55% N; found: 59·54% C, 6·82% H, 15·75% N.

N-Nitroso-N-benzylglycine (*VI*)

A solution of N-benzylglycine[9] (26·2 g; 0·16 mol; prepared by reduction[10] of N-benzylideneglycine with sodium borohydride) in 3·2M-HCl (100 ml) was diluted with ethyl acetate (300 ml) and then treated dropwise under stirring with a solution of sodium nitrite (22·0 g; 0·32 mol) in water (50 ml) at such a rate to keep the temperature below 30°C (for about 30 min). The stirring was

continued at 25°C for one hour, the ethyl acetate layer separated, and the aqueous layer extracted with ethyl acetate (100 ml). The organic layers were combined, washed with two 100 ml portions of ice-cold water, and evaporated under diminished pressure. Crystallisation of the residue from ethyl acetate afforded 25·0 g (80%) of compound *VI*, m.p. 144–146°C. UV spectrum (in ethanol): λ_{max} 237 nm (log ε 3·90). IR spectrum (in chloroform): 1769 cm^{-1} (C=O monomer), 1729 cm^{-1} (C=O dimer), 1460 cm^{-1} (N=O). For $C_9H_{10}N_2O_3$ (194·2) calculated: 55·66% C, 5·19% H, 14·43% N; found: 55·53% C, 5·20% H, 14·43% N.

Electrochemical Reduction of N-Nitroso Compounds *V* and *VI*

The apparatus for the electrochemical reduction[5] was charged with a solution of the N-nitroso compound (0·1 mol) in methanol (350 ml), the content cooled down to 5°C, and treated with 1M-HCl (350 ml). In the case of the compound *VI*, a fine suspension was formed. Current was supplied from a selenium rectifier (24 Volt, maximum current load 10 A). Initial current intensity (2 A) gradually decreased in the course of the reduction. The temperature was kept below 15°C during the reduction. The course of the reduction was controlled by thin-layer chromatography on silica gel in 10 : 3 ethyl acetate–methanol solvent system. The starting nitroso compounds *V* and *VI* appear under ultraviolet light as absorbing spots of the R_F value of about 0·5; the hydrazino acids *I* and *II* are not visible under ultraviolet light and remain at the start line in the solvent system stated. After disappearance of the starting compound (approximately after 6 h) the mixture was filtered, the filtrate concentrated to the volume of about 100 ml, and the concentrate applied to a 4 × 20 cm column of ammonium Dowex 50 ion exchange resin. The column was washed with water (1000 ml) and the product eluted with 3% aqueous ammonia (250–300 ml). The eluate was evaporated under diminished pressure, the residual sirup coevaporated with two 150 ml portions of ethanol, the final residue dissolved in ethanol (100 ml), and allowed to crystallize at 5°C overnight. Reduction of the N-nitroso compound *V* (prepared according to ref.[7]) afforded 52·5% of the acid *I*, m.p. 158–159°C, undepressed on admixture with the specimen obtained above. Reduction of the N-nitroso compound *VI* led to the acid *II*, m.p. 163–164°C, undepressed on admixture with the specimen prepared by the above procedure; yield, 64%.

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