[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Synthesis of Methyl 6-Phenyl-3-methyl-3-azapimelate[1]

C. F. KOELSCH AND FRANKLIN M. ROBINSON

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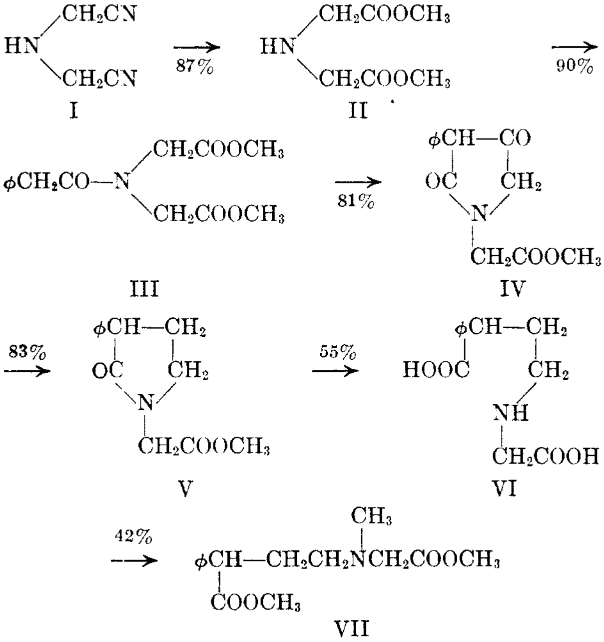
Reproducible methods for obtaining iminodiacetonitrile and methyl iminodiacetate are described. The N-phenylacetyl derivatives of methyl iminodiacetate was subjected to Dieckmann cyclization, and the resulting 2,4-dioxopyrrolidine was partially deoxidized to a lactam. Ring opening by hydrolysis, followed by methylation gave the desired end product, named in the title.

A method was needed for preparation of methyl 6-aryl-3-methyl-3-azapimelates, for such esters might be converted into piperidones useful in a projected morphine synthesis.

The present paper describes some experiments undertaken to develop such a method. Methyl 6-phenyl-3-methyl-3-azapimelate (VII) was obtained using the reactions shown in the accompanying chart.



Several variations in the indicated route were tried, but no better way was found. Application of the Thorpe reaction to the phenylacetyl derivative of iminodiacetonitrile gave at best a 10% yield of 1-cyanomethyl-3-phenyl-4-imino-2-pyrrolidone. Conversion of IV to V stepwise, through the corresponding 4-hydroxypyrrolidone and Δ^3-pyrrolone was accomplished, an important point in establishing the nature of V, but as a preparative procedure this indirect route was of no value.

EXPERIMENTAL

Iminodiacetonitrile (I). Treatment of methyleneaminoacetonitrile with aqueous sodium cyanide and hydrochloric acid gave iminodiacetonitrile in a yield of 70%, but isolation was laborious. Use of anhydrous hydrogen cyanide as described in detail below was more satisfactory.

Methyleneaminoacetonitrile[2] (245 g.) and 0.9 ml. of concentrated hydrochloric acid were added to 103 g. of hydrogen cyanide which had been frozen in a two-liter flask. The flask was closed tightly and kept at room temperature for six days. Excess hydrogen cyanide was then removed under reduced pressure and the brown residue was dissolved in 500 ml. of hot ethyl acetate and boiled for two minutes with Norit. Addition of *ca.* 200 ml. of benzene precipitated a small amount of tar, and subsequent cooling to 0° gave 229 g. of slightly brown product. An additional 31 g. was obtained by concentrating the mother liquor. The substance had m.p. 75–78° and was pure enough for further use. Crystallization of 5-gram samples from water or from 12 ml. of ethyl acetate plus 4 ml. of benzene gave 3.5 g. of colorless crystals, m.p. 77–79°, reported 75°,[3] 78°[4].

Methyl iminodiacetate hydrochloride (II). To a solution of 430 g. of hydrogen chloride in two liters of methanol was added 272 g. of iminodiacetonitrile in small portions, while the mixture was stirred and cooled to prevent too vigorous refluxing. The addition required about 45 minutes. Then 105 ml. of water was added, and the mixture was boiled for two hours, then treated with an additional 200 ml. of 27% methanolic hydrogen chloride and boiled for 1.5 hours longer. Ammonium chloride was removed by filtration of the hot mixture and washed with 400 ml. of hot methanol. Cooling the solution to −15° overnight gave 308 g., and concentration of the mother liquors gave an additional 133 g., m.p. 166–170°. This product contained some ammonium chloride, but was pure enough for acylation. A sample free of ammonium chloride was obtained with 50% loss by combined fractional extraction and crystallization from methanol, m.p. 177–178° (dec.); reported,[5] 183°.

Methyl N-phenylacetyliminodiacetate (III). A solution of 39.6 g. of methyl iminodiacetate hydrochloride in 100 ml. of water was added as rapidly as frothing permitted (10 minutes) to a cold (0°) stirred mixture of 120 ml. of water and 37 g. of sodium bicarbonate (carbonate gave much poorer results). Then during 20 minutes 34 g. of phenylacetyl chloride was added at −5 to 0°. Stirring was continued for one hour, and the product then was removed and washed with water. Recrystallization from a mixture of 60 ml. of methanol and 35 ml. of water gave 47–51 g. (84–91%) of colorless methyl N-phenylacetyliminodiacetate, m.p. 80–82°. An analytical sample m.p. 82–82.5° was obtained by a second crystallization.

Anal. Calc'd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1. Found: C, 60.3; H, 6.2.

Methyl 2,4-dioxo-3-phenylpyrrolidylacetate (IV). Sodium methoxide was prepared from 4.1 g. of powdered sodium and 15 ml. of methanol in 120 ml. of toluene. To this was added

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[1] From the Ph. D. Thesis of F. M. Robinson, August 1950.

[2] Ammundsen and Velitzkin, *J. Am. Chem. Soc.*, **61**, 212 (1939).

[3] Eschweiler, *Ann.*, **278**, 230 (1894).

[4] Dubsky, *Ber.*, **54**, 2659 (1921).

[5] Jonkees, *Rec. trav. chim.*, **27**, 287 (1908).

46 g. of III, and the mixture was distilled slowly (15 minutes) until no more methanol was obtained. The solid then was removed by filtration, washed with ether, and stirred into a solution of 20 ml. of hydrochloric acid in 200 ml. of water. The crude product m.p. 145–148° was crystallized from a mixture of 20 ml. of methanol and 40 ml. of water, giving 34 g. (81%) of colorless crystals m.p. 155–157°. Further crystallization gave an analytical sample, m.p. 157–158°.

Anal. Calc'd for $C_{13}H_{13}NO_4$: C, 63.1; H, 5.3. Found: C, 63.1; H, 5.6.

With alcoholic ferric chloride, the compound gave a dark green color that became violet when water was added. The *phenylhydrazone*, prepared in methanol containing a trace of acetic acid, formed colorless crystals m.p. 183–184° dec.

Anal. Calc'd for $C_{19}H_{19}N_3O_3$: C, 67.7; H, 5.7. Found: C, 67.7; H, 5.8.

When cyclization of III was carried out using sodium ethoxide in toluene, ester interchange took place, and the *ethyl ester* corresponding to IV was formed; colorless crystals from ethyl acetate, m.p. 149–150°.

Anal. Calc'd for $C_{14}H_{15}NO_4$: C, 64.3; H, 5.8; Neut. equiv., 261. Found: C, 64.2; H, 5.8; Neut. equiv., 242.

When the sodium salt obtained by cyclization of III was allowed to stand in water solution, hydrolysis of the ester group took place. The product, *2,4-dioxo-3-phenylpyrrolidylacetic acid,* was better obtained by boiling a solution of 3 g. of IV in 20 ml. of 10% sodium hydroxide for ten minutes; precipitation with hydrochloric acid and crystallization from dil. acetic acid gave 2 g. of colorless needles m.p. 234–239°. Further crystallization from alcohol gave a product m.p. 238–239°.

Anal. Calc'd for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.8; N, 6.0. Found: C, 62.0; H, 5.0; N, 6.0.

Re-esterification to III (20% yield) took place when the acid was boiled for 20 minutes with 10% methanolic hydrogen chloride.

Methyl 3-phenyl-2-pyrrolidone-N-acetate (V). A solution of 37 g. of IV in 200 ml. of methanol containing 4 g. of Raney nickel was shaken under hydrogen at 30–40 lbs. and 50°. After 22 hours about half the calculated amount of hydrogen had been taken up and further absorption was very slow. The solution was filtered, fresh catalyst was added, and hydrogenation was continued for 18 hours, or until the reaction was complete. Distillation gave 29 g. of a colorless oil, b.p. 183–189° at 5 mm; an analytical sample b.p. 186–187° was obtained by redistillation; n_D^{26}, 1.5378.

Anal. Calc'd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5. Found: C, 66.8; H, 6.3.

3-Phenyl-2-pyrrolidone-N-acetic acid obtained by saponification with hot 10% sodium hydroxide, formed colorless crystals from 50% acetic acid of a hydrate, m.p. 62–64°. From benzene, the anhydrous compound was obtained, m.p. 108–109°.

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.7; H, 6.0; Neut. equiv., 219. Found: C, 65.8; H, 6.0; Neut. equiv., 222.

When hydrogenation of 13 g. of IV was interrupted after one equivalent of hydrogen had been taken up and methanol was removed under reduced pressure, an oil containing some alkali-insoluble solid was obtained. Treatment with cold ether left 2.8 g. of crude *methyl 4-hydroxy-3-phenyl-2-pyrrolidone-N-acetate,* m.p. 125–130°. Recrystallization from dilute methanol gave the pure substance, m.p. 145–146°.

Anal. Calc'd for $C_{13}H_{15}NO_4$: C, 62.6; H, 6.1. Found: C, 62.9; H, 6.4.

Dehydration of the 4-hydroxy compound (2.4 g.) was accomplished by boiling it for 25 hours with 20 ml. of acetic anhydride and 1 g. of potassium acetate, followed by distillation of the crude acetate at 200–210° and 5 mm. The resulting *methyl 3-phenyl-Δ^3-2-pyrrolone-N-acetate* (0.5 g.) formed yellow crystals from benzene, m.p. 80–81°; it decolorized bromine in carbon tetrachloride.

Anal. Calc'd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7. Found: C, 67.8; H, 5.7.

When a solution of 0.9 g. of the Δ^3-pyrrolone in methanol was shaken with charcoal, then with Raney nickel, and finally reduced in presence of colloidal palladium, it absorbed the calculated amount of hydrogen in one hour. Fractionation through a micro Craig column gave four 0.1-g. fractions, b.p. about 200°; the third fraction had n_D^{26} 1.5382, and was identical with V described above (Found: C, 66.7; H, 6.3).

6-Phenyl-3-azapimelic acid (VI). A solution of 18.2 g. of V in 65 ml. of 42% hydrobromic acid was boiled for 7 hours, then distilled until the solution had b.p. 122°, boiled for one hour more, then evaporated under reduced pressure. The residue was dissolved in 35 ml. of water, brought to *p*H 6 with 10% sodium hydroxide, and kept for several hours at 0°. There was obtained 10.1 g. of colorless crystals, m.p. 159–164°; recrystallization from water gave a product m.p. 164–165° decomp. (bath pre-heated to 150°).

Anal. Calc'd for $C_{12}H_{15}NO_4$: C, 60.7; H, 6.4. Found: C, 60.3; H, 6.4.

Acidification of the mother liquors from the preparation gave 4.8 g. of the hydrate of 3-phenylpyrrolidone-N-acetic acid, m.p. 60–64°.

3-Benzenesulfonyl-6-phenyl-3-azapimelic acid, from the acid with benzenesulfonyl chloride and aqueous alkali, formed colorless crystals from a mixture of benzene and ethyl acetate, m.p. 148–150°.

Anal. Calc'd for $C_{18}H_{19}NO_6S$: C, 57.3; H, 5.1; Neut. equiv., 189. Found: C, 57.4; H, 5.3; Neut. equiv., 183.

Methyl 3-methyl-6-phenyl-3-azapimelate (VII). A mixture of 10.1 g. of VI, 20 g. of formalin, and 50 g. of 90% formic acid was boiled for 1.1 hours, then distilled to dryness under reduced pressure. The residue was dissolved in 50 ml. of methanol saturated with hydrogen chloride, and boiled for one hour. Methanol was removed under reduced pressure and replaced with 20 ml. of ice-water. Treatment with cold sodium hydroxide solution and ether gave 5 g. of VII, a colorless liquid, b.p. 180–185° at 10 mm; n_D^{26} 1.4981.

Anal. Calc'd for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6. Found: C, 64.2; H, 7.5.

The *picrolonate* formed bright yellow crystals from methanol, m.p. 158–159° decomp.

Anal. Calc'd for $C_{25}H_{27}N_5O_9$: C, 55.2; H, 5.4; N, 12.9. Found: C, 55.4; H, 5.7; N, 13.0.

Experiments on the Thorpe cyclization. N-Phenylacetyliminodiacetonitrile was obtained in 61% yield by treatment of 47.5 g. of I in 250 ml. of cold water with 46 g. of sodium bicarbonate and 80 g. of phenylacetyl chloride. It formed colorless crystals from alcohol or ethyl acetate, m.p. 128–129°.

Anal. Calc'd for $C_{12}H_{11}N_3O$: C, 67.6; H, 5.2. Found: C, 67.3; H, 5.4.

Efforts to hydrolyze or alcoholize the nitrile groups always led to removal of the phenylacetyl group.

Treatment of the compound with sodium methoxide in various reaction media and in varying amounts led to exothermic reaction, ammonia evolution, and formation of dark brown tars, with only small yields of crystalline products. For example, a suspension of 5 g. of N-phenylacetetiminodiacetonitrile in 25 ml. of methanol was treated with 0.5 ml. of 23% sodium methoxide in methanol. The mixture was warmed for two minutes until solution had occurred, boiled for one minute and then cooled rapidly, and distilled to dryness under reduced pressure at 15°. The dark product was crystallized five times from dil. ethanol (charcoal) giving 0.5 g. of *3-phenyl-4-imino-2-pyrrolidone-N-acetonitrile,* m.p. 235–236°, decomp. (bath pre-heated to 225°).

Anal. Calc'd for $C_{12}H_{11}N_3O$: C, 67.6; H, 5.2; N, 19.2. Found: C, 67.8; H, 5.4; N, 19.6

A similar experiment, in which the basic catalyst (0.1 g. of sodium in 50 ml. of methanol) was neutralized with 3 ml. of concd. hydrochloric acid in 5 ml. of water before the solvent was removed gave no imino-nitrile but only a small amount of *2,4-dioxo-3-phenylpyrrolidylacetamide,* colorless crystals from alcohol, m.p. 179–180°.

Anal. Calc'd for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.2; N, 12.1. Found: C, 61.9; H, 5.2; N, 12.4.

The amide was not obtained when 5 g. of methyl 2,4-diketo-3-phenylpyrrolidyl acetate (IV) was kept for two days at room temperature in solution in 30 ml. of conc'd ammonium hydroxide. Instead, this experiment yielded 3 g. of *4-imino-3-phenyl-2-pyrrolidone-N-acetic acid*, colorless plates from ethanol, m.p. 239–241°.

Anal. Calc'd for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.2; N, 12.1. Found: C, 62.3; H, 5.5; N, 12.3.

All three of the substances described in this section, the imino-nitrile, the acetamide, and the imino-acetic acid were converted into IV by treatment with methanolic hydrogen chloride, and into 2,4-dioxo-3-phenylpyrrolidyl acetic acid by treatment with aqueous hydrochloric acid.

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