CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

SYNTHESIS OF SOME 2-IMIDAZOLINES FROM ETHYL 4,4-DIMETHYL-1-ISOPROPYL-2-IMIDAZOLINYL-2-ACETATE[1]

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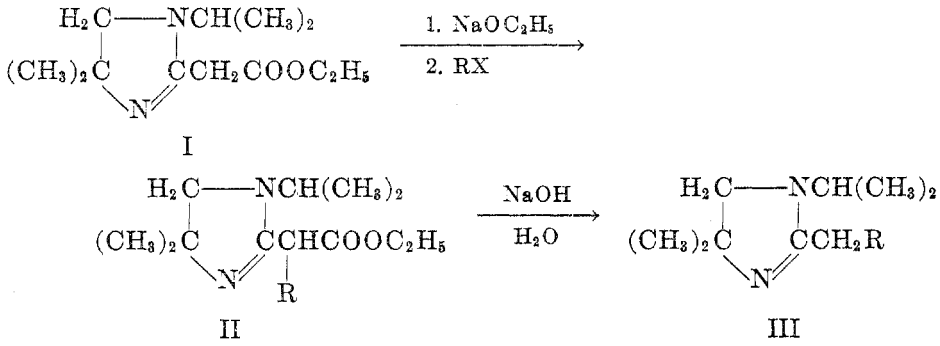
In a previous communication (1) the synthesis of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (I) was described and it was shown that the sodio derivative of I could be alkylated with benzyl chloride to give a product which upon hydrolysis and decarboxylation produced 4,4-dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline (III, R = $C_6H_5CH_2$).



I II III

In the present investigation the synthesis of I from diethyl malonate and N-(2-aminoisobutyl)isopropylamine was carried out in 60–64% yield by the procedure previously described (1). A methiodide of I was prepared and an analysis gave results which are in agreement with its structure.

The reaction of the sodio derivative of the ester (I) with excess ethyl iodide in ethanol gave a 67% yield of ethyl α-(4,4-dimethyl-1-isopropyl-2-imidazolinyl)-butyrate (II, R = C_2H_5). When *n*-propyl iodide and *n*-butyl bromide were used in the alkylation the corresponding alkylated esters (II, R = *n*-C_3H_7 and R = *n*-C_4H_9) were obtained in 62% and 41% yield respectively. These compounds (II, R = C_2H_5, *n*-C_3H_7, *n*-C_4H_9) formed picrates and had the expected neutral equivalents for monoacid bases. Analysis of the compounds (II) and their picrates were in agreement with the proposed structures.

Hydrolysis and decarboxylation of II, R = C_2H_5 and *n*-C_3H_7, in hot aqueous-ethanolic sodium hydroxide afforded the corresponding 2-alkyl-4,4-dimethyl-1-isopropyl-2-imidazolines (III, R = C_2H_5, *n*-C_3H_7) in 78% and 73% yields respectively. The *n*-butyl analog (III, R = *n*-C_4H_9) was obtained as a side product in the isolation of II, R = *n*-C_4H_9. The properties of these compounds (III) were in agreement with those previously reported (2).

[1] From the thesis presented by Mr. Shapira to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the M.S. degree. Mr. Shapira's present address is Department of Chemistry, University of Florida.

EXPERIMENTAL[2]

Ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (I). This compound was prepared essentially according to the procedure described previously (1) using 2 moles of malonic ester (b.p. 91°/15 mm.) and 1 mole of N-(2-aminoisobutyl)isopropylamine (b.p. 68–69°/50 mm.). The yield of crude product was 60–64%, m.p. 52–55°. The crude product was distilled under reduced pressure and 54–58% of colorless crystalline material, b.p. 148–151°/5 mm., m.p. 58–59°, was obtained. The yield of pure product was not substantially lowered when 1.5 moles of malonic ester and 1 mole of diamine were used. Addition of a small amount of concentrated hydrochloric acid to the reaction mixture decreased the yield while small amounts of potassium hydroxide had no effect on the yield.

A methiodide of I was prepared by adding 1.5 g. (0.01 mole) of methyl iodide to 2.26 g. (0.01 mole) of I dissolved in 15 ml. of anhydrous ethyl acetate. After standing overnight at room temperature the solution was cooled to 0° and the methiodide crystallized. Recrystallization from an ethyl acetate-ethanol mixture gave the colorless methiodide derivative, m.p. 163–163.5° (corr.).

Anal. Calc'd for $C_{13}H_{25}IN_2O_2$: I, 34.4. Found: I, 34.0.

Preparation of ethyl α-(4,4-dimethyl-1-isopropyl-2-imidazolinyl)butyrate (II, R = C_2H_5). To 2.5 g. (0.1 mole) of sodium dissolved in 100 ml. of ethanol was added 22.6 g. (0.1 mole) of the ester (I), m.p. 55–57°. The mixture was heated to reflux and allowed to cool. Over a period of 15 minutes, 48 g. (0.3 mole) of ethyl iodide (Eastman) was added and the resulting solution was refluxed for five hours. The alcohol was then removed under reduced pressure and to the resulting semi-solid was added 40 ml. of concentrated hydrochloric acid in 60 ml. of water. The resulting solution was decanted from the residual solid and made basic with 20% sodium hydroxide. The oil which separated was distilled to give 16.7 g. (67% yield) of crude II, R = C_2H_5, b.p. 130–141° (15 mm.). Redistillation gave the pure compound, b.p. 139.5–140° (15 mm.), as well as a considerable forerun.

Anal. Calc'd for $C_{14}H_{26}N_2O_2$: Neut. equiv., 254; N, 11.1.
Found: Neut. equiv., 251; N, 11.1.

The *picrate*, m.p. 121.5–122° (corr.), was prepared by the usual method.

Anal. Calc'd for $C_{20}H_{22}N_5O_9$: N, 14.5. Found: N, 14.4.

Preparation of ethyl α-(4,4-dimethyl-1-isopropyl-2-imidazolinyl)-n-valerate (II, R = n-C_3H_7). To 3.0 g. (0.125 mole) of sodium dissolved in 40 ml. of absolute ethanol was added 22.6 g. (0.1 mole) of the ester (I), m.p. 55–57°. The mixture was heated to reflux and allowed to cool. Over a period of 15 minutes, 25.5 g. (0.15 mole) of n-propyl iodide, b.p. 96–98.5° at 643 mm., was added and the resulting solution was kept at 35° overnight. The mixture was then refluxed gently at 80° for two hours. The alcohol was removed under reduced pressure and to the resulting semi-solid was added 150 ml. of water. When this mixture was cooled to 0° and seeded with I, 7.3 g. of I, m.p. 58–60°, crystallized. This was separated and to the filtrate was added 100 g. of potassium carbonate and 25 ml. of ethyl acetate. The organic layer was separated and washed twice with 75-ml. portions of 20% aqueous potassium carbonate solution. Distillation of this organic solution gave, as a main fraction, 16.6 g. (62% yield) of crude II, R = n-C_3H_7, b.p. 113–132° at 5 mm. Three further distillations gave the pure compound, b.p. 125.5–129° at 5 mm.

Anal. Calc'd for $C_{15}H_{28}N_2O_2$: Neut. equiv., 268; N, 10.5.
Found: Neut. equiv., 272; N, 10.5.

The *picrate*, m.p. 143–144.5° (corr.), was prepared by the usual method.

Anal. Calc'd for $C_{21}H_{31}N_5O_9$: N, 14.1. Found: N, 13.9.

Preparation of ethyl α-(4,4-dimethyl-1-isopropyl-2-imidazolinyl)-n-caproate (II, R = n-C_4H_9). To 2.5 g. (0.1 mole) of sodium dissolved in 100 ml. of absolute ethanol was added 22.6 g. (0.1 mole) of the ester (I), m.p. 55–57°. The mixture was heated to reflux and allowed to cool, and over a period of 15 minutes, 41.1 g. (0.3 mole) of n-butyl bromide (East-

[2] All melting points are uncorrected unless otherwise specified.

man) was added during which time a white precipitate formed. The mixture was refluxed gently for 1½ hours and then held at 80° for ten hours.

The reaction product was worked up as was the ethyl derivative to give 12 g. (41%) of crude II, R = *n*-C_4H_9, b.p. 159–165° at 15 mm. Repeated distillation gave the pure compound as an oil, b.p. 130–132.5° at 5 mm.

Anal. Calc'd for $C_{16}H_{30}N_2O_2$: Neut. equiv., 282; N, 9.9.

Found: Neut. equiv., 281; N, 10.0.

A *picrate*, m.p. 125–125.5° (corr.), was prepared by the usual method.

Anal. Calc'd for $C_{22}H_{33}N_5O_9$: N, 13.7. Found: N, 13.5.

Preparation of 4,4-dimethyl-1-isopropyl-2-n-propyl-2-imidazoline (III, R = C_3H_5) *by the hydrolysis of ethyl α-(4,4-dimethyl-1-isopropyl-2-imidazolinyl)butyrate* (II, R = C_2H_5). Sodium hydroxide (5.0 g.) in 20 ml. of 80% ethanol containing 9.3 g. (0.037 mole) of crude II (R = C_2H_5) was refluxed gently for six hours. After cooling, the liquid was decanted from a solid residue and the ethanol was removed on a water-bath. The resulting oil was distilled to give 5.2 g. (78% yield) of III, R = C_2H_5, as a colorless liquid, b.p. 89–90.5° at 15 mm. [reported b.p. 97–100° at 20 mm. (2)].

Anal. Calc'd for $C_{11}H_{22}N_2$: Neut. equiv., 182; N, 15.4.

Found: Neut. equiv., 181; N, 15.1.

The *picrate*, m.p. 127.5–128° (corr.) was prepared by the usual method.

Anal. Calc'd for $C_{17}H_{25}N_5O_7$: N, 17.0. Found: N, 17.0.

Preparation of 4,4-dimethyl-1-isopropyl-2-n-butyl-2-imidazoline (III, R = *n*-C_3H_7) *by the hydrolysis of ethyl α-(4,4-dimethyl-1-isopropyl-2-imidazolinyl)-n-valerate* (II, R = *n*-C_3H_7). The hydrolysis and decarboxylation were performed as described above using 11.0 g. (0.04 mole) of crude II, R = *n*-C_3H_7. Distillation of the product gave 5.9 g. (73% yield) of III, R = *n*-C_3H_7, b.p. 108–112° at 15 mm. [reported b.p. 112–115° at 18 mm. (2)].

Anal. Calc'd for $C_{12}H_{24}N_2$: Neut. equiv., 196; N, 14.3.

Found: Neut. equiv., 193; N, 14.3.

The *picrate*, m.p. 115.5–116.5° (corr.), was prepared by the usual method.

Anal. Calc'd for $C_{18}H_{27}N_5O_7$: N, 16.5. Found: N, 16.3.

Isolation of 4,4-dimethyl-1-isopropyl-2-n-pentyl-2-imidazoline (III, R = *n*-C_4H_9). In the repeated distillations used for the isolation of pure II, R = *n*-C_4H_9 (see above), a fraction was obtained, b.p. 84–87° at 2 mm., which was found to be III, R = *n*-C_4H_9, recorded b.p. 125–128° at 15 mm. (2). This probably arose from hydrolysis and decarboxylation of II, R = *n*-C_4H_9 while working up the reaction mixture.

Anal. Calc'd for $C_{13}H_{26}N_2$: Neut. equiv., 210; N, 13.3.

Found: Neut. equiv., 216; N, 12.9.

The *picrate*, m.p. 80–83° (corr.), was prepared by the usual method.

Anal. Calc'd for $C_{19}H_{29}N_5O_7$: N, 15.9. Found: N, 15.8.

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SUMMARY

Alkylation of the sodio derivative of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (I) with ethyl iodide, *n*-propyl iodide, and *n*-butyl bromide gave the corresponding ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-alkylacetates (II) which on hydrolysis and decarboxylation afforded 2-alkyl-4,4-dimethyl-1-isopropyl-2-imidazolines (III).

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