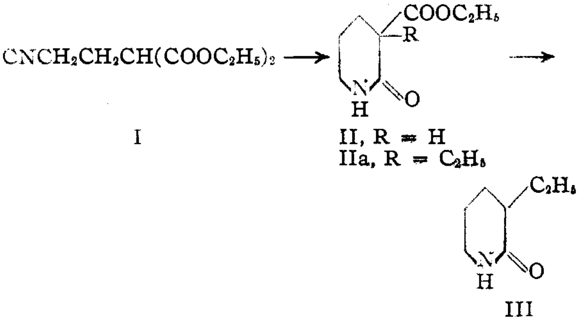
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

A Synthesis of 3-Alkylpiperidones

BY C. F. KOELSCH

Catalytic reduction of γ-cyanoesters affords a convenient synthesis of piperidones.[1] Two of the several rather obvious methods for applying this synthesis to the preparation of alkylated piperidones have been studied, and an example of each is reported in the present paper.

If the cyanoester contains a malonic ester grouping, it may be alkylated either before or, as shown in the accompanying formulas, after it has been reduced and allowed to cyclize.



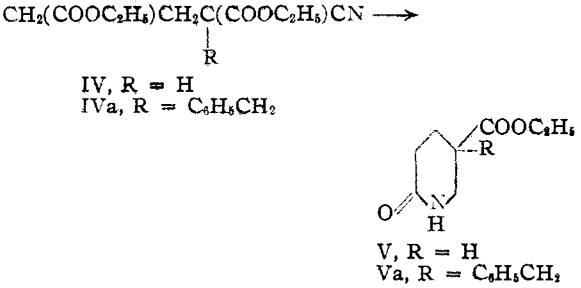
$CNCH_2CH_2CH(COOC_2H_5)_2 \longrightarrow$

I

II, R = H
IIa, R = C_2H_5

III

If, however, the cyanoester contains a cyanoacetic ester grouping, it must be alkylated before it has been reduced.



$$\underset{\displaystyle R}{CH_2(COOC_2H_5)CH_2\underset{|}{C}(COOC_2H_5)CN} \longrightarrow$$

IV, R = H
IVa, R = $C_6H_5CH_2$

V, R = H
Va, R = $C_6H_5CH_2$

Experimental

Ethyl α-Carbethoxy-γ-cyanobutyrate, I.—Twenty-five grams of acrylonitrile in 25 ml. of the alcohol was added at 40° to a solution of 11 g. of sodium and 75 g. of ethyl malonate in 200 ml. of alcohol. The mixture was kept at 65° for four hours and then neutralized with acetic acid. The product, isolated in yields of 40–45%, was a colorless oil, b. p. 175–180° at 25 mm.

Anal. Calcd. for $C_{10}H_{15}NO_4$: C, 56.4; H, 7.0. Found: C, 56.4; H, 7.2.

Ethyl 2-Ketonipecotate, II.—The ester I (39.5 g.) was reduced without a solvent at 100°, using Raney nickel and hydrogen at a pressure of 2000 lb.; the reaction was complete in ten minutes. The product boiled at 205–215° at 12 mm. and separated from benzene in the form of colorless plates (18 g., 57%), m. p. 78–79°.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.1; H, 7.6. Found: C, 56.0; H, 7.7.

Ethyl 3-Ethyl-2-ketonipecotate, IIa.—Seventeen grams of II was added to a solution of 2.3 g. of sodium in 30 ml. of alcohol. The resulting white, cheesy salt suspension was treated with 17 g. of ethyl iodide, and the mixture was boiled until it was neutral (forty-five minutes). Water was added, the alcohol was distilled, and the very hygroscopic product was removed by extraction with twenty-five 20 ml. portions of ether. Distillation gave 13 g. (66%) of IIa, b. p. 190–198° at 12 mm.; the compound separated from ligroin in the form of fine needles, m. p. 46–49°, which deliquesced in a humid atmosphere.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6. Found: C, 60.2; H, 8.6.

3-Ethylpiperidone-2, III.—A mixture of 12.5 g. of ethyl 3-ethyl-2-ketonipecotate, 12 ml. of water, and 4 g. of potassium hydroxide was heated in an oil-bath at 105°. The oily ester layer, salted out by the alkali, dissolved in ten minutes, but the heating was continued for four hours. The mixture was then cooled, acidified with 3.8 g. of sulfuric acid, and evaporated under reduced pressure at 100°. The residue was distilled under reduced pressure without removing the potassium sulfate, since other experiments had shown that the 3-ethyl-2-ketonipecotic acid which it contained was a hygroscopic sirup. The distillate was redistilled, giving 7.0 g. of III, b. p. 149° at 15 mm., m. p. 66–68°. The piperidone was too soluble to be crystallized from either water or ligroin.

Anal. Calcd. for $C_{17}H_{13}NO$: C, 66.1; H, 10.2. Found: C, 66.1; H, 10.1.

Reduction of the piperidone (6 g.) in butyl alcohol (100 ml.) with sodium (10 g.) gave 3-ethylpiperidine, isolated and identified as its characteristic hydrochloride, fine white needles (5 g.) from benzene, m. p. 137–140°.

Ethyl γ-Carbethoxy-α-cyanobutyrate, IV.—To a suspension of ethyl sodiocyanoacetate made from 5.75 g. of sodium in 75 ml. of ethanol was added 21.5 g. of methyl acrylate.[2] Each drop of the unsaturated ester caused the development of a transient red color and the solution of some of the sodio derivative; solution was complete and the red color was permanent at the end of the addition. The mixture was heated on a water-bath for one hour, cooled, treated with 7.5 ml. of acetic acid and then with 30 ml. of water. The alcohol was distilled, more water was added, and the product was extracted with ether. Distillation gave 36 g. of crude ester, b. p. 175–205° at 27 mm., and redistillation gave 20 g. of pure IV, b. p. 180° at 25 mm.

Anal. Calcd. for $C_{10}H_{15}NO_4$: C, 56.4; H, 7.0. Found: C, 56.2; H, 6.9.

Ethyl 5-Ketonipecotate, V.—The ester IV (19 g.) was reduced in 20 ml. of alcohol at 140° using Raney nickel and hydrogen at 2000 lb. The product was obtained in excellent yield, b. p. 163° at 2 mm. (it decomposed partly when it was distilled at 20 mm.), m. p. 62–64°; it was too soluble to be recrystallized.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.1; H, 7.6. Found: C, 55.7; H, 7.3.

Ethyl γ-Carbethoxy-γ-cyano-δ-phenylvalerate, IVa.—The Michael reaction between ethyl sodiocyanoacetate and methyl acrylate was carried out as described above, but the resulting sodio derivative was decomposed by treating it with 32 g. of benzyl chloride. The mixture was heated on a water-bath for three hours, and the product was isolated in the usual way. Distillation gave 51 g. of benzylated ester, b. p. 187–195° at 2 mm.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.4; H, 6.9. Found: C, 67.4; H, 6.9.

Ethyl 3-Benzyl-5-ketonipecotate, Va.—Forty grams of the ester IVa in 20 ml. of alcohol containing Raney nickel rapidly took up the calculated amount of hydrogen at 2000

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[1] Koelsch, THIS JOURNAL, **65** 2093 (1943).

[2] Ester interchange accompanies the Michael reaction.

lb. and 165°. The catalyst was removed, and the solvent was distilled at 100° under reduced pressure. The product did not crystallize when it was kept at room temperature for three weeks or at −80° in ether–ligroin for several days. It solidified immediately and completely, however, when it was shaken with 10% aqueous potassium hydroxide. This solidification was caused by hydrate formation, and subsequent lots of the ester rapidly crystallized when they were placed in contact with water and seeded. From a mixture of benzene and ligroin the hydrate separated in the form of shining white plates, m. p. 64–65°.

Anal. Calcd. for $C_{15}H_{19}NO_3 \cdot H_2O$: C, 64.5; H, 7.5. Found: C, 64.9; H, 7.2.

Saponification of the ester with the calculated amount of 2% sodium hydroxide gave **3-benzyl-5-ketonipecotic acid,** colorless plates from 5% acetic acid, m. p. 221–222°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.0; H, 6.7. Found: C, 67.1; H, 6.7.

The author thanks Mr. E. E. Renfrew and Mr. S. T. Rolfson for the analyses reported in this paper.

Summary

Reduction of an α-carbethoxy-γ-cyanobutyric ester followed by alkylation of the resulting piperidone, or alkylation of a γ-carbethoxy-γ-cyanobutyric ester followed by reduction, afford methods whereby 3-alkylpiperidones may be prepared.

MINNEAPOLIS, MINNESOTA RECEIVED SEPTEMBER 7, 1943

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

A Synthesis of 4-Phenylpiperidines

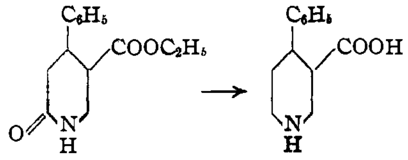
BY C. F. KOELSCH

Reactions analogous to those used for the preparation of 3-phenylpiperidines[1] can be used for the preparation of 4-phenylpiperidines. Two routes to the necessary γ-cyano-β-phenylbutyric esters have been investigated. An example of each of these routes is illustrated in the accompanying formulas, and both examples are described in the experimental part of the present paper.

$$C_6H_5CH{=}CHCOOC_2H_5 + CH_2(CN)COOC_2H_5 \longrightarrow$$

$$C_6H_5CH(CH_2COOC_2H_5)CH(CN)COOC_2H_5 \longrightarrow$$

I

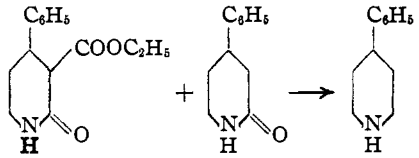


II III

$$C_6H_5CH{=}CHCN + CH_2(COO_2H_5)_2 \longrightarrow$$

$$C_6H_5CH(CH_2CN)CH(COOC_2H_5)_2 \longrightarrow$$

IV



V VI

Experimental

Ethyl 6-Keto-4-phenylnipecotate, II.—The ester I was prepared in 85% yield in one-mole runs, essentially according to the method of Desai[2]; it boiled at 172–175° at 2 mm. It was reduced in an equal weight of alcohol at 140°, using Raney nickel and hydrogen at 2000 lb.; reduction was usually complete after forty-five minutes. The product separated from a mixture of benzene and ligroin in the form of colorless needles, m. p. 91–94°; yield, 67%. A small content of impurity (stereoisomer?) could be removed only by dissolving the substance in warm concentrated sulfuric acid and then reprecipitating it with water; this treatment caused the compound to lose almost no weight, but the recovered substance (II) melted sharply at 102–103°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9. Found: C, 68.0; H, 7.1.

The ester was hydrolyzed within one minute when it was boiled with 5% aqueous sodium hydroxide. The resulting **6-keto-4-phenylnipecotic acid** separated from water in the form of colorless needles that fell to a white powder when they were dried at 130°; m. p. 214–215°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.8; H, 5.9. Found: C, 66.0; H, 5.9.

4-Phenylnipecotic Acid, III.—A solution of 20 g. of ethyl 6-keto-4-phenylnipecotate in 200 ml. of dry butyl alcohol was reduced with 20 g. of sodium. Then 150 ml. of water was added, and the resulting layers were separated. The aqueous layer contained 2.5 g. of organic material, from which no pure substance could be isolated. The butyl alcohol layer was brought to *p*H 4 with concd. hydrochloric acid (12 ml.) and then distilled with steam. The aqueous solution remaining was distilled to a volume of 25 ml. and cooled, giving a crystalline deposit (6.8 g.) of the amino acid; it became brown at 270° and melted at 280–285° with decomposition. Since the free acid could not be recrystallized satisfactorily, it was analyzed as its hydrochloride, shining tan plates from dilute hydrochloric acid. The salt lost no weight at 130° in a vacuum; it became yellow at 150°, sintered at 250° and melted at 257–259° to a bubble-filled liquid.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: N, 5.8. Found: N (Dumas), 5.7.

When 4 g. of the amino acid hydrochloride was heated with 12 ml. of 40% formalin in a bath at 100° for forty-eight hours, it was converted into **1-methyl-4-phenylnipecotic acid hydrochloride.** The excess formaldehyde was removed by distilling the mixture to dryness twice with concd. hydrochloric acid, and the amino acid hydrochloride was crystallized from a mixture of alcohol and ether; it weighed 3.5 g. and formed colorless prisms; m. p. 219–222°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.0; H, 7.0. Found: C, 60.9; H, 7.0.

When the methylated amino acid hydrochloride was boiled with ethyl alcoholic hydrogen chloride for twenty-four hours, it was converted into **ethyl 1-methyl-4-phenylnipecotate hydrochloride,** fine white needles from a mixture of alcohol and ether, m. p. 171–173°.

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.5; H, 7.8. Found: C, 63.6; H, 8.0.

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(1) Koelsch, THIS JOURNAL, 65, 2093 (1943).

(2) Desai, *J. Chem. Soc.*, 1084 (1932).