ethanol proceeded smoothly. The reduction product of IIIa, β-hydroxy-β-(2-methoxy-5-hydroxyphenyl)-ethylmethylamine hydrochloride, III, was also isolated and purified with ease. The corresponding 2,5-dihydroxy derivative, expected from the reduction of IVa, could not be induced to crystallize. The solutions darkened rapidly and resulted in unmanageable tars. In the case of IIa, the product, β-hydroxy-β-(2,5-dihydroxyphenyl)-ethylamine hydrochloride crystallized without difficulty, but could not be obtained free of color although charcoaled repeatedly and crystallized under nitrogen.

2,5-Dihydroxyphenethylamine Hydrochloride (I).—Five grams of 2,5-dimethoxyphenethylamine was dissolved in 35 cc. of concentrated hydrochloric acid and heated at 170° for two hours in a glass bomb. The dark brown solution was evaporated to dryness *in vacuo* giving a dark gum that crystallized overnight. It was crystallized repeatedly from ethanol–ether mixtures with charcoaling, but could not be obtained in a colorless form although analytically pure.

Demethylation by the same procedure of β-(2,5-dimethoxyphenyl)-isopropylamine[5] gave colored material that could not be induced to crystallize. Samples received preliminary testing in solution.

Summary

1. The preparation of β-hydroxy-β-(2,5-dihydroxyphenyl)-ethylamine, of 2,5-dihydroxyphenethylamine and of β-hydroxy-β-(2-methoxy-5-hydroxyphenyl)-ethylmethylamine as their hydrochlorides is described.

2. As pressors these compounds are inferior to the corresponding 2,5-dimethoxy compounds.

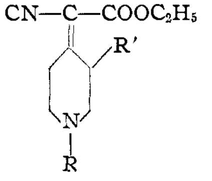
TUCKAHOE 7, NEW YORK RECEIVED JUNE 11, 1949

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

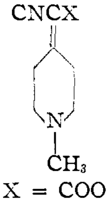
Piperidine Derivatives. XXII. The Condensation of 1-Methyl-4-piperidone with Active Methylene Compounds

BY S. M. MCELVAIN* AND ROBERT E. LYLE, JR.[1]

In paper XVI[2] of this series the Knoevenagel condensation of 1-benzyl-4-piperidone and 1-benzoyl-3-ethyl-4-piperidone with cyanoacetic ester to the corresponding piperidylidene compounds (I and II) in the presence of ammonium acetate[3] was reported. The piperidylidene derivative II was hydrogenated and then converted to *dl*-ethyl cincholoiponate. Later, 1-benzoyl-4-piperidone was similarly condensed with cyanoacetic ester.[4] The resulting compound (III) was found to add hydrogen cyanide readily, but with phenylmagnesium bromide there was obtained only a magnesium enolate, from which III was recovered.



I, R = $C_6H_5CH_2$, R′ = H
II, R = C_6H_5CO, R′ = C_2H_5
III, R = C_6H_5CO, R′ = H



IV, X = $COOC_2H_5$
V, X = CN
VI, X = C_6H_5

In extending these studies to 1-methyl-4-piperidone, it now has been found that this piperidone condenses readily (within one hour) with cyanoacetic ester in the presence of ammonium acetate to yield IV, which was isolated as the hydrochloride in 95% yield. The free base IV slowly polymerizes on standing to a solid, m. p. 234–235°, that shows the same analyses as IV. Malononitrile condenses quite rapidly (fifteen minutes) with the piperidone, and the hydrochloride of V was isolated in 98% yield. The free base V polymerizes immediately on liberation from its salt.

In contrast to the above nitriles, such active methylene compounds as diacetylmethane, acetoacetic ester and malonic ester undergo no condensation with 1-methyl-4-piperidone in the presence of ammonium acetate. From each of these attempted reactions the piperidone was recovered unchanged. These results show that at least one of the activating groups of an active methylene compound must be a cyano group if a condensation with the piperidone in the presence of ammonium acetate is to be successful.

Recently, Anker and Cook[5] described the condensation of this piperidone with phenylacetonitrile to VI in 52% yield in the presence of sodium methoxide; VI was reported to be a liquid, b. p. 150° (0.5 mm.). Repetition of this work in this Laboratory gave a 94% yield of the hydrochloride of VI. The free base (VI) could be readily purified by distillation after extraction from the reaction mixture. It boils at 144–148° (0.4 mm.) together with a small amount of phenylacetamide resulting from the hydration of the nitrile by the water formed in the condensation. After separation of the amide (ether insolubility), VI was obtained as a crystalline solid, m. p. 55–56.5°.

In view of these results the sodium methoxide-catalyzed condensation of the piperidone with those active methylene compounds that had failed to react in the presence of ammonium acetate was attempted. In no case could a simple piperidylidene compound be obtained; usually a complex mixture of products resulted, but with

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* Editorial Board 1946-.

[1] Wisconsin Alumni Research Foundation Research Assistant, 1948-1949.

[2] Stork and McElvain, THIS JOURNAL, 68, 1053 (1946).

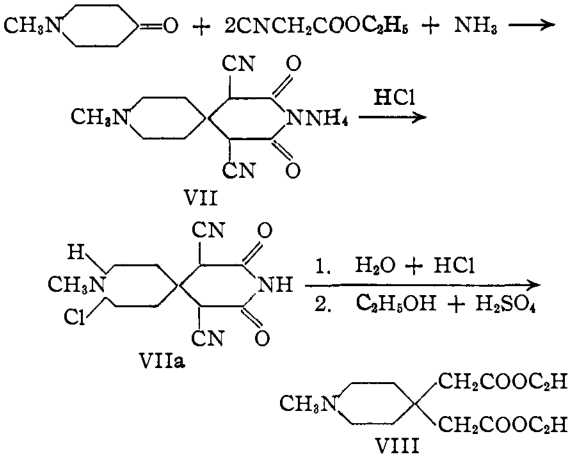
[3] Cope, *et al.*, *ibid.*, 63, 3452 (1941).

[4] McElvain and McMahon, *ibid.*, 71, 901 (1949).

[5] Anker and Cook, *J. Chem. Soc.*, 806 (1948).

malonic ester approximately 60% of the unreacted piperidone was recovered from the reaction.

1-Methyl-4-piperidone readily undergoes the Guareschi reaction[6] with an alcoholic ammonia solution to give the imide salt (VII). Acidification converted VII to the hydrochloride (VIIa), which was separated in 70% yield. Hydrolysis and decarboxylation, followed by esterification converted VIIa to the 4,4-disubstituted piperidine (VIII) in 65% yield.

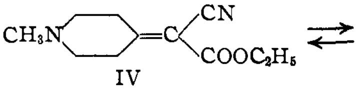


VII

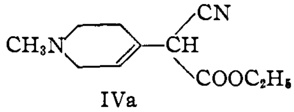
VIIa

VIII

The reactions of the piperidylidene-cyanoacetic ester indicate that it is a mixture of the two forms,[7] IV and IVa, in a very mobile equilibrium. The molar refraction of the compound shows an exaltation of 1.8 units similar to that noted for alkylidene and cyclohexylidene cyanoacetic esters[7d]; however, its rapid reaction with bromine and potassium permanganate (*cf.* ref. 7b) indicates the presence of some of IVa and the rapid shift in its direction of the equilibrium



IV



IVa

In contrast to the 1-benzoyl derivative III, the 1-methyl derivative (IV) does not add either hydrogen cyanide or sodium cyanide in aqueous solution. When treated with the latter reagent, it dissolves *via* IVa and may be recovered after acidification. Similar to III the compound reacts with phenylmagnesium bromide as IVa to precipitate a crystalline enolate, from which 79% of the starting product may be recovered. With methylmagnesium iodide IVa reacts to give an 88% yield of methane.[8]

The picrate derivative prepared from the hydrochloride of IV melts at 163–164° while the picrate prepared from a distilled sample of the free base melts at 150–152°, at which point it remains unchanged after numerous recrystallizations. However, the picrate prepared directly from the free base obtained by neutralization of the magnesium enolate (reaction of IV with phenylmagnesium bromide) melts at 168–170°. A mixture of the two higher melting picrates melts at 150–152°. Treatment of IV with sodium hydride, followed by neutralization, yields a product, the picrate of which also melts at 168–170°. The molar refractions of both products immediately after recovery from treatment with these alkaline reagents show no exaltation, but on standing the refractive index rises to a constant value which is characteristic of the equilibrium mixture of IV and IVa. These results indicate that the picrate, m. p. 163–164°, is derived from IV while the one melting at 168–170° is derived from IVa and that the picrate, m. p. 150–152°, is an unresolvable mixture, or possibly a molecular complex, of the two higher melting picrates.

The hydrolysis and decarboxylation of IV and the esterification of the resulting acid yields an amino-ester which appears to have the structure IX. It shows no exaltation of the molar refraction. It reacts with phenylmagnesium bro-

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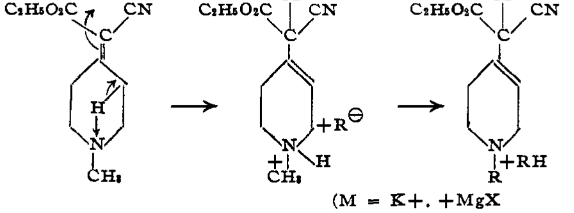
(6) Guareschi, *Atti. accad. sci. Torino*, **34**, 928 (1899); Farmer and Ross, *J. Chem. Soc.*, **127**, 2358 (1925).

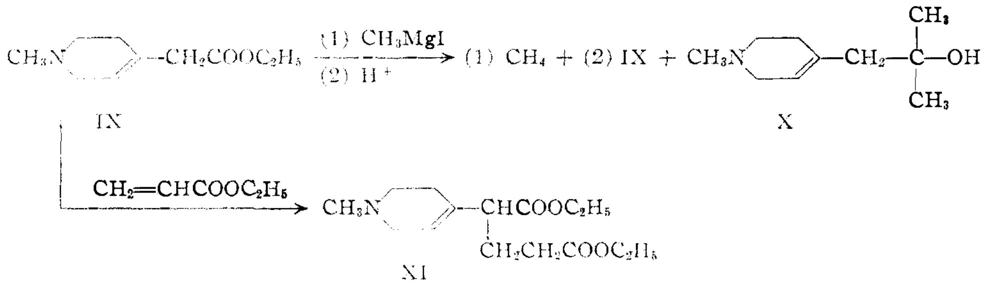
(7) There has been a considerable discussion in the literature of the structure of the analog of IV, cyclohexylidene-cyanoacetic ester. (a) Harding, Haworth and Perkin (*J. Chem. Soc.*, **93**, 1943 (1908)) assigned to it the β,γ-unsaturated structure (corresponding to IVa) because of its α-methylation with sodium and methyl iodide and its hydrolysis to Δ^1-cyclohexenylacetic acid. (b) Lapworth and McRae (*ibid.*, **121**, 2748 (1922)) preferred the α,β-unsaturated structure (corresponding to IV) because of the failure of the compound to react with bromine or potassium permanganate, its facile addition of sodium cyanide and sodium hydrosulfide, and its ozonolysis to cyclohexanone. They explained the results in (a) on the basis of an equilibrium of the two forms, with the α,β-form being more stabile. (c) Birch, Kon and Norris (*ibid.*, 1361 (1923)) added more support for the α,β-unsaturated structure by showing that the compound undergoes the Guareschi reaction with cyanoacetic ester. (d) Cope (THIS JOURNAL, **59**, 2327 (1937)) found an exaltation of 1.7 units in the molar refraction of ethyl cyclohexylidenecyanoacetate as further support of the α,β-structure. This exaltation corresponds to that shown by certain alkylidene cyanoacetates (Cowen and Vogel, *J. Chem. Soc.*, 1528 (1940)). (e) Birch and Robinson (*ibid.*, 501 (1943)) in further confirmation of the α,β-structure found that this compound reacted with methylmagnesium iodide to give a 45% yield of ethyl 1-methylcyclohexylcyanoacetate.

(8) This result prompted a repetition of the reaction of methylmagnesium iodide with ethyl cyclohexylidenecyanoacetate.[7e] Only a 10% yield of methane was obtained and the reaction product, separated in 90% yield, was mainly that reported by Birch and Robinson.[7e] These results indicate that the heterocyclic structure of IV plays a decisive role in promoting the facile rearrangement to isomeric structure IVa.

A referee has suggested the following explanation of the role of the nitrogen in IV in promoting the enolization



(M = K^{+}, $^{+}\mathrm{MgX}$
R = $\mathrm{CN}^{\ominus}$, $\mathrm{C_6H_5}^{\ominus}$, $\mathrm{CH_3}^{\ominus}$)



mide, as does IV, to give a magnesium enolate, from which IX may be recovered after neutralization. With methylmagnesium iodide IX gives a 68% yield of methane and a product, the analyses of which indicate it to be a mixture of IX and the carbinol (X). The structure of IX and the activity of its α-hydrogen is most strikingly demonstrated by its addition to ethyl acrylate under the conditions of the Michael reaction to yield the tetrahydropyridyl-substituted glutaric ester (XI) in 69% yield.

The lability of the α-hydrogen of IX indicates that the β,γ-unsaturation of this ester is an effective activating group. It is, therefore, quite understandable why the cyanoacetic ester derivative reacts so rapidly and completely with basic reagents in the form IVa, in which the α-hydrogen is labilized by three activating groups: cyano, carbethoxy and the substituted-vinyl structure.

Experimental

1-Methyl-4-piperidone and Its Self-Condensation.—The distillation of this piperidone after its liberation from the hydrochloride resulting from the decarbethoxylation of 1-methyl-3-carbethoxy-4-piperidone in 20% hydrochloric acid[9] generally gives only 65-80% yields of product, b. p. 58-60° (13 mm.). The remainder of the material is a forerun, b. p. 28-30° (13 mm.), and a higher boiling residue representing about 10% and 10-20%, respectively, of the theoretical yield of the piperidone. The forerun is an azeotrope consisting of about one-third water and two-thirds piperidone from which the former may be separated by azeotropic distillation with benzene.

The higher boiling residues from several runs were combined and distilled. Approximately 50% of this material boiled without decomposition at 125-130° (0.4 mm.); $n^{25}\text{D}$ 1.5111. The remaining material underwent decomposition, as evidenced by the pressure increase within the system, when further distillation was attempted. Molecular weight determinations (cryoscopic in benzene) on the distillate averaged 207; this value and analyses (Found: C, 67.54; H, 10.07) indicate this material to be a mixture of two parts of 1-methyl-3-(1-methyl-4-piperidylidene)-4-piperidone (mol. wt. 208; calcd. for $C_{12}H_{20}N_2O$: C, 69.18, H, 9.68) and one part of 1-methyl-3-(1-methyl-4-hydroxy-4-piperidyl)-4-piperidone (mol. wt. 226; calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80).

The self-condensation of the piperidone that forms these products and the non-distillable associated material was found to occur in the saturated hydrochloric acid solution of the piperidone hydrochloride during its evaporation after the decarbethoxylation of the 3-carbethoxy-piperidone, and may be minimized by distilling this acid solution as rapidly as possible under diminished pressure. For example, when a saturated solution of the piperidone hydrochloride was allowed to stand for several days in a 20% hydrochloric acid solution, 60% of the piperidone remained as higher boiling residue after the piperidone was liberated from its salt and distilled. In contrast to this behavior, a 5.61-g. sample of 1-methyl-4-piperidone, after standing for four months at room temperature, yielded 4.86 g. (87%) of the piperidone on distillation, indicating that the free base shows no appreciable tendency to undergo self-condensation.

Ethyl (1-Methyl-4-piperidylidene)-cyanoacetate (IV) Hydrochloride.—A mixture of 11 g. of 1-methyl-4-piperidone (0.1 mole), 17 g. of ethyl cyanoacetate (0.15 mole), 1.6 g. of ammonium acetate, 4.6 g. of acetic acid and 50 ml. of benzene was heated at reflux in an apparatus described by Cope, *et al.*[3] After about one hour no more water appeared with the benzene; any further heating of the reaction mixture promoted the formation of colored decomposition products. The benzene solution was cooled and 100 ml. of dry ether added. The ether-benzene solution was decanted from the ammonium acetate that separated and was treated with hydrogen chloride until the precipitation of the hydrochloride was complete. This product was filtered by suction, washed several times with ether and the excess hydrogen chloride removed in a vacuum desiccator over sodium hydroxide. A yield of 23 g. (96%) of the hydrochloride, m. p. 172-176° (dec.), was obtained. Recrystallization from absolute alcohol gave a white product melting at 176-177° (dec.).

Anal. Calcd. for $C_{11}H_{17}ClN_2O_2$: C, 53.98; H, 7.00; Cl, 14.5; N, 11.5; OC_2H_5, 18.4. Found: C, 53.43; H, 7.48; Cl, 14.4; N, 11.2; OC_2H_5, 17.7.

A picrate of IV was prepared by treating an alcoholic solution of the hydrochloride with a saturated solution of picric acid in alcohol. Recrystallization of the precipitated picrate from alcohol gave a product melting at 163-164°.

Anal. Calcd. for $C_{17}H_{19}N_5O_9$: C, 46.68; H, 4.38. Found: C, 46.45; H, 4.44.

Ethyl (1-methyl-4-piperidylidene)-cyanoacetate (IV) was prepared by evaporation of the benzene from the original reaction mixture, neutralization of the acetic acid with sodium bicarbonate and extraction of the semi-solid material with five 100-ml. portions of ether. After drying the ether solution for twenty-four hours over Drierite, the ether was removed by distillation and the residual oil distilled under reduced pressure to give 8.5 g. (41%) of a light yellow oil, b. p. 108-110° (0.4 mm.), $n^{25}\text{D}$ 1.4960, d^{25}_4 1.0602.

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; OC_2H_5, 21.6; *M*D 55.6. Found: C, 63.61; H, 7.90; OC_2H_5, 22.2; *M*D 57.4.

A picrate prepared from this oil melted at 150-152°; this m. p. remained unchanged after three recrystallizations from alcohol. A mixture of equal amounts of the picrate, m. p. 163-164° (see above) and the picrate, m. p. 169-170.5° (see below), also melted at 150-152° and did not depress the m. p. of the picrate prepared from IV.

After standing for several weeks the amino ester IV solidified. This solid, after washing with ether and hot alcohol, was a light yellow material, m. p. 234-235.5°. Analyses (Found: C, 63.63; H, 7.42) indicated this product to be a polymer of IV.

(1-Methyl-4-piperidylidene)-malononitrile (V) Hydrochloride.—The procedure for the preparation of the hydrochloride of IV was followed using 16.9 g. of 1-methyl-

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[9] McElvain and Rorig, This Journal, **70**, 1820 (1948).

4-piperidone, 9.9 g. of malononitrile, 3 g. of ammonium acetate and 6.9 g. of acetic acid in 50 ml. of benzene. All the water produced by the condensation separated in fifteen minutes; precipitation with hydrogen chloride yielded 27.6 g. (98%) of the hydrochloride of V, m. p. 180–183° (dec.). Recrystallization from alcohol–ether gave a light yellow solid which melted with decomposition at 182–183°.

Anal. Calcd. for $C_9H_{12}ClN_3$: Cl, 18.0; N, 21.3. Found: Cl, 18.5; N, 21.4.

Attempted Condensation of 1-Methyl-4-piperidone with Diacetylmethane, Malonic Ester or Acetoacetic Ester.—Using the procedure for the preparation of ethyl (1-methyl-4-piperidylidene)-cyanoacetate hydrochloride the condensation of the piperidone with each of these active methylene compounds was attempted. A mixture of 5.65 g. (0.005 mole) of 1-methyl-4-piperidone, 0.05 mole of the active methylene compound, 0.8 g. of ammonium acetate, 2.6 g. of acetic acid and 30 ml. of benzene was refluxed until no more water[10] separated from the benzene. Precipitation with hydrogen chloride in each case gave a quantitative recovery of 1-methyl-4-piperidone hydrochloride hydrate, m. p. 90–92°; lit.,[11] m. p. 94–95°.

(1-Methyl-4-piperidylidene)-phenylacetonitrile (VI) Hydrochloride.—To a solution of sodium ethoxide, prepared by dissolving 2 g. of sodium in 60 ml. of absolute alcohol, were added 10 g. of benzyl cyanide (0.088 mole) and 5 g. (0.044 mole) of 1-methyl-4-piperidone. The mixture was refluxed for one hour, cooled and poured into 300 ml. of ice-water. The water was acidified with hydrochloric acid and extracted with three 250-ml. portions of ether to remove the excess benzyl cyanide. The acid solution then was neutralized with solid sodium carbonate; the oil that separated was taken up in ether and the aqueous solution extracted with three 200-ml. portions of ether. After drying the combined ether extracts over Drierite, the dissolved amine was precipitated with hydrogen chloride. A yield of 10.36 g. (94%) of the hydrochloride of VI in the form of a mixture of solid and oil was obtained. The oil portion crystallized after further drying by mixing with benzene and distilling the latter from it. Recrystallization from absolute alcohol gave a white solid that melted at 202–204°; Anker and Cook[5] report this compound to melt at 203°.

(1-Methyl-4-piperidylidene)-phenylacetonitrile (VI) was obtained by distilling the dried ether solution instead of precipitating the hydrochloride as described above. The product distilled at 144–148° (0.4 mm.) and condensed to a mixture of an oil and solid. The oil dissolved readily in ether leaving the insoluble solid, which was found to be phenylacetamide, m. p. 157–158°. Evaporation of the ether left VI as a solid, which on recrystallization from petroleum ether (b. p. 60–80°) melted at 56–57.5°. Anker and Cook[5] obtained this free base as an oil, for which no properties were reported.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60. Found: C, 79.12; H, 7.68.

Attempted Condensation of 1-Methyl-4-piperidone with Diacetylmethane and Malonic Ester in the Presence of Sodium Ethoxide.—Following the above procedure for the preparation of VI, 2 g. of sodium was dissolved in 50 ml. of absolute alcohol. To this solution was added 10 g. of diacetylmethane and 5.6 g. of the piperidone. Precipitation of the hydrochloride after the reaction gave 8 g. of a mixture of 1-methyl-4-piperidone hydrochloride mixed with some other hydrochlorides. From this mixture a small amount of the hydrochloride of the hydrate of the piperidone,[10] m. p. 90–92°, could be isolated pure but the remainder of the mixture could not be resolved into its components.

Following the above procedure 4.6 g. of sodium was dissolved in 120 ml. of absolute ethanol and a mixture of 32 g. of malonic ester and 11.3 g. of the piperidone added. After reaction, the ether solution of the basic reaction products was distilled to give 4 g. of the piperidone and 3 g. of a fraction boiling at 116–117° (0.5 mm.); $n^{25}D$ 1.5018. The analyses of the latter fraction did not correspond to those calculated for diethyl (1-methyl-4-piperidylidene)-malonate ($C_{13}H_{21}NO_4$), but instead indicated the reaction product to have the molecular formula $C_{10}H_{17}NO_2$. No further effort was made to identify this product.

1,5-Dicyano-9-methyl-3,9-diazaspiro[5.5]hendecane-2,4-dione Hydrochloride (VIIa).—To 40 ml. of absolute alcohol saturated with ammonia was added 5.6 g. of 1-methyl-4-piperidone and 11.3 g. of ethyl cyanoacetate. After standing in a refrigerator for three days, the imide ammonium salt (VII) had separated from the solution and was removed by filtration; it melted at 270–273°. This material was dissolved in a minimum of water and dilute hydrochloric acid added until the solution was acidic to litmus; 9.8 g. (70%) of the hydrochloride (VIIa) precipitated. Recrystallization of this salt from dilute hydrochloric acid gave a product, m. p. 224–226° (dec.).

Anal. Calcd. for $C_{12}H_{15}ClN_4O_2$: C, 50.97; H, 5.35; Cl, 12.6. Found: C, 50.90; H, 5.62; Cl, 12.4.

1,5-Dicyano-9-methyl-3,9-diazaspiro[5.5]hendecane-2,4-dione.—An aqueous solution of the hydrochloride (VIIa) when neutralized with sodium bicarbonate deposited this free base as a finely divided solid, m. p. 268–269° (dec.). Neutralization with sodium carbonate gave no precipitate of the imide as the acidity of the imido group caused the compound to dissolve in this base.

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: N, 22.7. Found: N, 22.3.

1-Methyl-4,4-dicarbethoxymethylpiperidine (VIII).—A solution of 5 g. of the ammonium salt (VII) in a mixture of 7 ml. of concentrated sulfuric acid and 6 ml. of water was refluxed for one hour, after which the solution was diluted with 8 ml. of water and the refluxing continued for an additional five hours. The solution then was neutralized, acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. To ensure complete dryness, benzene was added to and distilled from the solid. A mixture of 8 ml. of concentrated sulfuric acid and 70 ml. of absolute alcohol was added to this dried solid residue and the resulting solution refluxed for ten hours. The sulfuric acid was neutralized with moist sodium bicarbonate and then 5 g. of anhydrous potassium carbonate was added to remove the water from the alcohol. The alcoholic solution of the amine (VIII) was diluted with 75 ml. of ether, and the insoluble inorganic salt separated and extracted with five 100-ml. portions of ether. After drying the combined ether extracts for twenty hours over Drierite, the ether was removed and the residual oil distilled under reduced pressure to give 3.2 g. (65%) of VIII, b. p. 121–122° (0.4 mm.), $n^{25}D$ 1.4627, d^{25}_4 1.0389.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.50; OC_2H_5, 33.2; *M*D 71.9. Found: C, 62.52; H, 9.52; OC_2H_5, 32.8; *M*D 71.9.

The hydrochloride of VIII was obtained by adding the base to a saturated solution of hydrogen chloride in ether. Recrystallization of the precipitated salt from an alcohol-ether mixture gave a white solid, m. p. 149–150°.

Anal. Calcd. for $C_{14}H_{26}ClNO_4$: Cl, 11.6. Found: Cl, 12.0.

Reaction of Ethyl (1-Methyl-4-piperidylidene)-cyanoacetate (IV) with Phenylmagnesium Bromide.—A solution of 6 g. (0.03 mole) of IV in 50 ml. of absolute ether was placed in a 200-ml. 3-necked flask fitted with condenser, mercury-sealed stirrer and dropping funnel. The system was filled with nitrogen and then 0.042 mole of phenylmagnesium bromide in 60 ml. of ether added slowly. An immediate precipitate formed which remained crystalline during the hour in which the Grignard reagent was added. The resulting mixture was refluxed gently for thirty minutes in an oil-bath, cooled and acidified with dilute hydrochloric acid. The ether layer was separated and the water layer made basic with sodium bicarbonate, after which 5 g. of anhydrous potassium carbonate was

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[10] A small amount of water is always formed in these reactions by the dehydration of ammonium acetate to acetamide.

[11] Craig and Tarbell, THIS JOURNAL, 71, 465 (1949).

added to salt out the amine. The solution was extracted with five 75-ml. portions of ether and the combined ether extracts dried over Drierite. The ether solution then was fractionated; after the ether had distilled, 3.3 g. (100%) of benzene was collected. The residue was distilled to give 4.5 g. (77%) of an oil, b. p. 103–105° (0.3 mm.); n^{25}_D 1.4650; d^{25}_4 1.0339; M_D 55.7 (calcd. 55.6). A picrate of this oil was prepared immediately; after recrystallization from alcohol it melted at 169–170.5° and gave the same analyses as the picrate, m. p. 163–164°, prepared from the hydrochloride of IV.

Anal. Calcd. for $C_{17}H_{19}N_5O_9$: C, 46.68; H, 4.38. Found: C, 46.51; H, 4.93.

These data indicate that the amine recovered from this reaction is **ethyl [1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-cyanoacetate (IVa)**.

Reaction of Ethyl (1-Methyl-4-piperidylidene)-cyanoacetate (IV) with Methylmagnesium Iodide.—The reaction was carried out in a 200-ml. 3-necked flask fitted with a dropping funnel, a mercury-sealed stirrer and a reflux condenser, the top of which was connected through a Dry Ice-trap to a 125-ml. separatory funnel in which gas samples could be collected. The stem of the separatory funnel was connected through a calcium chloride tube to an inverted liter graduate filled with water, the displacement of which measured the volume of gas produced by the reaction. The 3-necked flask was carefully dried by heating and cooling while being flushed with nitrogen. Into this flask was introduced 5.85 g. (0.028 mole) of IV dissolved in 30 ml. of dry di-*n*-butyl ether. A solution of 0.04 mole of methylmagnesium iodide in 35 ml. of this ether was placed in the dropping funnel and the system allowed to reach a pressure equilibrium. The Grignard solution was added slowly over a period of one hour, during which time 615 ml. (88% after reduction to standard conditions) of methane was evolved. The reaction was heated for thirty minutes on a steam-bath and allowed to cool after disconnecting the gas collection train. The reaction mixture then was centrifuged, the supernatant ether layer discarded, and the solid enolate washed twice with 50-ml. portions of diethyl ether. The enolate was dried under vacuum and analyzed.

Anal. Calcd. for $C_{11}H_{15}IN_2O_2Mg$: I, 35.5. Found: I, 35.0.

The solid enolate then was decomposed with dilute hydrochloric acid and the solution made basic with sodium bicarbonate, after which excess sodium carbonate was added to salt out the amine. The basic solution was extracted with ten 50-ml. portions of ether and the combined ether extracts dried over anhydrous sodium sulfate. Vacuum distillation of the material remaining after evaporation of the ether gave 3.85 g. (66%) of an oil, b. p. 108–111° (0.3 mm.), n^{25}_D 1.4883. The picrate, m. p. 152–154°, prepared from this oil showed no depression of melting point when mixed with the picrate prepared from a distilled sample of IV.

The gas collected in the separatory funnel as it was evolved from this reaction had a carbon-hydrogen ratio of 2.89 (calcd. for CH_4: 2.98).

The results of this and the preceding Grignard reaction indicate that ethyl (1-methyl-4-piperidylidene)-cyanoacetate (IV) is quantitatively converted by these basic reagents to the magnesium enolate of IVa and the hydrocarbon corresponding to the Grignard reagent.

Ethyl (1-Methyl-4-piperidylidene)-cyanoacetate (IV) with Potassium Cyanide and Hydrogen Cyanide.—(a) To a solution of 6 g. (0.1 mole) of potassium cyanide in 25 ml. water was added 5 g. (0.02 mole) of the hydrochloride of IV. The solution was allowed to stand twenty minutes and then acidified with acetic acid. After standing twelve hours in the refrigerator the solution was neutralized with sodium bicarbonate and extracted with ether. Treatment of the dried ether solution with hydrogen chloride gave 3.5 g. (70%) of the hydrochloride of IV, m. p. 170–173° (dec.).

(b) The hydrochloride of IV (5 g.) was added to 25 ml. of a saturated solution of potassium cyanide in water, and after standing twelve hours in the refrigerator, the solution was acidified with acetic acid. After neutralization with sodium bicarbonate, the solution was extracted with ether and the ether solution dried. Treatment of the ether extract with hydrogen chloride gave no precipitate.

Attempted Condensation of the Enolate of Malonic Ester with IV.—(a) An alcoholic solution of 0.04 mole of sodium ethoxide was prepared by the reaction of 1 g. of sodium with 50 ml. of absolute ethanol. To this solution was added a mixture of 3.5 g. of malonic ester and 5 g. (0.02 mole) of the hydrochloride of IV dissolved in 40 ml. of absolute alcohol. After standing thirty-five hours the alcohol solution was neutralized with 2.6 g. of acetic acid and the alcohol removed by distillation under reduced pressure. The residue was triturated with absolute ether; distillation of the ether solution gave 1.50 g. of malonic ester, b. p. 50–54° (0.8 mm.), and 2.01 g. (48%) of IV, b. p. 110–115° (0.6 mm.); n^{45}_D 1.4951.

(b) A catalytic amount (5 mole %) of sodium hydride was completely dissolved in 6.4 g. (0.04 mole) of malonic ester, and then 6.25 g. (0.03 mole) of IV added. The mixture was warmed for eight hours on a steam-bath and then distilled under reduced pressure to give 5.94 g. (93%) of malonic ester, b. p. 54–56° (0.8 mm.) and 4.03 g. (65%) of ethyl [1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-cyanoacetate (IVa), b. p. 105–108° (0.5 mm.); n^{25}_D 1.4656. The picrate derivative of the latter, after three recrystallizations from alcohol, melted 169–171° and was identical with the one obtained from the product of the reaction of IV with phenylmagnesium bromide.

The Reaction of Ethyl Cyclohexylidenecyanoacetate with Methylmagnesium Iodide.—In the apparatus described for the reaction of IV with methylmagnesium iodide was placed 9.6 g. (0.05 mole) of ethyl cyclohexylidenecyanoacetate dissolved in 20 ml. of di-*n*-butyl ether. A solution of 0.06 mole of methylmagnesium iodide in 60 ml. of di-*n*-butyl ether was added over a period of one-half hour while the reaction was cooled in an ice-bath. Only 10% of the theoretical yield of methane was collected during this addition. A precipitate formed immediately but dissolved when the reaction mixture was heated to 100°. After heating for fifteen minutes, the reaction was cooled and the precipitate reappeared. The precipitate was decomposed with 60 ml. of dilute hydrochloric acid, the ether layer was separated and the water layer extracted with two 50-ml. portions of diethyl ether. The ether was evaporated under vacuum and the residue treated for one hour with a solution of 10 g. of potassium cyanide in 15 ml. of water. The undissolved material was extracted with two 100-ml. portions of ether; after drying the ether solution, it was distilled to give 8.7 g. of material, b. p. 152–154° (12 mm.); n^{25}_D 1.4650; d^{25}_4 1.0159. Although this material gave a slight test for unsaturation, analyses of the product indicated that it was largely ethyl (1-methylcyclohexyl)-cyanoacetate.

Anal. Calcd. for $C_{12}H_{19}NO_2$: N, 6.69; OC_2H_5, 21.5; M_D 56.8. Found: N, 7.07; OC_2H_5, 21.9; M_D 57.0.

The results of this reaction indicate that methylmagnesium iodide reacts by 1,4-addition with ethyl cyclohexylidenecyanoacetate as reported by Birch and Robinson.[7e]

Ethyl [1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]-acetate (IX).—A solution of 5 g. of ethyl (1-methyl-4-piperidylidene)-cyanoacetate (IV) hydrochloride in 20 ml. of concentrated hydrochloric acid was refluxed for twelve hours. The resulting solution then was evaporated to dryness under diminished pressure on a steam-bath. The remaining solid mixture was dissolved in water, treated with potassium hydroxide until basic to litmus, and the basic solution evaporated to dryness under diminished pressure. The solid was dissolved in water, made acidic with hydrochloric acid and again evaporated to dryness. The residue was extracted with absolute alcohol and, after removal of the potassium chloride, the **hydrochloride of [1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-acetic acid** was precipitated as a crystalline solid, melting at 225–227° (dec.), by the addition of ether.

Anal. Calcd. for $C_8H_{14}ClNO_2$: Cl, 18.7; N, 7.4. Found: Cl, 19.1; N, 8.5.

In the preparation of IX this amino-acid salt need not be isolated. The solid remaining after the first evaporation of the hydrochloric acid was dissolved in a solution of 4 ml. of concentrated sulfuric acid in 30 ml. of absolute alcohol and the alcoholic solution refluxed for twenty-four hours. The sulfuric acid in the solution then was neutralized with sodium bicarbonate, and the precipitated sodium sulfate was washed with ether. After drying the combined alcohol and ether solution over Drierite, the solvents were evaporated and the remaining oil distilled at reduced pressure to give 2.3 g. (62%) of IX, b. p. 105–110° (11 mm.), n^{25}_D 1.4643, d^{25}_4 0.9857.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.83; OC_2H_5, 24.5; M_D 51.3. Found: C, 64.85; H, 9.48; N, 7.95; OC_2H_5, 24.7; M_D 51.4.

The ester IX was prepared also from (1-methyl-4-piperidylidene)-malononitrile (V) hydrochloride by the procedure described above. In this case the intermediate amino acid was dissolved in 60 ml. of absolute ethanol saturated with hydrogen chloride and allowed to stand for two days to accomplish esterification. From 10 g. of the dinitrile salt 6.1 g. (66%) of IX was obtained. Treatment of the amino ester IX with methyl iodide yielded a methiodide, which, after recrystallization from ethanol, melted at 134–135°.

Anal. Calcd. for $C_{11}H_{20}INO_2$: C, 40.62; H, 6.30. Found: C, 40.70; H, 6.76.

Reaction of IX with Grignard Reagents. (a) **Phenylmagnesium Bromide.**—A solution of 3.5 g. (0.02 mole) of IX in 100 ml. of absolute ether was placed in a 500-ml. 3-necked flask fitted with stirrer, dropping funnel and condenser. The system was filled with nitrogen and then 0.02 mole of phenylmagnesium bromide dissolved in 100 ml. of ether was added slowly from the dropping funnel. After addition of the Grignard reagent the reaction mixture was heated at reflux for two hours. The enolate was filtered off and the filtrate distilled to give 1.01 g. (29%) of IX, b. p. 110–115° (10 mm.); m. p. of methiodide 134–136°. The enolate was decomposed with dilute hydrochloric acid and the solution was neutralized with sodium bicarbonate. Extraction with ether and distillation of the dried ether solution gave 1.04 g. (30%) of IX, b. p. 65–70° (0.5 mm.), m. p. of methiodide 133–135°.

(b) **Methylmagnesium Iodide.**—In the 3-necked flask of the apparatus described for the reaction of IV with methylmagnesium iodide was placed 0.1 mole of methylmagnesium iodide dissolved in 100 ml. of di-*n*-butyl ether. To this solution was added slowly 7.5 g. (0.047 mole) of IX in 30 ml. of di-*n*-butyl ether; after the addition was complete, 785 ml. (68%) of methane had been collected. Heating the reaction mixture at 100° for one-half hour gave no further evolution of methane.

The enolate formed in the reaction was partially decomposed with saturated ammonium chloride solution, then made acidic with dilute hydrochloric acid, and finally neutralized with sodium bicarbonate. The solution was extracted with ten 75-ml. portions of ether; distillation of the combined and dried ether extracts gave 5.64 g. of a product, b. p. 88–90° (1 mm.), n^{25}_D 1.4813. The difficulty in crystallizing the methiodide of this material indicated it to be a mixture. Subsequent distillations failed to resolve the mixture but analyses showed that the components were probably 2-methyl-3-[1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-propanol-2 (X) and IX.

Anal. Calcd. for $C_{10}H_{18}NO$ (X): C, 70.94; H, 10.31. Calcd. for $C_{10}H_{17}NO_2$ (IX): C, 65.54; *H*, 9.35. Found: C, 69.23; H, 10.15.

The gas evolved during the reaction was shown to be methane by the carbon to hydrogen ratio (calcd. 2.98; found, 2.92).

Diethyl α-[1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]-glutarate (XI).—To 7.3 g. (0.04 mole) of IX in a distilling flask was added 5 mole % (0.05 g.) of sodium hydride and the system evacuated to remove the hydrogen. When all the sodium hydride had reacted, 4 g. (0.04 mole) of ethyl acrylate was added. After standing for three days the unreacted ethyl acrylate was removed under diminished pressure and the residual oil distilled. The first fraction recovered was 4.2 g. of unreacted IX, which was identified as the methiodide. The second fraction consisted of 3.3 g. of XI, b. p. 140–145° (0.4 mm.), n^{25}_D 1.4704, d^{25}_4 1.0414.

Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 63.57; H, 8.89; OC_2H_5, 31.8; M_D 76.1. Found: C, 63.36; H, 8.83; OC_2H_5, 31.7; M_D 76.2.

Summary

The condensation of 1-methyl-4-piperidone with cyanoacetic ester and malononitrile to the corresponding piperidylidene derivatives with ammonium acetate as a catalyst is described. It is shown that an active methylene group must be activated by at least one cyano group to undergo condensation with 1-methyl-4-piperidone with this catalyst.

The preparation of (1-methyl-4-piperidylidene)-phenylacetonitrile by the condensation of 1-methyl-4-piperidone with phenylacetonitrile in the presence of sodium ethoxide is described.

The reaction of cyanoacetic ester, 1-methyl-4-piperidone and ammonia in the Guareschi reaction and the conversion of the resulting imide to 1-methyl-4,4-dicarbethoxymethylpiperidine are described.

Ethyl (1-methyl-4-piperidylidene)-cyanoacetate (IV) reacts as its isomer, ethyl [1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-cyanoacetate (IVa), with Grignard reagents, sodium hydride, sodium ethoxide and alkali cyanides to yield metal enolates of this β,γ-unsaturated ester with no indication of any reaction as the α,β-unsaturated form (IV). Picrates of IV and IVa have been isolated.

The preparation of ethyl [1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-acetate (IX) from ethyl (1-methyl-4-piperidylidene)-cyanoacetate (IV) is described. The properties and reactions of the former compound indicate that the vinyl and carbethoxy groups of the β,γ-unsaturated structure, in which this ester exists, activates the α-methylene group sufficiently to cause enol formation with Grignard reagents or sodium hydride. The sodium enolate of IX condenses by the Michael reaction with ethyl acrylate to form diethyl α-[1-methyl-4-(1,2,5,6-tetrahydropyridyl)]-glutarate (XI).

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