had resolidified. Benzoic acid appeared as a sublimate on the cooler portions of the test-tube and a faint odor of benzoyl chloride was noticeable. After cooling, chloroform was added to the remaining solid to dissolve any benzoic acid and unchanged IX; the white solid remaining undissolved by this solvent was guvacine hydrochloride and it was substantially pure as obtained, m. p. 304–305° d. with previous darkening (previously reported melting points: 309–314° d.,[8] 312°,[11] 316° d.[12]). The product weighed 0.49 g. (84%) and decolorized aqueous permanganate immediately.

Anal. Calcd. for $C_6H_{10}O_2NCl$: Cl, 21.67. Found: Cl, 21.54.

The *p*-toluenesulfonyl derivative of guvacine, prepared according to Freudenberg,[12] melted at 166–167° (reported, 167–168°).

(11) Winterstein and Weinhagen, *Z. physiol. Chem.*, **104**, 48 (1918).

(12) Freudenberg, *Ber.*, **51**, 978 (1918).

Summary

The preparation of di-(β-carbethoxyethyl)-amine and tri-(β-carbethoxyethyl)-amine from ethyl acrylate and ammonia, and the conversion of both of these aminoesters, either singly or as a mixture, to N-benzoyl-di-(β-carbethoxyethyl)-amine are described.

1-Benzoyl-3-carbethoxy-4-piperidone is prepared in quantity by the Dieckmann cyclization of N-benzoyl-di-(β-carbethoxyethyl)-amine.

Catalytic reduction of this piperidone and the conversion of the resulting 1-benzoyl-3-carbethoxy-4-hydroxypiperidine to guvacine hydrochloride are described.

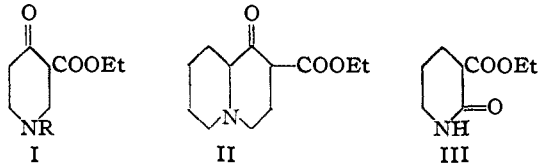
MADISON, WISCONSIN RECEIVED FEBRUARY 15, 1946

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

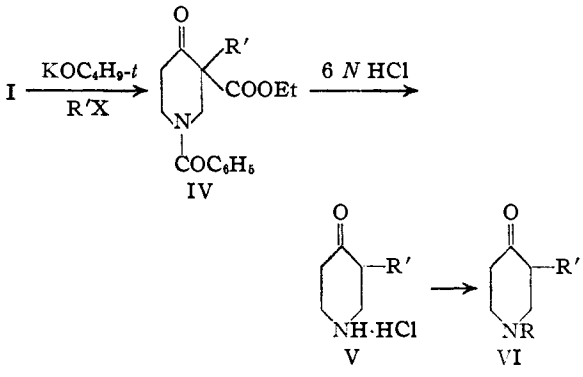
Piperidine Derivatives. XVI. C-Alkylation of 1-Benzoyl-3-carbethoxy-4-piperidone. Synthesis of Ethyl 3-Ethyl-4-piperidylacetate (*dl*-Ethyl Cincholoiponate)

BY GILBERT STORK AND S. M. MCELVAIN

The availability of 1-benzoyl-3-carbethoxy-4-piperidone[1] (I, R is benzoyl) suggested a study of the C-alkylation of its β-ketoester structure as a method of introducing a 3-substituent into the piperidine nucleus. It seemed that the non-basic character of this piperidone would permit C-alkylation at the 3-position without the involvement of the nuclear nitrogen, which was observed when the C-alkylation of 1-methyl-3-carbethoxy-4-piperidone (I, R is methyl) was attempted.[2] The only basic β-ketoester which appears to have been alkylated is ethyl 1-keto-octahydropyridocoline-2-carboxylate (II). Clemo and Metcalfe[3] were able to C-alkylate the potassio derivative of this compound at the 2-position with methyl iodide, but, for some unknown reason, the alkylation failed when ethyl iodide was used. Presumably, the hindered condition of the nitrogen of II prevented the formation of the quaternary salt, which was observed in the attempted C-alkylation of I (R is methyl).[2] The alkylation of the amide I (R is benzoyl) would correspond to the 3-alkylation of ethyl 2-ketonipecotate (III) recently reported by Koelsch.[4]



The alkylation of the potassio derivative of I (R is benzoyl) with ethyl iodide and benzyl chloride proceeded satisfactorily in refluxing *t*-butyl alcohol. Under these conditions about ten hours are required to produce the requisite amount of potassium halide and to convert I (R is benzoyl) to IV (R′ is ethyl or benzyl), which gives no coloration with ferric chloride. The 3-ethyl and 3-benzyl derivatives (IV) were obtained in 80% and 88% yields, respectively; each formed semicarbazones readily.



After various unsuccessful attempts to remove the carbethoxyl group of IV without the loss of the benzoyl group, these compounds were decarboxylated by means of 6 *N* hydrochloric acid. With this reagent, which simultaneously removed the benzoyl group, the theoretical amount of carbon dioxide was evolved and collected in about nine hours. The crystalline hydrochlorides of V (R′ is ethyl or benzyl) were isolated in 60–70% yields. These piperidones could be methylated or benzoylated to VI (R is methyl or benzoyl);

(1) See paper XV of this series, THIS JOURNAL, **68**, 1049 (1946).

(2) Thomas, Ph.D. Thesis, University of Wisconsin, 1932.

(3) Clemo and Metcalfe, *J. Chem. Soc.*, 1518 (1937).

(4) Koelsch, THIS JOURNAL, **65**, 2458 (1943).

however attempts to distil a piperidone corresponding to V were unsuccessful due to decomposition and polymerization of the free base.[5]

When the above alkylation procedure was applied to I, using either β-phenoxyethyl bromide or iodide as R'X, no evidence of alkylation was obtained. The formation of the expected amount of potassium halide was extremely slow, requiring about ninety hours in the case of the iodide and being only 70% complete in this length of time when the bromide was used. The product isolated at the point where IV should appear had an ethoxyl content (16.0%) approximating that (16.4%) of the starting piperidone (I, R is benzoyl) instead of that (11.4%) of the alkylated product IV. Furthermore, this reaction product did not form a semicarbazone, nor did it evolve carbon dioxide normally when heated with 6 *N* hydrochloric acid. The ethoxyl content indicated that this reaction product had formed from the self-condensation of the original piperidone (I) during the long period of heating; in fact, when I was heated in refluxing *t*-butyl alcohol for ninety hours a product with properties and ethoxyl content similar to that isolated from the attempted alkylation was obtained. The disappearance of the alkalinity of the reaction mixture and the formation of potassium halide during the attempted alkylation most likely was the result of a slow dehydrohalogenation of the β-phenoxyethyl halide by the potassio derivative of I to form potassium halide, vinyl phenyl ether,[6] and I, the latter of which underwent self-condensation to yield the product isolated.

When γ-phenoxypropyl bromide was used instead of the β-phenoxyethyl halides, 90% of the theoretical amount of potassium bromide was formed after sixty hours of reaction. An 87% yield of an alkylated product (IV, R' is γ-phenoxypropyl), as indicated by carbon, hydrogen and ethoxyl analyses, was obtained. However, this product showed peculiar and, as yet, unexplainable properties: it did not form a semicarbazone, and it did not decarboxylate under the conditions that the 3-ethyl- and 3-benzyl derivatives readily evolved carbon dioxide.[7]

A 3-alkyl-4-piperidone, such as VI, has a structure suitable for the introduction of a 4-substituent into the piperidine nucleus. In the present work the acetic acid residue was introduced through condensation with cyanoacetic ester. Since no piperidone has been used hitherto in the Knoevenagel reaction, a preliminary study of the behavior of 1-benzyl-4-piperidone (VI, R is benzyl, R' is H) was made. This piperidone and cyanoacetic ester, when heated in refluxing benzene for twelve hours in the absence of a catalyst, showed no sign of reaction. However, addition of a catalytic amount of piperidine brought about reaction, but the product formed was very difficult to purify. The use of ammonium acetate as a catalyst, as recommended by Cope and coworkers,[8] produced a more satisfactory product as well as a more rapid condensation, the requisite amount of water separating from the reaction in about four hours. The condensation product, ethyl (1-benzyl-4-piperidylidene)-cyanoacetate, was isolated as the water-insoluble, chloroform-soluble hydrochloride, m. p. 146–148°, in about 40% yield.

When this reaction was applied to 1-benzoyl-3-ethyl-4-piperidone (VIa) the condensation product, ethyl (1-benzoyl-3-ethyl-4-piperidylidene)-cyanoacetate (VII), was obtained as a thick, amber-colored oil, which could be evaporatively distilled to a colorless oil, in about 80% yield. The hydrogenation of VII over Adams platinum oxide catalyst yielded ethyl (1-benzoyl-3-ethyl-4-piperidyl)-cyanoacetate (VIII) which was converted by hydrolysis and decarboxylation with concentrated hydrochloric acid into (3-ethyl-4-piperidyl)-acetic acid (IX); the latter compound could not be obtained in crystalline form either as a salt or as the free base. The latter form, obtained by treatment of the mixture of salts (hydrochloride of IX and ammonium chloride) from the hydrolysis and decarboxylation of VIII with silver oxide followed by hydrogen sulfide, was an amorphous, hygroscopic, solid glass which could be powdered, but could not be induced to crystallize. The free acid, however, showed the characteristic solubility behavior of an amino-acid: it was insoluble in acetone and ether, but soluble in water and alcohol. In order to obtain IX in a form that could be purified, the crude hydrogenation product from VIII was converted to the ethyl ester (X), which was purified by distillation. This ester was obtained in 57.5% yield from the cyanoester VIII. The properties of the ester X are listed below; it readily forms a crystalline hydrochloride, m. p. 130–131°.

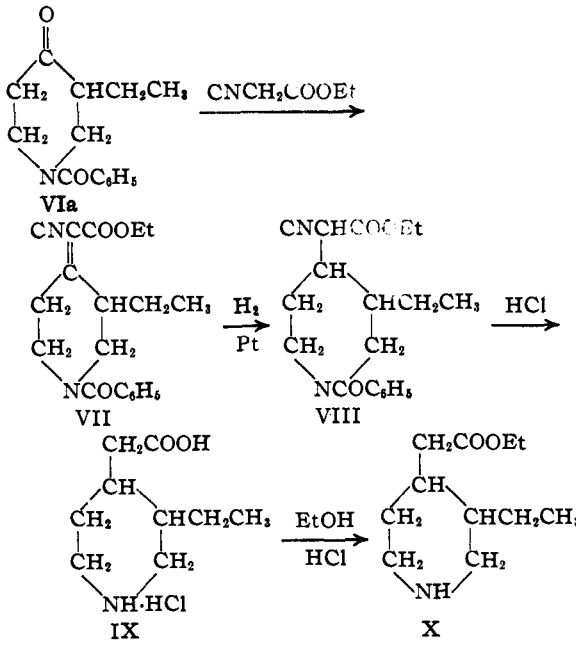
It is believed that the 3- and 4-substituents of the piperidine nuclei of VIII, IX and X are in the *cis* configuration, since Linstead and his collabo-

(5) In this connection it should be noted that nortropinone evolves ammonia on heating (Willstätter, *Ber.*, **29**, 1581 (1896).

(6) The unreactivity of β-phenoxyethyl halides in replacement reactions is well known. von Braun (*Ber.*, **46**, 1782 (1913)) observed that the product of the reaction of sodium cyanamide with β-phenoxyethyl iodide was mainly vinyl phenyl ether; Malkiel and Mason (*J. Org. Chem.*, **8**, 199 (1943)) reported that β-phenoxyethyl chloride is only one-twelfth as reactive as the corresponding β-phenyl compound; Prelog (*Ann.*, **545**, 247 (1940)) has reported the failure of the alkylation of a malonic ester with β-phenoxyethyl bromide.

(7) Apparently the 3-(γ-phenoxypropyl) substituent inhibits the carbonyl and β-ketonic ester functions of IV. Just how or why this occurs is not known at present: however, it may be noted that Belotsvetov and Izmail'skii (*J. Chem. Soc.* (U. S. S. R.), **14**, 216 (1944); *Chem. Abstr.*, **39**, 2287 (1945)) reported that N-(γ-*p*-aminophenoxypropyl)-phthalimide is colored orange, a fact that cannot be explained by the interaction of electron donor and acceptor groups along a conjugated chain, but must be due to a direct interaction of these two groups. Another example of the direct interaction of a carbonyl and an ether group is the quantitative isomerization of δ-ethoxyvaleryl chloride into ethyl δ-chlorovalerate at 150° (Prelog and Heimbach, *Ber.*, **74**, 1702 (1941)).

(8) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).



rators[9] have observed that hydrogenations of the condensation products of such ketones as ethyl cyclopentanone-2-acetate, methyl cyclohexanone-2-β-propionate and 2-methylcyclohexanone-2-carboxylic ester with cyanoacetic ester, which have structures analogous to VII, produce compounds having exclusively the *cis* configuration. If this analogy is valid, then IX represents *dl*-cincholoipon and X is its ethyl ester. Since no derivatives of *dl*-cincholoipon[10] are known, the properties of the ester X may be compared to those recently reported[11] for the *l*-ethyl ester of cencholoipon obtained from natural sources:

	B. p., °C.	Mm.	$n^{20}D$	d^{20}_4
l-Ethyl cincholoiponate	137–139	11	1.4675	0.9918
X	133–135	11	1.4672	0.9910

With the possible exception of the boiling points, it is seen that there is a close agreement between the physical properties of these two esters. In connection with the boiling point of X, it should be noted that the boiling point of *homo*-cincholoipon ethyl ester is reported as 136° (11 mm.).[12]

Regardless of the configuration of X, the above results indicate that 1-benzoyl-3-carbethoxy-4-piperidone (I, R is benzoyl) may be conveniently used to prepare a variety of 3,4-disubstituted piperidines.

Experimental

1-Benzoyl-3-benzyl-3-carbethoxy-4-piperidone.—To a solution of potassium *t*-butoxide, prepared from 4.6 g. of potassium and 150 ml. of dry *t*-butyl alcohol, were added 32.4 g. of 1-benzoyl-3-carbethoxy-4-piperidone in 20 ml. of *t*-butyl alcohol and 14.9 g. of benzyl chloride. The potassium enolate of the carbethoxypiperidone immediately separated as a voluminous precipitate. The mixture was refluxed on the steam-bath and in a nitrogen atmosphere; as the alkylation proceeded the voluminous precipitate of the enolate changed to a finely divided and more dense precipitate of potassium chloride, which settled to the bottom of the reaction flask. After ten hours of heating, the reaction mixture was cooled and the supernatant alcohol decanted from the precipitated potassium chloride. This salt was washed with 150 ml. of ether and the latter added to the *t*-butyl alcohol solution. The potassium chloride amounted to 95% of the theoretical amount (Volhard titration). The ether-alcohol solution, after successive washings with 10% sodium hydroxide, 5% hydrochloric acid, water, saturated sodium bicarbonate solution and a saturated salt solution, was evaporated on a steam-bath and kept at this temperature under the vacuum of an oil pump for an hour. The alkylated product so obtained weighed 37.9 g. (88%) and gave a negative test with ferric chloride. It was a thick, clear glass, which was difficult to crystallize, but after trituration with petroleum ether (60–68°) and allowing to stand for several days, it was obtained as a colorless, crystalline solid, m. p. 70–72° with previous softening.

Anal. Calcd. for $C_{22}H_{23}O_4N$: C, 72.31; H, 6.34; C_2H_5O, 12.33. Found: C, 71.93; H, 6.61; C_2H_5O, 11.95.

The semicarbazone, prepared in methyl alcohol and pyridine, melted at 133–134°.

Anal. Calcd. for $C_{23}H_{26}O_4N_4$: C, 65.38; H, 6.20. Found: C, 65.60; H, 6.38.

1-Benzoyl-3-ethyl-3-carbethoxy-4-piperidone.—A mixture of a potassium *t*-butoxide solution, prepared from 14.2 g. of potassium and 350 ml. of *t*-butyl alcohol, 100 g. of 1-benzoyl-3-carbethoxy-4-piperidone in 100 ml. of *t*-butyl alcohol, and 85 g. (50% excess) of ethyl iodide was heated for ten hours and then treated according to the above procedure. The 1-benzoyl-3-ethyl-3-carbethoxy-4-piperidone, a thick, light amber oil, which did not solidify at room temperature but appeared to crystallize when cooled by dry ice, weighed 87.4 g. (80%). The compound evaporatively distilled[13] at a jacket temperature of 160° and under 0.03 mm. of pressure.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.32; H, 6.98; C_2H_5O, 14.86. Found: C, 66.94; H, 7.12; C_2H_5O, 15.25.

The semicarbazone melted at 219–220°.

Anal. Calcd. for $C_{18}H_{24}O_4N_4$: C, 59.98; 6.71. Found: C, 59.73; H, 6.85.

3-Benzoyl-4-piperidone Hydrochloride.—The rate of decarboxylation of 1-benzoyl-3-alkyl-3-carbethoxy-4-piperidones was first determined on a 0.001 mole sample in an apparatus that permitted the evolved carbon dioxide to be collected and measured. The piperidone was heated with 5 ml. of 6*N* hydrochloric acid under an efficient reflux condenser in a bath maintained at 170° After about five minutes of heating, the top of the condenser was connected to a measuring buret and the evolution of carbon dioxide was plotted against time. In this manner it was found that both the 3-benzyl- and 3-ethyl-3-carbethoxy-4-piperidones gave about 28 ml. of gas in eight or nine hours. The evolution of gas usually continued slightly beyond the theoretical quantity, but this increase amounted to only 1–3 ml. during several hours after the theoretical amount had been evolved. When the time for quantitative decarboxylation had been thus determined, this time was used for the decarboxylation of larger samples.

A mixture of 19.8 g. 1-benzoyl-3-benzyl-3-carbethoxy-4-piperidone and 250 ml. of 6 *N* hydrochloric acid was refluxed for eight hours. After cooling, the benzoic acid that precipitated was filtered off and the acid solution ex-

(9) Linstead, *et al.*, *J. Chem. Soc.*, 935 (1934); 1065 (1935); 478 1936).

(10) An unsuccessful attempt to synthesize this compound was made by Koenigs (*Ann.*, **347**, 143 (1906)); see also Prelog, Sostaric and Gustak, *ibid.*, **545**, 247 (1940).

(11) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 535 (1944).

(12) Kaufmann, Rothlin and Brunnschweiler, *Ber.*, **49**, 2299 (1916); *cf.* also ref. 11.

(13) See McElvain, Jelinek and Rorig, THIS JOURNAL, **67**, 1578 (1945), for a description of the apparatus used for this distillation.

tracted twice with ether. These extracts were combined with the filtered benzoic acid, the benzoic acid extracted from the ether with 10% sodium hydroxide and reprecipitated with concentrated hydrochloric acid; 5.9 g. (calcd. 6.1 g.) was obtained. The 6 *N* hydrochloric acid solution, after the removal of the benzoic acid, was evaporated to dryness under diminished pressure. The residue was taken up in absolute alcohol, decolorized with charcoal, and dry ether added until the solution was turbid. On cooling, 8 g. (70%) of the white, crystalline, non-hygroscopic hydrochloride of 3-benzyl-4-piperidone separated. Recrystallization of this salt from ethyl acetate and a small amount of ether gave a product that melted at 186–188°.

Anal. Calcd. for $C_{12}H_{16}ONCl$: Cl, 15.71. Found: Cl, 15.96.

1-Methyl-3-benzyl-4-piperidone Hydrobromide.—A solution of 2 g. of the hydrochloride of 3-benzyl-4-piperidone in the minimum quantity of water was saturated with potassium carbonate and extracted twice with ether. The ether extract of the free base, after washing with a saturated salt solution, was stirred and treated slowly with a solution of 1.3 g. (1 mole) of methyl iodide in 15 ml. of ether. Then 12 ml. of a saturated solution of sodium bicarbonate was added, the mixture stirred for six hours and then allowed to stand overnight. The ether layer was separated, evaporated to a small volume and the residue shaken with 1 ml. of benzoyl chloride and 10 ml. of 10% sodium hydroxide solution. The mixture was treated with ether and the tertiary amine extracted from the ether solution with hydrochloric acid. Neutralization of this extract with base liberated the tertiary amine which was taken up in ether. After removal of the ether, the residue was dissolved in absolute alcohol containing dry hydrogen bromide. Removal of the alcohol left a glass which, after recrystallization from ethyl acetate, gave 1 g. of the hydrobromide of 1-methyl-3-benzyl-4-piperidone, m. p. 154–156°.

Anal. Calcd. for $C_{13}H_{18}ONBr$: Br, 28.12. Found: Br, 27.75.

3-Ethyl-4-piperidone Hydrochloride.—A mixture of 25.5 g. of 1-benzoyl-3-ethyl-3-carbethoxy-4-piperidone and 200 ml. of 6 *N* hydrochloric acid was refluxed for 10 hours and the resulting reaction mixture worked up as described above. The crude 3-ethyl-4-piperidone hydrochloride was obtained as a glass and weighed 13.2 g. (98%). Crystallization was attended with considerable loss, but it was effected with an alcohol–ether mixture and 8.2 g. (60%) of the pure hydrochloride, m. p. 157–158°, obtained.

Anal. Calcd. for $C_7H_{14}ONCl$: Cl, 21.67. Found: Cl, 21.45.

Alkylations with β-Phenoxyethyl Halides.—After a mixture of the potassium enolate from 10 g. of 1-benzoyl-3-carbethoxy-4-piperidone and 7 g. of β-phenoxyethylbromide in 60 ml. of *t*-butyl alcohol had been heated for ninety hours only 70% of the calculated amount of potassium bromide had formed. After working up the reaction mixture as described above, the product obtained was heated for several hours at 150° and 0.1 mm. pressure. This product was evaporatively distilled under 0.03 mm. pressure (jacket temperature, 225°) to give a pale yellow viscous oil that contained 16.3% ethoxyl (calcd. for the expected alkylated product, 11.4%).

When β-phenoxyethyl iodide was used instead of the bromide in the above experiment, the theoretical amount of potassium iodide was obtained after ninety hours of reaction. The product isolated from the reaction contained 15.9% ethoxyl.

To determine whether a product, similar to those obtained from the phenoxyethyl halides, could be obtained from 1-benzoyl-3-carbethoxy-4-piperidone alone, a 5.3 g. sample was heated for ninety hours with one-half an equivalent of potassium *t*-butoxide in refluxing *t*-butyl alcohol. When this reaction mixture was worked up and the product evaporatively distilled, 2.6 g. (50%) of a pale yellow oil, containing 15.9% ethoxyl and similar in appearance to the products isolated above in the attempted alkylations with the phenoxyethyl halides, was obtained.

None of these products reacted with semicarbazide nor did they yield any substantial amounts of gas when refluxed with 6 *N* hydrochloric acid.

Alkylation of 1-Benzoyl-3-carbethoxy-4-piperidone with γ-Phenoxypropyl Bromide.—When the alkylation procedure described above was applied to the potassium enolate from 25.3 g. of the piperidone and 19.8 g. of γ-phenoxypropyl bromide, sixty hours of heating was required to produce 90% of the theoretical amount of potassium bromide. The reaction product, after heating at 180° under a vacuum for thirty minutes, was a thick oil and weighed 32.6 g. Evaporative distillation under 0.03 mm. pressure (jacket temperature 230°) gave an oil that yielded analytical data corresponding to 1-benzoyl-3-(γ-phenoxypropyl)-3-carbethoxy-4-piperidone.

Anal. Calcd. for $C_{24}H_{27}O_5N$: C, 70.39; H, 6.65; C_2H_5O: 11.0. Found: C, 69.89; H, 7.05; C_2H_5O, 10.92.

This product, however, failed to form a semicarbazone and it gave no appreciable evolution of carbon dioxide when refluxed with 6 *N* hydrochloric acid.

1-Benzyl-4-piperidone.—This ketone was prepared by the decarboxylation of 1-benzyl-3-carbethoxy-4-piperidone[14] in 20% hydrochloric acid. It was obtained as a water-white liquid, boiling at 114–116° (0.3 mm.); $n^{23}D$ 1.5374; d^{23}_{23} 1.0626. The semicarbazone, prepared in alcohol in the presence of pyridine, melted at 194–195°.

Anal. (carbazone). Calcd. for $C_{13}H_{18}ON_4$: C, 63.39; H, 7.37. Found: C, 62.94; H, 7.08.

Ethyl (1-Benzyl-4-piperidylidene)-cyanoacetate.—A mixture of 10 g. of 1-benzyl-4-piperidone, 8.5 g. of ethyl cyanoacetate, 0.82 g. of ammonium acetate, 2.6 g. of glacial acetic acid and 11 ml. of benzene was heated in an apparatus described by Cope, *et al.*,[8] for four hours, after which time no more water collected in the separator. The reaction mixture was poured into a dilute solution of potassium carbonate and the mixture extracted with several portions of ether. The ether was evaporated, the residue taken up in benzene, and petroleum ether (60–68°) added to turbidity. This solution was passed through a column of aluminum oxide, giving a spreading red band at the top of the column and a light yellow band at the bottom. The column was eluted with a mixture of 3 parts of benzene and 5 parts of petroleum ether until the red band just reached the bottom of the column. The eluate was evaporated, the residue dissolved in dry ether and the resulting solution treated with hydrogen chloride. The hydrochloride of ethyl (1-benzyl-4-piperidylidene)-cyanoacetate which precipitated, melted, after recrystallization from an alcohol–ether mixture, at 146–148°.

Anal. Calcd. for $C_{17}H_{21}O_2N_2Cl$: Cl, 11.1. Found: Cl, 10.8.

Ethyl (1-Benzoyl-3-ethyl-4-piperidylidene)-cyanoacetate (VII).—To 45 g. of the crude 3-ethyl-4-piperidone hydrochloride, obtained from the decarboxylation of 86.4 g. of 1-benzoyl-3-ethyl-3-carbethoxy-4-piperidone with 6 *N* hydrochloric acid, was added a solution of 180 g. of potassium carbonate in 350 ml. of water, 260 ml. of chloroform and 62 g. of benzoyl chloride. This mixture was stirred overnight at room temperature, the chloroform layer separated and washed successively with 50 ml. of 1:1 ammonia water, water, dilute hydrochloric acid, water, a saturated sodium bicarbonate solution, and water. After drying over anhydrous sodium sulfate, the chloroform was distilled off and the residue heated at 130° and 10 mm. for two hours; yield 58.5 g. (92%).

This product was mixed with 31.7 g. of ethyl cyanoacetate, 5 g. of ammonium acetate, 13.5 g. of glacial acetic acid and 60 ml. of benzene and heated as described above for 12 hours. After cooling, the benzene solution was mixed with ether, washed with water, and sodium bicarbonate, and dried over anhydrous sodium sulfate. Then the

(14) Thayer and McElvain, THIS JOURNAL, **49**, 2862 (1927); Bolyard, *ibid.*, **52**, 100 (1930).

ether was removed and the residue dried on a steam-bath at 0.05 mm. for an hour.

After preliminary experiments had shown that the product at this stage could not be catalytically hydrogenated, the residue was dissolved in 250 ml. of benzene and passed through a column of aluminum oxide. The column was then eluted with 110 ml. of benzene, and then with a mixture of 55 ml. of benzene and 55 ml. of ether. A small brown band of impurities remained at the top of the column. The solvent was removed from these eluates and the residue heated at 150° at 10 mm. for an hour. Ethyl (1-benzoyl-3-ethyl-4-piperidylidene)-cyanoacetate so obtained was an oil that weighed 65 g. (81%). A sample of this material evaporatively distilled at 0.05 mm. (jacket temperature, 215°) as a pale yellow oil with no apparent decomposition.

Anal. Calcd. for $C_{19}H_{22}O_3N_2$: C, 69.91; H, 6.80; C_2H_5O, 13.81. Found: C, 69.52; H, 6.91; C_2H_5O, 13.50.

The absorption spectrum of this ester, which was kindly determined by Mr. Carl Djerassi in this Laboratory, showed an absorption maximum at 219 mμ, the region in which α,β-unsaturated cyanoacetic esters are known to absorb.[15] The characteristic spectrum of the benzene nucleus also was noted.

Ethyl (1-Benzoyl-3-ethyl-4-piperidyl)-cyanoacetate (VIII).—A solution of 11 g. of VII in 50 ml. of absolute alcohol was shaken with hydrogen and 0.22 g. of Adams platinum oxide catalyst. The required amount of hydrogen was absorbed in about four hours. In this manner a total of 62 g. of VII was reduced. The combined alcohol solutions, after removal of the catalyst and evaporation of the solvent, left 58 g. (93%) of ethyl (1-benzoyl-3-ethyl-4-piperidyl)-cyanoacetate as a viscous pale yellow oil. A sample of this material evaporatively distilled at 0.03 mm. and a jacket temperature of 220°.

Anal. Calcd. for $C_{19}H_{24}O_3N_2$: C, 69.49; H, 7.37; C_2H_5O, 13.72. Found: C, 69.01; H, 7.63; C_2H_5O, 13.65.

Ethyl 3-Ethyl-4-piperidylacetate (Ethyl *dl*-Cincholoiponate (X)).—The clear reddish solution resulting from the addition of 19.5 g. of VIII to 200 ml. of concentrated hydrochloric acid was refluxed for twenty-four hours. On cooling the solution, benzoic acid crystallized out and was filtered off; the yield was practically quantitative. The aqueous filtrate then was evaporated to dryness under diminished pressure, 200 ml. of 10% alcoholic hydrogen chloride added, and the solution refluxed for twenty-four hours. The alcohol was removed under diminished pressure and the resulting salt mixture treated with chloroform, which dissolved the salt of the amino ester X but left 3.1 g. (calcd. 3.25 g.) of ammonium chloride undissolved. The chloroform solution was evaporated and the residue taken up in a mixture of 20 ml. of alcohol and 25 ml. of ether. This solution was cooled to 0° and treated with a cold 30% solution of sodium hydroxide, and the resulting sludge extracted four times with ether. After drying the ether solution over anhydrous sodium sulfate and distilling the ether, the residue was distilled. Redistillation gave 6.8 g. (57.5% from VIII) of ethyl 3-ethyl-4-piperidylacetate (X), b. p. 133–135° (11 mm.); $n^{30}D$ 1.4672; d^{20}_4 0.9910.

Anal. Calcd. for $C_{11}H_{21}O_2N$: C, 66.29; H, 10.62; C_2H_5O, 22.6. Found: C, 66.03; H, 10.84; C_2H_5O, 22.1.

A solution of X in dry ether when treated with dry hydrogen chloride gave a white, crystalline precipitate of ethyl 3-ethyl-4-piperidylacetate hydrochloride which, after recrystallization from a chloroform–ethyl acetate mixture, melted at 130–131° with previous softening.

Anal. Calcd. for $C_{11}H_{22}O_2NCl$: Cl, 15.04. Found: Cl, 15.25.

(15) Andrews, Cristol, Lindenbaum and Young, THIS JOURNAL, **67**, 715 (1945).

Summary

The C-alkylations of the potassium enolate of 1-benzoyl-3-carbethoxy-4-piperidone with ethyl iodide and benzyl chloride are described. Attempted alkylations with β-phenoxyethyl bromide and iodide were unsuccessful. γ-Phenoxypropyl bromide appeared from the analyses of the product to give 3-alkylation, but the chemical properties of this product are anomalous.

The conversion of the 1-benzoyl-3-alkyl-3-carbethoxy-4-piperidones, obtained from alkylations with ethyl iodide and benzyl chloride, to the 3-alkyl-4-piperidones is described.

The usefulness of the 3-alkyl-4-piperidones for the synthesis of 3,4-disubstituted piperidines is illustrated by the synthesis of ethyl 3-ethyl-4-piperidylacetate (*dl*-ethyl cincholoiponate).

MADISON, WISCONSIN RECEIVED FEBRUARY 15, 1946

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Studies of 1,3-Dienes. II. Stereoisomerism of Bromides and Glycols Derived from 2,3-Dimethyl-1,3-butadiene[1]

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The addition of bromine to aliphatic 1,3-dienes is a well known reaction but with few exceptions the structure and configuration of the resulting bromides and the corresponding alcohols have not been definitely established. The older work in this field was not always interpreted correctly as the early investigators did not take cognizance of the marked tendency of the 1,2- and 1,4-dibromides to undergo anionotropic transformations (allylic rearrangements). Thus, the liquid and solid dibromide of 1,3-butadiene were believed at first to be the stereoisomeric *cis*- and *trans*-1,4-dibromo-2-butenes[3] but more recent studies have shown them to be the structurally isomeric 1,2- and 1,4-dibromides, which are quite readily interconverted.[4,5] 1,3-Cyclopentadiene is reported to yield three dibromides: a liquid 1,2-dibromide,[6] a liquid (*cis*) 1,4-dibromide, and a solid (*trans*) 1,4-dibromide.[7] The present paper deals

(1) First paper, THIS JOURNAL, **63**, 131 (1941).

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(3) Griner, *Compt. rend.*, **116**, 723 (1893); **117**, 553 (1894).

(4) Prévost, *Ann. chim.*, (10) **10**, 113, 356 (1928); *Bull. soc. chim.*, (4) **43**, 996 (1928).

(5) Farmer, Lawrence and Thorpe, *J. Chem. Soc.*, 729 (1928).

(6) Farmer and Scott, *ibid.*, 174 (1929).

(7) Thiele, *Ann.*, **308**, 333 (1899); see also, Blomquist and Mayes, *J. Org. Chem.*, **10**, 134 (1945).