was purified by solution in dilute ammonium hydroxide and reprecipitation after treatment with charcoal; m. p. 244–246°; yield, 4.3 g. (74%).

Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.3; H, 4.1. Found: C, 49.3; H, 4.2.

In another preparation, under quite similar conditions, complete solution was obtained during the reaction and the product appeared to contain a considerable amount of the diacetyl derivative. When this material was refluxed for ten minutes with dilute ammonium hydroxide the product obtained above resulted.

2-(N^3-Acetylmetanilamido)-5-chloropyrimidine.—The procedure was as above with the addition of two drops of sulfuric acid to the acetic anhydride; m. p. 258–260°; yield, 76%.

Anal. Calcd. for $C_{12}H_{11}ClN_4O_3S$: C, 44.1; H, 3.4. Found: C, 44.1; H, 3.3.

Sodium Salts of XVII and XIX.—The sodium salts of both of these compounds were best prepared by reaction with sodium ethoxide in boiling absolute alcohol. A solution of 1.5–2 equivalents of sodium in 10 parts of alcohol was used. The salts were quite soluble in aqueous alcohol and were prepared with difficulty by the usual method of diluting a concentrated aqueous solution of the salt with a large volume of alcohol.

2-Amino-5-bromo-4-methoxypyrimidine.—2-Amino-4-methoxypyrimidine was reacted with one mole of bromine in water over a period of one hour by the general directions of the preceding paper.[2] After neutralization with sodium hydroxide a 95.2% yield was obtained. After crystallization from benzene the m. p. was 125–126°.

Anal. Calcd. for $C_5H_6BrN_3O$: N, 20.6. Found: N, 20.0.

Acknowledgment.—The authors wish to express their appreciation to Drs. S. Brackett and E. Waletzky for many helpful discussions during the course of this work and for the antimalarial results quoted here.

Summary

1. The synthesis of twenty-seven new metanilamides, three new orthanilamides, and seventeen variously substituted 2-phenylsulfonamidopyrimidines has been described.

2. The antimalarial activities of these compounds in avian malaria have been reported and discussed with respect to their structure.

3. Among the metanilamides studied, a majority of the N^1-heterocyclic compounds showed antimalarial activity; other types of metanilamides were ineffective.

4. Of the benzenesulfonamides, only 2-phenylsulfonamido-5-halogenpyrimidines and their derivatives had antimalarial activity.

5. The most active compounds were 2-metanilamido-5-chloropyrimidine ("Metachloridine") and its bromine and iodine analogs. Metachloridine was six times as effective as sulfadiazine and sixteen times as active as quinine against *P. gallinaceum* in chicks.

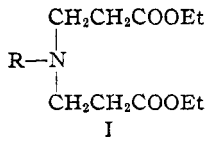
STAMFORD, CONNECTICUT RECEIVED FEBRUARY 28, 1946

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

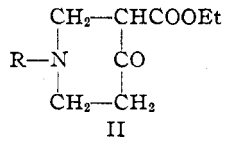
Piperidine Derivatives. XV. The Preparation of 1-Benzoyl-3-carbethoxy-4-piperidone. A Synthesis of Guvacine

BY S. M. MCELVAIN AND GILBERT STORK

Previous papers[1] from this Laboratory have reported the preparation of a number of 1-alkyl-3-carbethoxy-4-piperidones (II) by the Dieckmann cyclization of alkyl-di-(β-carbethoxyethyl)-amines (I)



I



II

While this reaction produced compounds of structure II in quite satisfactory yields (63–78%) when R is an alkyl group,[1c] the yield of the piperidone (II) dropped to 11% when the reaction was applied to the diester (I) in which R is hydrogen.[2] This undoubtedly is due to the greater tendency of the secondary amino group of both this particular diester and the corresponding piperidone to become involved in other competitive reactions during and after the cyclization.

For the preparation of certain piperidine derivatives, however, it is desirable to have such a carbethoxypiperidone as II in which R is hydrogen or a group that may be readily replaced by hydrogen. Ruzicka and Fornasir[3] have reported the cyclization of N-benzoyl-di-(β-carbethoxyethyl)-amine (VI). While they did not isolate the carbethoxypiperidone (VIII), the oil they obtained from the reaction gave the characteristic test with ferric chloride and was hydrolyzed[4] to the hydrochloride of 4-piperidone, which was isolated as its dibenzylidene derivative. No yields were given for any of these products.

The work reported in the present paper was concerned with the development of satisfactory methods for the preparation of 1-benzoyl-3-carbethoxy-4-piperidone (VIII) and its immediate precursor N-benzoyl-di-(β-carbethoxyethyl)-amine (VI). The preparation of this latter compound, which is dependent upon the benzoylation of di-(β-carbethoxyethyl)-amine (IV), hitherto has been quite unsatisfactory because of the difficulties encountered in the preparation of this secondary amino ester. The interaction of ethyl β-iodopropionate and the ethyl ester of β-alanine,[3] and

(1) (a) McElvain, THIS JOURNAL, **46**, 1721 (1924); **48**, 2179 (1926); (b) Thayer and McElvain, *ibid.*, **49**, 2862 (1927); (c) Bolyard and McElvain, *ibid.*, **51**, 922 (1929).

(2) Kuettel and McElvain, THIS JOURNAL, **53**, 2692 (1931).

(3) Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 806 (1920).

(4) Ruzicka and Seidel, *Helv. Chim. Acta*, **5**, 715 (1922).

the reaction of ethyl β-bromopropionate with ammonia in the presence of silver oxide[2] both give low yields and use relatively expensive starting materials. Morsch[5] studied the addition of ammonia to methyl acrylate in alcohol solutions and reported that the same conditions that gave only a 6.5% yield of the secondary amino ester from methyl acrylate in methyl alcohol, produced a 54% yield of the same secondary amino ester when methyl acrylate was used in ethyl alcohol solution. A study of these reactions in the present work showed no such striking difference in the behavior of ethyl alcohol. Practically none of the desired ester IV was obtained; instead resinous material, which boiled higher than the tertiary amino ester (III), was the main product. Of the three experiments performed by Morsch with liquid ammonia, only one led to the desired secondary amino ester. Methyl acrylate was used and the reactants were allowed to stand one hundred hours at room temperature; a 42% yield of the dimethyl ester corresponding to IV was reported.

A study of the reaction of liquid ammonia with ethyl acrylate in the present work has shown that the optimum yields (40–44%) of the secondary amino ester (IV) are obtained when the ratio of ammonia to ethyl acrylate is 5:1 and the reactants are allowed to stand at room temperature (or at a lower temperature) for one to three hours. Larger amounts of ammonia did not materially increase the yield, and longer periods of reaction were not only unnecessary but actually detrimental to the yield; the products from the longer runs were very much darker in color and contained appreciable amounts of amides.

Under the optimum conditions for the formation of the secondary amino ester (IV) an approximately equal weight of the tertiary amino ester (III) was always present in the reaction mixture. The formation of this compound could not be prevented either by the use of larger excesses of ammonia or by the initial addition to the reaction mixture of the amount of the tertiary amino ester that would normally be formed in the reaction. This fact, together with the observation that ethyl acrylate was always present when the reaction bomb was opened, leads to the conclusion that the addition of ammonia to ethyl acrylate and the transformation of the resulting ester of β-alanine (V) to the secondary and tertiary amino esters (IV and III) are a series of reversible reactions

$$\underset{\text{III}}{N(CH_2CH_2COOEt)_3} \rightleftharpoons HN(CH_2CH_2COOEt)_2 + CH_2{=}CHCOOEt$$
$$\text{IV} \uparrow\downarrow$$
$$NH_3 + CH_2{=}CHCOOEt \rightleftharpoons H_2NCH_2CH_2COOEt + CH_2{=}CHCOOEt$$
$$\text{V}$$

On the basis of the above reactions, it seemed that the tertiary amino ester (III) might be converted, to some extent at least, into the secondary amino ester (IV) by heat. However, when this was attempted, both ammonia and ethyl acrylate were evolved and the undistilled material consisted mainly of unchanged III. Apparently the thermal decomposition of IV and V are just as rapid, if not more so, as that of III. Since the formation of ethyl acrylate and ammonia from III requires at least a transitory existence of IV, it appeared likely that the decomposition of III could be stopped at the secondary amino ester stage if it were carried out in the presence of benzoyl chloride, which would convert IV into its benzoyl derivative as rapidly as it was formed and thereby prevent continuation of the pyrolysis to V and ammonia.

This proved to be possible. When two equivalents of the tertiary amino ester (III) and one equivalent of benzoyl chloride were heated in refluxing toluene for twenty hours, a 90% yield of the benzamide (VI) and an 89% yield of the crystalline hydrochloride of tri-(β-carbethoxyethyl)-amine (VII) were obtained. Incidentally, this was the only method by which the hydrochloride of III could be obtained in crystalline form. The thermal stability of this hydrochloride is worthy of note since it is well known that many similarly constructed amino ketone salts resulting from the Mannich reaction are readily decomposed by heat into the secondary amines and the α,β-unsaturated ketones.[6]

$$\underset{\text{III}}{2N(CH_2CH_2COOEt)_3} + C_6H_5COCl \longrightarrow \underset{\text{VI}}{C_6H_5CON(CH_2CH_2COOEt)_2} + \underset{\text{VII}}{ClH{\cdot}N(CH_2CH_2COOEt)_3} + CH_2{=}CHCOOEt$$

In the above reaction half of the amino ester III is used to combine with the hydrogen chloride produced in the formation of VI. It was found that this portion of III also could be converted to the amide VI if a thermally more stable tertiary amine, such as tributylamine, were added to the pyrolysis–benzoylation reaction mixture. Under these conditions III is converted to the amide VI after eight hours of heating in refluxing xylene in 80% yield according to the reaction

$$III + C_6H_5COCl + (C_4H_9)_3N \longrightarrow VI + (C_4H_9)_3N{\cdot}HCl + CH_2{=}CHCOOEt$$

This reaction is conveniently followed by the drop in the temperature of the refluxing liquid as the liberation of ethyl acrylate proceeds.

Since both the secondary and tertiary amino esters (IV and III) may be converted to the amide VI, it is not necessary to separate the mixture of these esters obtained from the reaction of ammonia and ethyl acrylate.

(5) Morsch, *Monatsh.*, **63**, 220 (1933).

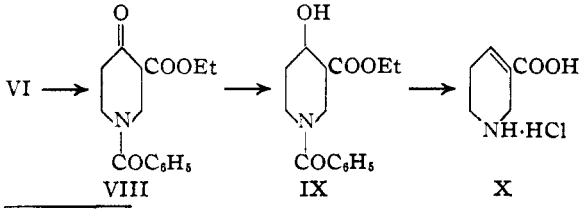
(6) Blicke and Burckhalter, THIS JOURNAL, **64**, 451 (1942) Mannich and Honig, *Arch. Pharm.*, **265**, 598 (1927).

The reaction product, after removal of excess ammonia and unchanged ethyl acrylate, may be benzoylated directly in the presence of tributylamine and the amide VI obtained in approximately 70% yield based on the ethyl acrylate not recovered from the initial reaction of this ester with ammonia.

The cyclization of N-benzoyl-di-(β-carbethoxyethyl)-amine (VI) was readily accomplished in benzene solution by means of powdered sodium. The yield of 1-benzoyl-3-carbethoxy-4-piperidone (VIII) was 66% of the theoretical. It was obtained generally as a thick pale yellow oil which could be induced to crystallize only with difficulty. Nevertheless, a considerable amount of a cream colored sample, m. p. 54–56°, was obtained and used for analyses and seeding. For the purpose of further reactions the oily material proved quite satisfactory.

Attempts were made to cyclize two other derivatives of the secondary amino ester (IV) which contained readily removable N-substituents. The N-acetyl derivative gave only a small yield (*ca.* 10%) of a product that showed the characteristic coloration of a 3-carbethoxy-4-piperidone with ferric chloride; this reaction and its product were not studied further. The N-nitroso derivative under the conditions of the cyclization evolved nitrogen and gave only a trace of a product showing a coloration with ferric chloride. The main product isolated from this reaction was neutral[7] (3-carbethoxy-4-piperidones are readily soluble in aqueous sodium hydroxide solution).

The ready availability of 1-benzoyl-3-carbethoxy-4-piperidone (VIII) from the cyclization of the benzamide (VI) makes possible the synthesis of a variety of piperidine derivatives containing no 1-substituent. As an example, the hydrochloride of guvacine[8] (X), one of the alkaloids of the areca nut, was prepared by the sequence of reactions



(7) Since cyclizations of the type expected in this case occur quite readily, it is likely that the neutral product and the nitrogen obtained in this reaction resulted from a decomposition of the desired 1-nitroso-3-carbethoxy-4-piperidone by sodium ethoxide

$$ONNCH_2CH_2COCH(COOEt)CH_2 \longrightarrow$$
$$CH_2{=}CH_2COCH(COOEt)CH_2N{=}NOH \longrightarrow$$
$$H_2O + N_2 + CH_2{=}CHCOC(COOEt){=}CH_2 \longrightarrow \text{polymer}$$

Decompositions of this type have been reported by Jones and Kenner, *J. Chem. Soc.*, 363 (1933); a particular example is the decomposition of β-(nitrosomethylamino)-isobutyl methyl ketone by sodium isopropoxide into mesityl oxide and diazomethane (Adamson and Kenner, *ibid.*, 286 (1935)).

(8) Wohl and Losanitch (*Ber.*, **40**, 4685, 4698 (1907)) have prepared this compound from an intermediate in their synthesis of cincholoiponic acid. Their synthesis starts with acrolein and the over-all yield for the eight steps involved amounts to about 3%.

The reduction of the piperidone VIII to the alcohol (IX) took place very slowly (twenty hours) over Adams platinum oxide catalyst,[9] but proceeded quite rapidly (one hour) over Raney nickel. Both hydrogenations yielded a product with a melting range of 106–116° from which the pure hydroxy compound (IX), m. p. 125–126°, was obtained in 72% yield. The configuration of this stereoisomer is not certain, but it is believed that the hydroxyl and carbethoxyl groups are in the *trans* position with respect to each other because of the resistance this β-hydroxyester shows to dehydration.[10] The compound was recovered unchanged after heating with *p*-toluenesulfonic acid; phosphorus oxychloride in pyridine produced a dark resinous substance from which no definite product could be isolated. The dehydration finally was accomplished by passing a stream of dry hydrogen chloride through molten IX heated to 180°. This treatment not only removed the elements of water but the benzoyl and the ethyl groups as well, and converted IX directly to guvacine hydrochloride (X) in 84% yield.

Experimental

Di-(β-carbethoxyethyl)-amine (IV) and Tri-(β-carbethoxyethyl)-amine (III).—To 190 ml. of liquid ammonia (5 moles), contained in a 600-ml. beaker, was added 180 g. (1 mole) of ethyl acrylate, previously cooled in a Dry Ice–alcohol bath. The beaker was enclosed in a steel bomb and allowed to stand for one to three hours at room temperature. The bomb then was opened gradually to permit the excess of ammonia to escape and the remaining liquid transferred to a distilling flask. After removal of the residual ammonia and ethyl acrylate under the vacuum of a water pump, the remaining oil was distilled under the vacuum of an oil pump. Practically none of the ester of β-alanine was obtained; 85 g. (44%) of di-(β-carbethoxyethyl)-amine (IV), b. p. 119–125° (1–2 mm.); $n^{27}D$ 1.4391 (previously reported: 137–138° (12 mm.),[2] 112–114° (0.2 mm.),[3] $n^{25}D$ 1.4380[2]) and 80 g. of tri-(β-carbethoxyethyl)-amine (III),[2] b. p. 150–164° (1–2 mm.), were collected.

N-Benzoyl-di-(β-carbethoxyethyl)-amine (VI). (a) **From IV.**—To a solution of 217 g. (1 mole) of the secondary aminoester (IV) in 400 ml. of dry benzene was added 169 g. (1.2 moles) of benzoyl chloride; considerable heat was evolved during this addition. The resultant clear solution was refluxed for ten hours, after which time the evolution of hydrogen chloride ceased. Then 70 ml. of absolute alcohol was added and the mixture refluxed for another hour. The benzene solution was cooled, washed successively with 10% sodium hydroxide solution, 10% hydrochloric acid, a saturated solution of sodium bicarbonate and finally distilled. After removal of the benzene, fractionation of the residue yielded 260 g. (80%) of VI as a clear, viscous, yellow oil, b. p. 196–198° (0.4 mm.); $n^{25}D$ 1.5040; d^{25}_{25} 1.1282. Ruzicka and Fornasir[3] report a "good" yield of a product boiling at 195–205° (0.2 mm.).

(b) **From the Tertiary Amino Ester (III). Tri-(β-carbethoxyethyl)-amine Hydrochloride (VII).**—To a solution of 270 g. of III in 250 ml. of toluene was added 150 g. (20% excess) of benzoyl chloride and the resulting solution refluxed for twenty hours. After cooling, the crystalline precipitate which had separated was filtered off and

(9) *Cf.* the rate of reduction of other piperidones with this catalyst, ref. 1a.

(10) The dehydration of a compound in which the hydrogen and hydroxyl to be removed are in the *cis* position is generally much more difficult than when these groups are in the *trans* position, *cf.* Woodward and Doering, THIS JOURNAL, **67**, 860 (1945).

washed with dry ether. The tri-(β-carbethoxyethyl)-amine hydrochloride so obtained weighed 130 g. (87%) and melted at 81–83°.

Anal. Calcd. for $C_{15}H_{28}O_6NCl$: Cl, 10.02. Found: Cl, 10.24.

The toluene solution from which the hydrochloride was filtered, after washing with dilute potassium carbonate solution, dilute (5%) hydrochloric acid and water, yielded on distillation 123 g. (90%) of the N-benzoyl derivative (VI).

(c) **From III in the Presence of Tributylamine.**—To a solution of 63 g. of the tertiary aminoester (III) in 60 ml. of xylene were added 42 g. (10% excess) of tributylamine and 37 g. (20% excess) of benzoyl chloride. The solution was refluxed for eight hours. The temperature of the refluxing liquid dropped from about 167° at the beginning to 144° at the end of the heating period. Toward the end of the reaction the lower part of the reflux condenser was filled with an ammonium chloride-like smoke (tributylamine hydrochloride?). After the eight-hour heating period, 30 ml. of alcohol was added to the reaction mixture, which was then refluxed for another hour and worked up as described in (b). The yield of the N-benzoyl derivative (VI) was 50 g. (78%).

When this reaction was run with toluene as the solvent twenty hours of heating was required to complete the reaction.

(d) **From a Mixture of III and IV.**—The procedure described in (c) may be applied to either the distilled or undistilled mixture of III and IV that remains after the removal of the low boiling material from the ammonia–ethyl acrylate reaction. Tributylamine is used in the quantity that would be required if the mixture were considered to consist of only the secondary aminoester IV. Thus, 217 g. of the mixture of III and IV, remaining from the reaction of 248 g. of ethyl acrylate and 270 ml. of ammonia (reaction time, two hours), was treated with 205 ml. of xylene, 185 g. of tributylamine and 145 g. of benzoyl chloride. A considerable amount of heat was evolved on the addition of the latter compound, due to the presence of the secondary aminoester (IV). The mixture was refluxed and worked up as described in (c) and gave 220 g. of the benzoyl derivative (VI). This yield amounts to 55% based on the 248 g. of ethyl acrylate initially used or 70% based on the acrylate not recovered as the low boiling material from the original reaction mixture.

N-Acetyl-di-(β-carbethoxyethyl)-amine.—A mixture of 10.8 g. of the secondary aminoester (IV) and 15 ml. of acetic anhydride was refluxed for thirty minutes. Distillation of the reaction mixture gave 11.8 g. (90%) of N-acetyl-di-(β-carbethoxyethyl)-amine as a viscous, colorless oil, b. p. 183–185° (5 mm.).

Anal. Calcd. for $C_{12}H_{21}O_5N$: C, 55.58; H, 8.16. Found: C, 55.34; H, 8.32.

N-Nitroso-di-(β-carbethoxyethyl)-amine.—A solution of 14.6 g. of di-(β-carbethoxyethyl)-amine hydrochloride[2] in 30 ml. of water was treated with a solution of 4.9 g. (20% excess) of sodium nitrite in 15 ml. of water and the mixture heated to 80° on a steam-bath for forty-five minutes. After cooling, the solution was extracted with ether and this extract washed successively with a sodium bicarbonate solution and water. After drying over anhydrous sodium sulfate, the ether solution was distilled; 12 g. (85%) of N-nitroso-di-(β-carbethoxyethyl)-amine was obtained as a light yellow, viscous oil, b. p. 133–137° (0.04 mm.); $n^{24}D$ 1.4570.

Anal. Calcd. for $C_{10}H_{18}O_5N_2$: C, 48.76; H, 7.37. Found: C, 48.42; H, 7.45.

1-Benzoyl-3-carbethoxy-4-piperidone (VIII).—The cyclization of N-benzoyl-di-(β-carbethoxyethyl)-amine (VI) was run under a variety of conditions. Benzene was found to be a somewhat better reaction medium than xylene; an excess of sodium did not improve the yield; neither did the use of sodium ethoxide nor a nitrogen atmosphere. The following procedure represents the most satisfactory conditions that were used.

To a suspension of 23 g. of sodium sand in 1200 ml. of dry, thiophene-free benzene was added, in a single portion, 308 g. of N-benzoyl-di-(β-carbethoxyethyl)-amine and 2 ml. of absolute alcohol. In contrast to the N-alkyl compounds of this type, the reaction started rather slowly. After stirring under reflux for a short while the reaction product separated as a gummy ball that occluded much of the sodium. It was found advisable to stop the stirring at this point and continue heating the mixture on a steam-bath. After about two hours of heating the mixture became a thick, cream-colored paste which was further heated and stirred for an additional two hours. Then most of the benzene was removed under diminished pressure, and, after cooling, 600 ml. of ice water added to the mixture. The cold aqueous solution was extracted with ether to remove any non-acidic material and carefully acidified with cold 6*N* hydrochloric acid to congo red. The oil that separated was taken up in ether and the ether solution washed with cold, dilute sodium bicarbonate solution until the aqueous extracts were practically colorless. After the addition of 75 ml. of benzene, the ether was removed and the residual oil kept on the steam-bath for five hours under the vacuum of a water pump. The 1-benzoyl-3-carbethoxy-4-piperidone so obtained was a light yellow, transparent, viscous oil and weighed 173 g. (66%).

A sample of this material, after standing for several months, developed a few crystals on the side of the flask. Using these as seeds, it was possible to get the entire mass to crystallize by triturating it with petroleum ether (60–68°) and adding a small amount of benzene while cooling in an ice-bath. This crystalline 1-benzoyl-3-carbethoxy-4-piperidone melts at 54–56°.

Anal. Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.23. Found: C, 65.65; H, 6.27.

Attempts to cyclize the N-acetyl- and N-nitroso-di-(β-carbethoxyethyl)-amines were made with sodium ethoxide as the condensing agent. In the case of the former ester only a 10% yield of a viscous oil, which gave a strong purple color with ferric chloride, was obtained at the point where the carbethoxypiperidone should appear. In the case of the N-nitroso derivative, each drop of this compound produced a reddish coloration as it was added to a sodium ethoxide suspension in benzene. After a while a gummy reaction product collected around the stirrer. When the reaction mixture was treated with ice water, there was a vigorous evolution of nitrogen. The benzene–ether extract of this alkaline solution contained practically all of the reaction product, which was a pleasant smelling oil that could not be distilled without decomposition. Acidification of the aqueous alkaline solution gave only a trace of an oil that showed the characteristic enol coloration with ferric chloride.

1-Benzoyl-3-carbethoxy-4-hydroxypiperidine (IX).—A solution of 27.5 g. of 1-benzoyl-3-carbethoxy-4-piperidone in sufficient alcohol to make 50 ml. of solution was hydrogenated over 3 g. of Raney nickel at 120° and 2500 lb. of hydrogen pressure. The reduction appeared complete after one hour, since continuation of the hydrogenation for another four hours caused no further absorption of hydrogen. After filtering off the catalyst and evaporating the solvent, 27.2 g. of material, m. p. 106–116°, remained. After two recrystallizations from a chloroform–carbon tetrachloride mixture, 20 g. (72%) of white crystals, m. p. 123–125°, was obtained.

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 64.97; H, 6.91; C_2H_6O, 16.25. Found: C, 64.72; H, 7.04; C_2H_6O, 16.05.

The hydrogenation of the piperidone over Adams platinum oxide catalyst was very slow, requiring over twenty hours to reduce 2.25 g. of the piperidone. The product, however, was identical with that from the hydrogenation with nickel and was obtained in practically the same yield.

Guvacine Hydrochloride (X).—A slow stream of dry hydrogen chloride was passed through a 1.0-g. sample of molten 1-benzoyl-3-carbethoxy-4-hydroxypiperidine (IX), contained in a test-tube immersed in a metal-bath held at 180–200°, for two hours after the initially molten material

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.

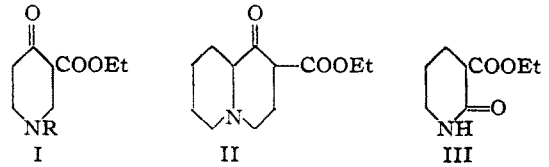
MADISON, WISCONSIN RECEIVED FEBRUARY 15, 1946

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

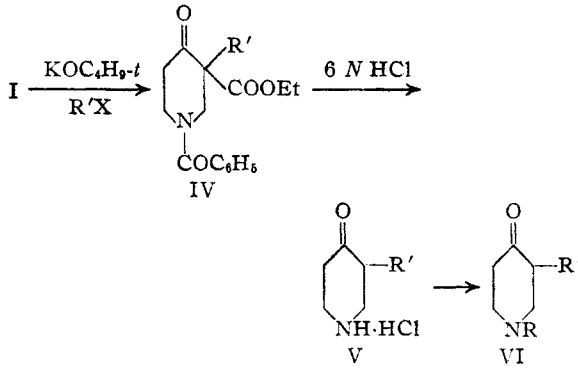
Piperidine Derivatives. XVI. C-Alkylation of 1-Benzoyl-3-carbethoxy-4-piperidone. Synthesis of Ethyl 3-Ethyl-4-piperidylacetate (*dl*-Ethyl Cincholoiponate)

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).