TABLE IV (*Concluded*)

M. p., °C.	Cold H_2SO_4	Formula	Analyses, % Calcd. C	H	S	N	Found C	H	S	N
107	No color	$C_{11}H_{11}OS_2N$	55.67	4.67	27.00	5.91	55.82	4.68	27.35	6.05
154	Intense yellow	$C_{13}H_{15}O_3S_2N$	52.50	5.09	21.55	4.71	52.56	5.25	21.52	4.92
106	No color	$C_{12}H_{13}O_2S_2N$	53.91	4.91	23.97	5.24	54.06	4.98	23.71	5.47
126	Intense yellow	$C_{12}H_{11}O_3S_2N$	51.23	3.94	22.77	4.98	51.15	4.09	22.82	5.31

The authors are indebted to Mr. W. S. Ide for the analyses (all micro) given above.

Summary

The ammonium dithiocarbamates, phenylethylammonium dithiocarbamates, dithiocarbamineglycolic acids and rhodanines derived from β-phenylethylamine, homoanisylamine, homopiperonylamine and homoveratrylamine are described, together with their preparations.

TUCKAHOE, NEW YORK

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

PIPERIDINE DERIVATIVES. XI. 3-CARBETHOXY-4-PIPERIDONE AND 4-PIPERIDONE HYDROCHLORIDE

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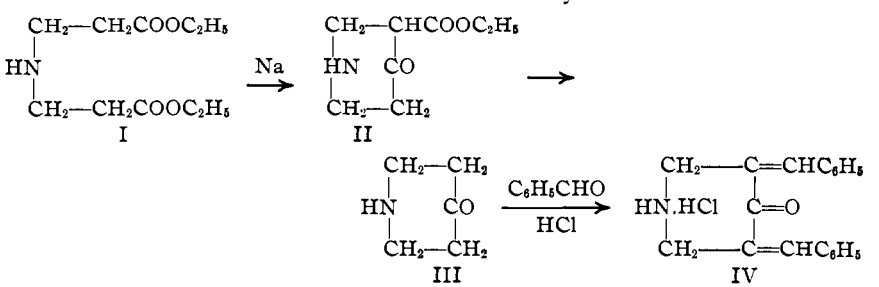
In an effort to prepare 4-piperidone, Ruzicka and Fornasir[1] carried out an internal acetoacetic ester condensation of β,β[1]-dicarbethoxydiethylamine. No attempt was made to isolate the intermediate 3-carbethoxy-4-piperidone. The reaction mixture containing this latter compound was subjected directly to reaction conditions which would bring about its hydrolysis and decarboxylation. The resulting 4-piperidone was not obtained in the form of a crystalline salt and since the free base appeared to be quite unstable it was isolated in the form of the hydrochloride of the dibenzal derivative. These transformations may be illustrated as follows



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

A considerable number of the 1-alkyl-4-piperidones have been prepared in excellent yields and isolated as crystalline hydrochlorides[2] in this Laboratory from the corresponding 1-alkyl-3-carbethoxy-4-piperidones. These latter compounds were obtained by a condensation similar to that shown above from the β,β'-dicarbethoxy diethyl alkyl amines and were isolated and purified in the form of the hydrochlorides.[3] It seemed quite probable from this work that if the intermediate 3-carbethoxy-4-piperidone (II) could be isolated and purified, the 4-piperidone (III) resulting from its hydrolysis and decarboxylation might be obtained in a useful form as a crystalline salt, since its purification would not be complicated by the association of side-reaction products resulting from the condensation of the β,β'-di-carbethoxydiethylamine (I). The carbethoxy compound (II) would appear to offer better opportunities for purification on account of its amino-β-ketonic ester structure which causes it to be soluble in acids and alkali hydroxides, but not in alkali carbonates. The present paper reports the results of this effort.

The β,β'-dicarbethoxydiethylamine which was used in the condensation was obtained from the hydrochloride which had been carefully purified by recrystallization. Whereas the di-esters of type (I) containing the various alkyl groups attached to the nitrogen instead of hydrogen are condensed by sodium to give 55–75% yields of the corresponding 1-alkyl-3-carbethoxy-4-piperidone, only a 11% yield of (II) was obtained by the condensation of β,β'-dicarbethoxydiethylamine (I). The major portion of the reaction product is a yellow gum which appears to be derived from a further condensation of (II) with itself. The 3-carbethoxy-4-piperidone was easily isolated and purified as the hydrochloride.

The hydrolysis and decarboxylation of (II) in the form of the hydrochloride took place quite readily and a crystalline hydrochloride of the piperidone (III) was obtained. Recrystallization of the latter compound from an alcohol–ether mixture gave an apparently pure product which melted at 138–140°, but gave chlorine analyses which were considerably lower than that calculated for the piperidone hydrochloride (calcd. 26.15% Cl; found, 17.41, 17.45%). All attempts to alter these values by drying the product under diminished pressure were unsuccessful. If this 138–140° melting material were dissolved in water and the solvent then evaporated off under diminished pressure, a product melting at 92–94° and containing 23.00% Cl was obtained. The analyses in the case of the product from the alcohol crystallization correspond to the piperidone hydrochloride with 1.5 C_2H_5OH of crystallization and in the case of the

[2] (a) Bolyard and McElvain, THIS JOURNAL, **51**, 922 (1929); (b) Bolyard, *ibid.*, **52**, 1030 (1930).

[3] McElvain, *ibid.*, **46**, 1721 (1924); **48**, 2179 (1926); Thayer and McElvain, *ibid.*, **49**, 2862 (1927).

water crystallization the analysis corresponds to the piperidone hydrochloride with $1H_2O$ of crystallization.

Similar abnormal analyses were obtained with certain of the 1-alkyl-4-piperidone hydrochlorides.[2] In these cases it was shown that these analyses were of no fundamental significance, since by reduction and benzoylation these 1-alkyl-4-piperidones were converted into the corresponding 1-alkyl-4-benzoyloxypiperidines. In the case of the 4-piperidone hydrochloride obtained in the present work a similar conclusion may be drawn from the fact that it was readily converted into the hydrochloride of the dibenzal-4-piperidone (IV), the structure of which has been established by Ruzicka and Fornasir.[1]

Experimental

All melting points and boiling points herein given are corrected.

β,β'-Dicarbethoxydiethylamine (I).—This compound was prepared by Ruzicka and Fornasir by the action of ethyl β-iodopropionate on ethyl β-aminopropionate and was purified by fractional distillation. The following procedure seems to be simpler and in general much more satisfactory. To a mixture of 306 g. of β-bromopropionic acid ("Organic Syntheses," Vol. III, p. 25) in 300 cc. of water, was added a suspension of 168 g. of sodium bicarbonate in 500 cc. of water. After complete neutralization and solution, 1100 cc. of ammonium hydroxide (sp. gr. 0.90) was added and the solution allowed to stand in a stoppered bottle at room temperature for four days with occasional stirring. The solution was then evaporated on a steam-bath to a volume of about 600 cc., and made acid to Congo red with dilute hydrochloric acid, using a small excess of the acid. The acidified solution was then evaporated to dryness under diminished pressure. The amino acid hydrochlorides were extracted from the gummy residue by thorough shaking with two 400-cc. portions of alcohol. After the inorganic salt was filtered off, this alcoholic solution was evaporated to dryness under reduced pressure over a steam-bath. The residue obtained after the removal of the alcohol was then esterified by refluxing with 1500 cc. of a 4% solution of dry hydrogen chloride in absolute alcohol for twelve hours. The alcohol was then completely removed under reduced pressure from a steam-bath. The thick residue was poured into a one-liter beaker and allowed to cool to room temperature. The distillation flask was rinsed with 50 cc. of water and the rinsings added, together with 70 g. of ice, to the mixture of the amino acid ester hydrochlorides. The beaker was placed in an ice–salt mixture, 200 cc. of ether was added and the contents stirred until the temperature of the liquid was below 10°. Then 100 cc. of cold concentrated potassium hydroxide solution (45% by weight) was added slowly and with rapid stirring. The temperature of the mixture was kept below 10° during the addition of the alkali. The ether layer, which now had assumed a brownish coloration, was removed and 200 cc. more of ether was added. A 50-cc. portion of the potassium hydroxide solution was then added. The ether layer was separated and the aqueous layer extracted with another 100 cc. of ether. The combined ether extracts were evaporated on a steam-bath and the residue immediately distilled under diminished pressure from an oil-bath.

The distillate was collected in two fractions. The first fraction, consisting of primary and secondary amino esters, distilled from 70–130° (10 mm.) and the second fraction, consisting of comparatively pure β,β'-dicarbethoxydiethylamine, distilled at 130–140° (10 mm.). The first fraction, upon refractionation, yielded a portion of ethyl β-aminopropionate which distilled at 70–80° (10 mm.), and a portion of the secondary

amino ester. The total yield was 15–20 g. (6–8%) of the primary amino ester and 51–57 g. (23–26%) of the β,β′-dicarbethoxydiethylamine fraction.

The secondary amino ester so obtained is best purified by recrystallization of the hydrochloride to constant melting point as described below. The pure β,β′-dicarbethoxydiethylamine is then obtained by the decomposition of the hydrochloride with potassium hydroxide in the manner described above for the liberation of the crude primary and secondary amino esters from their hydrochlorides. The pure β,β′-dicarbethoxydiethylamine boils at 137–138° (12 mm.); n_D^{25} 1.43802, d_{20}^{20} 1.0462. A recovery of 88–93% of the free secondary amino ester is possible from its hydrochloride. On account of the fact that the free secondary amino ester slowly undergoes self-condensation it is advisable to keep it as the hydrochloride.

β,β′-Dicarbethoxydiethylamine Hydrochloride.—The secondary amino ester fraction which boiled at 130–140° (10 mm.) was dissolved in 150 cc. of dry ether and any insoluble material filtered off. Dry hydrogen chloride was slowly passed into this ethereal solution. The hydrochloride, which formed readily in white flaky crystals, was filtered and washed several times with small portions of dry ether. These ether washings were similarly treated with hydrogen chloride and a second crop of crystals was obtained. In a like manner a third crop of crystals was obtained but succeeding ether washings and hydrogen chloride treatments yielded only a small amount of an oil that failed to crystallize. The secondary amine hydrochloride, upon first precipitation from the ether solution, must be thoroughly washed with ether, or be immediately recrystallized because the impure ester hydrochloride, upon standing a short time, assumes a reddish coloration that is difficult to remove. The hydrochloride after several recrystallizations from an alcohol–ether mixture melted at 79.5–80.5°.

Anal. Calcd. for $C_{10}H_{20}O_4Cl$: Cl, 14.02. Found: Cl, 13.98, 13.90.

3-Carbethoxy-4-piperidone Hydrochloride (II).—The pure β,β′-dicarbethoxydiethylamine (b. p. 137–138°, 12 mm.) as obtained from the decomposition of its hydrochloride in the manner described above was used in the preparation of the carbethoxypiperidone. To a mixture of 40 cc. of xylene and 3.9 g. of powdered sodium was added 37 g. of the secondary amino ester and the mixture warmed to 85° in an oil-bath until the reaction started. The condensation started in gradually but soon became sufficiently vigorous to cause the xylene to boil. After this initial reaction subsided, the mixture was cooled and treated with 200 cc. of ice water and the xylene extracted with ether. The water layer was made acid with hydrochloric acid and the free carbethoxy-piperidone base liberated with excess potassium carbonate. The free base was immediately extracted with ether and precipitated as its hydrochloride with dry hydrogen chloride. A yield of 4.0 g. (11%) was obtained.

The hydrochloride crystallized in the form of fine white needles and after recrystallization from alcohol–ether mixture melted at 168–169° with decomposition. It produced the characteristic deep red coloration with ferric chloride.

Anal. Calcd. for $C_8H_{14}O_3NCl$: Cl, 17.28. Found: Cl, 17.10, 17.10.

The greater portion of the reaction product consisted of a yellow gum insoluble in ether. This was dissolved in alcohol, the alcohol evaporated and the gum dried in a vacuum desiccator over sulfuric acid. It was then dissolved in 20% hydrochloric acid. A drop of the solution produced a distinct coloration with ferric chloride. Evolution of carbon dioxide resulted when this solution was refluxed and after thirty minutes' boiling no coloration was shown by ferric chloride. After removal of the water and excess hydrochloric acid under diminished pressure, an uncrystallizable gum was obtained. The original gummy reaction product appears to be a further condensation product of 3-carbethoxy-4-piperidone.

4-Piperidone Hydrochloride (III).—To 2.33 g. of 3-carbethoxy-4-piperidone was added 80 cc. of 20% hydrochloric acid and the solution refluxed until it showed no coloration with ferric chloride (about thirty minutes). The carbon dioxide which was evolved was carried by a current of carbon dioxide-free air from the reaction flask through a series of drying tubes and absorbed in a weighed ascarite bulb. A yield of 0.4451 g. (90%) of carbon dioxide was obtained. The acid solution was then evaporated to dryness under diminished pressure The resulting solid after recrystallization from an alcohol–ether mixture weighed 1.1 g. and melted at 139–141° with decomposition. After drying at 100° and 10 mm. it was analyzed.

Anal. Calcd. for $C_5H_{10}ONCl$ (4-piperidone hydrochloride): Cl, 26.15; calcd. for $C_5H_{10}ONCl \cdot 1.5C_2H_5OH$: Cl, 17.34. Found: Cl, 17.41, 17.45.

An attempt was made to free the hydrochloride from the associated solvent by recrystallization from other solvents, such as acetone, which have been found (*cf.* Ref. 2b) to give analytically pure piperidone hydrochlorides. These efforts were unsuccessful on account of the insolubility of the hydrochloride in these solvents. However, a solution of the 139–141° melting piperidone hydrochloride in water yielded a product after evaporation to dryness that melted at 92–94°. This product was found to contain 23.00% of chlorine; calcd. for $C_5H_{10}NCl \cdot H_2O$, 23.10.

3,5-Dibenzal-4-piperidone Hydrochloride (IV).—The identity of the 4-piperidone hydrochloride, melting at 138–140°, was established by converting it into the dibenzal-4-piperidone hydrochloride which has been characterized by Ruzicka and Fornasir.[1] A solution of 0.08 g. of the piperidone hydrochloride in 3 cc. of glacial acetic acid saturated with dry hydrogen chloride was treated with 0.15 cc. of benzaldehyde. After standing for twenty-four hours, a mass of yellow needle-like crystals had separated which after decantation of the acetic acid and recrystallization from alcohol weighed 0.069 g. (58%) and melted at 276–277° with decomposition. Ruzicka and Fornasir reported this compound as melting at 275–277°.

Summary

1. The preparation of 3-carbethoxy-4-piperidone hydrochloride and its hydrolysis and decarboxylation to 4-piperidone hydrochloride are described. The latter compound could not be obtained free from solvent used in its recrystallization but was characterized by its conversion into the known dibenzal-4-piperidone hydrochloride.

2. An improved method for the preparation of β,β'-dicarbethoxydiethylamine is given.

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