heated on the water-bath for thirty minutes with acetic anhydride (4 cc.) and fused sodium acetate (0.2 g.). The product crystallized on pouring the reaction mixture on ice, and was recrystallized from hot water; m. p. 114–115° (mixed m. p. unchanged); $[\alpha]^{21}_{D}$ +86.4° (*c*, 1.4; $CHCl_3$).

This pentaacetate was obtained from the acetobromoglucoheptulose, which proved that the second position was open in the former. Acetobromoglucoheptulose (0.8 g.), silver carbonate (0.6 g.), acetone (5 cc.) and water (3 drops) were placed together and kept for one hour with occasional shaking. After filtration and acetone removal, the resulting sirup crystallized and was recrystallized from ether by the addition of petroleum ether; yield, 0.4 g.; m. p. 113–114°. Pure material was obtained on one more recrystallization; yield, 0.3 g.; m. p. 114–115° (mixed m. p. unchanged); $[\alpha]^{20}_{D}$ +49°, $CHCl_3$.

Reaction between *d*-Glucoheptulose Hexaacetate and Ethyl Mercaptan.—Freshly fused zinc chloride (0.4 g.) was placed in a glass tube, followed by 3 cc. of ethyl mercaptan, 2 g. of soluble anhydrite and 1 g. of glucoheptulose hexaacetate. The tube was finally rinsed down with 3 cc. more of ethyl mercaptan, sealed and kept at room temperature for eighteen hours. The ethyl mercaptan was previously dried over soluble anhydrite.[6] The tube was then opened and the contents poured into a saturated solution of sodium bicarbonate. The precipitate and filtrate were extracted with chloroform, the extract washed with water, dried and the solvent removed with a stream of dry air. Petroleum ether was added to the resulting sirup and removed in the same manner. On repetition of the latter treatment, the product was obtained crystalline. Pure material was obtained after several recrystallizations from methanol by the addition of water; m. p. 92–93°; $[\alpha]^{25}_{D}$ +65° (*c*, 2.9; $CHCl_3$).

Anal. Calcd. for $C_{11}H_{18}O_5S_2(COCH_3)_4$: S, 13.75; acetyl, 8.58 cc. 0.1 *N* NaOH per 100 mg. Found: S, 13.49; acetyl, 8.60 cc.

The above substance was recovered unchanged after acetylation with 10 parts of dry pyridine and 20 parts of acetic anhydride for twenty-four hours at 40°. This proves that the compound contained no free hydroxyl groups. The substance showed no Fehling reduction, but was strongly reducing after acid hydrolysis. The odor of ethyl mercaptan was noted during the hydrolysis. This shows that the glycosidic hydroxyl was replaced by an ethylmercapto group.

Summary

1. α-Acetobromo-*d*-glucoheptulose and α-*d*-glucoheptulose pentaacetate have been synthesized in pure crystalline form.

2. Glucoheptulose hexaacetate reacts with ethyl mercaptan to form a crystalline product in which two acetate groups have been replaced with ethylmercapto groups.

3. The above constitutes evidence that glucoheptulose hexaacetate is a cyclic compound.

4. Evidence is given that glucoheptulose pentaacetate is a cyclic compound with an open glycosidic hydroxyl group.

COLUMBUS, OHIO RECEIVED JUNE 11, 1934

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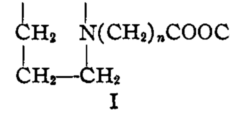
[6] W. A. Hammond and J. R. Withrow, *Ind. Eng. Chem.*, **25**, 1112 (1933).

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

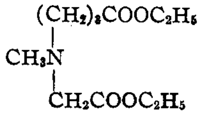
The Acetoacetic Ester Condensation. VIII. The Condensation of ω-Piperidino Esters

BY W. B. THOMAS AND S. M. MCELVAIN

In a study of the cyclization of certain 3-carbethoxypiperidino esters, it was found[1] that while ethyl β-(3-carbethoxypiperidino)-propionate (I, R is carbethoxy, *n* is 2) in xylene reacted vigorously with metallic sodium, the corresponding acetate (in which *n* is 1) remained practically unchanged when refluxed in xylene with either metallic sodium or sodium ethoxide.

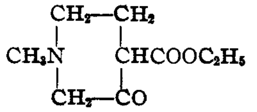


I



$$\begin{array}{l}(CH_2)_2COOC_2H_5\\ \quad |\\ CH_3N\\ \quad |\\ CH_2COOC_2H_5\end{array}$$

II



III

This apparent inability of the α-amino ester to enter into an acetoacetic ester condensation later led to the conclusion that the cyclization of such an ester as II would produce the 4-carbethoxy-3-piperidone (III) rather than the isomeric 2-carbethoxy derivative.[2] However, before such a conclusion could be made into a generalization it seemed necessary to study the behavior of various types of simple amino esters in the acetoacetic ester condensation.

The present paper reports the results obtained with a series of ω-piperidino esters (I) in which R is hydrogen, *n* varies from 1 to 4. The first at-

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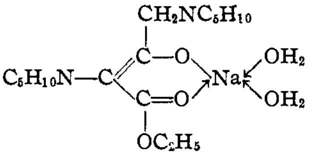
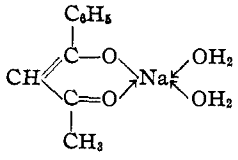
[1] McElvain and Adams, THIS JOURNAL, **45**, 2746 (1923).

[2] Prill and McElvain, *ibid.*, **55**, 1233 (1933).

tempts that were made to condense these esters were with sodium ethoxide at ordinary pressure and at temperatures that caused an active evolution of alcohol. These conditions, however, did not give satisfactory results except in the case of ethyl piperidinoacetate. Ethyl β-piperidinopropionate suffered considerable deamination and no definite condensation product could be isolated; in the case of ethyl γ-piperidinobutyrate, only γ-piperidinobutyric acid could be isolated from the reaction mixture after 70–90% of the theoretical quantity of alcohol for an acetoacetic ester condensation had distilled out. It was decided, therefore, to carry out these condensations under diminished pressure, using a modification of the procedure which has been found to be effective for the condensation of the higher aliphatic esters.[3] Under these conditions the condensations went smoothly.

Only in the case of ethyl piperidinoacetate was it possible to isolate the dipiperidino-β-keto ester. The properties of this particular compound are of considerable interest. When benzene was added directly to the reaction mixture resulting from the reaction of the acetate with sodium ethoxide and this solution diluted with ether, a clear solution resulted, from which a very small amount of sodium piperidinoacetate settled out after a few days standing. When, however, this benzene–ether solution was shaken with water, white crystals began to precipitate and soon the solution was semi-solid. This crystalline material gave 1,3-dipiperidino-acetone on hydrolysis and also gave carbon, hydrogen, nitrogen, sodium and carbon dioxide analyses corresponding to the dihydrate of sodio-α,γ-dipiperidinoacetoacetic ester. This hydrate is insoluble in water (cold or hot), ether and cold benzene, but quite soluble in boiling benzene or alcohol. It is best recrystallized from the latter solvent. It gradually darkens in color on exposure to air but appears to be perfectly stable when kept in an atmosphere of nitrogen. Attempts to dehydrate the compound at 100° in a vacuum resulted in decomposition. The anhydrous compound was obtained by removal of the solvent by distillation from a benzene solution of the hydrate. The anhydrous compound is very soluble in such solvents as petroleum ether and diethyl ether, and when a solution in the latter solvent is shaken with water the more insoluble hydrate separates out. These properties are best explained by the chelate structure (IV) in which the sodium atom assumes a co-valency of four.


IV


V

A similar structure (V) has been suggested[4] for the sodium derivative of benzoyl acetone. The latter compound, however, differs from the one reported in the present paper in that it shows salt-like properties in the anhydrous form, whereas (IV) does not show these properties in either form.

There was no evidence of chelation in the dipiperidino-keto esters resulting from the condensation of the higher piperidino esters. Attempts to isolate these keto esters were unsuccessful due to their decomposition on distillation. The reaction mixture, therefore, was subjected to hydrolysis and the condensation products isolated as the ω,ω′-dipiperidino ketones, $(C_5H_{10}N(CH_2)_n)_2CO$, the properties of which are listed in Table III.

Table I summarizes the reaction conditions and yields of products resulting from the condensation of the various piperidino esters.

TABLE I

CONDENSATION OF ω-PIPERIDINO ESTERS, $C_5H_{10}N(CH_2)_nCOOC_2H_5$ BY SODIUM ETHOXIDE AT 110–115

n is	Moles of ester used	Pressure, mm.	Reaction, time, min.	Yield of alcohol, %	Yield of product isolated,[a] %
1	0.29	37	60	83	52[b]
2	.27	30	40	79	68[c]
3	.38	20	120	82	53[d]
4	.24	20	240	74	65[e]

[a] Based on ester not recovered as such or as the hydrochloride of the ω-piperidino acid. [b] IV. [c] 1,5-Dipiperidinopentanone-3 dihydrochloride. [d] 1,7-Dipiperidinoheptanone-4. [e] 1,9-Dipiperidinononanone-5.

It may be seen from Table I that there is no great difference in the readiness with which the α- and β-piperidino esters undergo the acetoacetic ester condensation, judging from the time required for a substantial yield of alcohol to distil from the reaction mixture. The γ- and δ-piperidino esters are decidedly slower in the reaction than are the lower esters.

These results naturally suggested further experiments with ethyl (3-carbethoxypiperidino)-

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[3] Briese and McElvain, THIS JOURNAL, **55**, 1697 (1933).

[4] Sidgwick and Brewer, *J. Chem. Soc.*, **127**, 2379 (1925).

acetate which had previously failed to undergo any reaction with sodium or sodium ethoxide in xylene solution.[1] When this ester was allowed to react with sodium ethoxide under the conditions described above for the simple piperidino esters, alcohol distilled from the reaction mixture just as readily as it did in the case of ethyl piperidinoacetate. Apparently, the earlier failure to condense this ester with sodium ethoxide was due to dilution with xylene. With metallic sodium, however, the earlier results were confirmed, *i. e.*, after refluxing the ester in xylene solution for forty-five minutes with powdered sodium most of the ester was recovered unchanged. Indeed, it was found that sodium remained practically unchanged when heated to 150° for thirty minutes with the ester alone. Similar results were obtained with ethyl piperidinoacetate. With ethyl γ-piperidinobutyrate, however, there was a rather vigorous initial reaction and after thirty minutes at 150° most of the sodium had disappeared. These results, together with those obtained from ethyl (β-carbethoxypiperidino)-propionate[1] seem to indicate that the presence of a piperidino group in the α-position inhibits the reaction of an ester with sodium. The apparent ease with which these α-piperidino esters undergo condensation with sodium ethoxide, together with their failure to show any appreciable reaction with metallic sodium, would seem to offer convincing evidence that the metal is not the active condensing agent in the acetoacetic ester condensation.[5]

Experimental

ω-Piperidino Esters.—These esters were made by the reaction of 2 moles of piperidine with 1 mole of the corresponding ω-halogen ester in dry benzene solution. After filtering off the precipitated piperidine hydrohalide and removal of the benzene by distillation, the piperidino esters were distilled under diminished pressure. Their properties and the analyses of two not previously reported in the literature are listed in Table II.

TABLE II

ω-PIPERIDINO ESTERS, $C_5H_{10}N(CH_2)_nCOOC_2H_5$

n is	Formula	B. p., °C. (mm.)	d^{25}_{25}	n^{5}_{D}	Analyses, N, % Calcd.	Analyses, N, % Found
1[a]	......	94–94.5 (11)	....	....	..	..
2[b]	......	105–106 (11)	....	....	..	..
3	$C_{11}H_{21}O_2N$	128–130 (19)	0.9599	1.4539	7.03	7.13
4	$C_{12}H_{23}O_2N$	132–134 (10)	.9540	1.4552	6.57	6.90

[a] *Cf.* Gabriel and Leupold, *Ber.*, **31**, 2840 (1898).

[b] *Cf.* Wedekind, *ibid.*, **32**, 727 (1899).

Condensation of the ω-Piperidino Esters.—In a 200-cc. 2-necked round-bottomed flask carrying a side arm set for distillation and a brass stirrer fitted with machined conical bearings which allowed for its operation under diminished pressure was placed the amount of piperidino ester shown in Table I together with a one-half molecular equivalent of sodium ethoxide.[6] The side arm was attached to a distilling flask whose side arm connected with a trap cooled with solid carbon dioxide and acetone. The outlet of this trap was connected through a calcium chloride tube to a water pump. The flask was then heated in an oil-bath at 110–115° for the time and under the pressure indicated in Table I. The pressure was such that no appreciable amount of the ester collected in the distilling flask.

Sodio α,γ-Dipiperidinoacetoacetic Ester Dihydrate (IV).—After the alcohol distillation stopped in the case of ethyl piperidinoacetate, 35 cc. of benzene and 250 cc. of ether was added to the reaction mixture while still warm. The resultant solution was shaken with 25 cc. of water and, after separation of the aqueous layer, the ether layer was cooled. The compound (IV) precipitated, was filtered off and dried *in vacuo*. This material after recrystallization from alcohol softened at about 100°, but possessed no definite melting point, decomposing as the temperature was raised past this point.

Anal. Calcd. for $C_{16}H_{27}O_3N_2Na \cdot 2H_2O$: C, 54.24; H, 8.76; N, 7.91; Na, 6.50. Found: C, 54.67; H, 8.40; N, 8.11; Na, 6.82.

When the solvent was carefully removed from a solution of this dihydrate in benzene, an amorphous powder which was very soluble in petroleum ether, diethyl ether and benzene was obtained. An ether solution of this material gave the original dihydrate on shaking with water.

A 0.9261-g. sample of the dihydrate (IV) was hydrolyzed with 25 cc. of 20% sulfuric acid and the evolved carbon dioxide absorbed in an ascarite bulb and weighed. Calcd., CO_2: 0.1151 g. Found, 0.1149 g.

A 9.8-g. sample of (IV) was refluxed with a solution of 20 g. of sodium hydroxide in a mixture of 75 cc. of alcohol and 100 cc. of water in an atmosphere of nitrogen for one hour. Two layers were present at the end of this time. Then 200 cc. of ether was added to the reaction mixture, and after separation of the ether layer, the ether was removed by distillation. The residue from this distillation was dissolved in 20 cc. of absolute alcohol and treated with hydrogen chloride in the cold. There was obtained 3.5 g. (43%) of dipiperidino acetone dihydrochloride. The properties of this compound are shown in Table III. Attempts to distil the free amino ketone resulted in sufficient decomposition that it was not possible to obtain an analytically pure sample.

ω,ω'-Dipiperidino Ketones.—After the alcohol had distilled out from the reaction of the β-, γ- and δ-piperidino esters with sodium ethoxide, the remaining reaction mixture was refluxed for two hours with 150 cc. of a 20% hydrochloric acid solution. The solution was then cooled, made strongly alkaline with sodium hydroxide and the alkaline solution extracted with ether. After drying with anhydrous potassium carbonate the ether was removed by distillation and, in the cases of the γ- and δ-piperidino esters, the remaining ω,ω'-dipiperidino ketones distilled. In the case of the β-piperidino ester, because of the in-

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(5) *Cf.* Snell and McElvain, THIS JOURNAL, **53**, 2314 (1931).

(6) Houben-Weyl, 1922, Vol. II, p. 578.

stability of β-amino ketones the residue was dissolved in 50 cc. of absolute alcohol and the amino ketone converted to the dihydrochloride by treatment with dry hydrogen chloride. The properties and analyses of these ketones and their hydrochlorides are listed in Table III.

In one experiment the ethyl γ-piperidinobutyrate was condensed by sodium ethoxide in the manner described above. The reaction mixture was diluted with benzene and ether and the resulting solution shaken with water as in the isolation of the above chelate. There was no precipitate in either solution. The layers were separated, and the solvent removed from the non-aqueous layer. On hydrolysis of the remaining residue a 51% yield of the corresponding dipiperidino ketone was obtained. The aqueous layer was acidified with hydrochloric acid, evaporated to dryness, and the residue extracted with boiling absolute alcohol. The theoretical amount of sodium chloride remained undissolved by the alcohol, indicating hydrolysis rather than chelation of the sodium salt of the dipiperidino-β-keto ester.

ω-Piperidino Acid Hydrochlorides.—The aqueous solution remaining after the extraction of the dipiperidino ketones was acidified with hydrochloric acid, evaporated to dryness and extracted with absolute alcohol and after filtering off the sodium chloride the alcoholic solution was again evaporated to dryness. The remaining hydrochloride was then recrystallized from an alcohol–ether mixture. In this manner 7.4 g. of β-piperidinopropionic acid hydrochloride, 4.7 g. of γ-piperidinobutyric acid hydrochloride, and 8.1 g. of δ-piperidinovaleric acid hydrochloride were obtained from runs involving the quantities of piperidino esters indicated in Table I. The properties and analyses of the hydrochlorides of these piperidino acids are listed in Table IV.

When 25 g. of ethyl γ-piperidinobutyrate was condensed by sodium ethoxide at atmospheric pressure, 71% of the theoretical quantity of alcohol distilled from the reaction mixture. When the latter was treated with 4 cc. of glacial acetic acid in a mixture of 50 cc. of benzene and 200 cc. of ether, the sodium acetate filtered off, and the solvent distilled, 4 g. of a fraction, b. p. 162–164° (2 mm.) was obtained. The remainder of the reaction mixture was an undistillable tar. This fraction solidified and after recrystallization from benzene melted at 71–72°. It was identified as γ-piperidinobutyric acid by analysis and comparison with an authentic specimen prepared by the hydrolysis of ethyl γ-piperidinobutyrate.

Anal. Calcd. for $C_9H_{17}O_2N$: N, 8.19. Found: 7.98.

TABLE III

ω,ω′-DIPIPERIDINO KETONES, $(C_5H_{10}N(CH_2)_n)_2CO$

n is	Formula	B. p., °C. (mm.)	d^{25}_{25}	n^{25}_D	Analyses, N, % Calcd.	Found
3	$C_{17}H_{32}ON_2$[a]	188–190 (3)	0.9594	1.4865	10.00	10.10
4	$C_{19}H_{36}ON_2$[b]	220–221 (2)	.9508	1.4853	9.09	9.29

DIHYDROCHLORIDES

n is	Formula	M. p., °C.	Analyses, Cl, % Calcd.	Found
1	$C_{13}H_{26}ON_2Cl_2$	175–195 (dec.)	23.91	23.84
2	$C_{15}H_{30}ON_2Cl_2$[c]	212–214	21.84	21.73
3	$C_{17}H_{34}ON_2Cl_2$	241–242	20.10	20.00
4	$C_{19}H_{36}ON_2Cl_2$	222–223	18.64	18.73

[a] Semicarbazone, $C_{18}H_{35}ON_5$, m. p. 82–83°. Calcd.: N, 20.77. Found: 20.77. [b] Semicarbazone, $C_{20}H_{39}ON_5$, m. p. 88–89°. Calcd.: N, 19.18. Found: 19.12. [c] Semicarbazone, $C_{16}H_{31}ON_5$, m. p. 96–97°. Calcd.: C, 62.14; H, 10.03. Found: 62.13, 9.74. This compound gave high and inconsistent N analyses by the semi-micro Dumas method.

TABLE IV

HYDROCHLORIDES OF ω-PIPERIDINO ACIDS $C_5H_{10}N(CH_2)_nCOOH$

n is	Formula	M. p., °C.	Analyses, Cl, % Calcd.	Found
2	$C_8H_{16}O_2NCl$	206–209	18.36	18.40
3	$C_9H_{18}O_2NCl$	189–190	17.10	17.06
4	$C_{10}H_{20}O_2NCl$	198–200	16.03	16.00

Experiments with Ethyl (3-Carbethoxypiperidino)-acetate.—The condensation of this ester with sodium ethoxide was carried out in the same manner as described above. When 25 g. (2 mols) of this ester was heated with 3.5 g. (1 mol) of sodium ethoxide at 110–115° and 20 mm. pressure for thirty-five minutes, 3.9 g. (83%) of alcohol distilled from the reaction mixture. There was no indication of a chelate compound of the type of IV having formed; attempts to isolate a crystalline hydrochloride from the hydrolysis of the reaction mixture were unsuccessful.

To 1.3 g. of powdered sodium under 40 cc. of xylene was added 13.7 g. of the ester and the xylene refluxed for forty-five minutes. After this time the sodium appeared unchanged and after decanting the xylene solution 69% of the original ester was recovered from it by distillation.

To 10 g. of the ester was added 0.3 g. of sodium and the mixture heated in an oil-bath to 150° for thirty minutes. After this time practically all of the sodium remained unchanged.

The latter experiment was repeated using both ethyl piperidinoacetate and ethyl γ-piperidinobutyrate instead of ethyl (3-carbethoxypiperidino)-acetate. In the case of the former ester the behavior was analogous to that described above. With the γ-piperidino ester a vigorous reaction with the sodium set in at 125°. The temperature was gradually raised to 150° and after thirty minutes most of the sodium had disappeared.

Summary

A study of the acetoacetic ester condensation of ω-piperidino esters, $C_5H_{10}N(CH_2)_nCOOC_2H_5$, in which *n* varies from 1 to 4 has been made. In the case of *n* is 1 a hydrated chelate form of sodio-dipiperidino-acetoacetic ester was isolated. When *n* is greater than 1 the condensation products were isolated as their hydrolysis products, ω,ω-dipiperidino ketones.

The behavior of the α-piperidino esters toward sodium and sodium ethoxide furnishes further evidence that sodium is not the active condensing agent in the acetoacetic ester condensation.

MADISON, WISCONSIN RECEIVED JUNE 13, 1934