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THE SCHMIDT REACTION WITH 3-ETHOXYCARBONYL-4-PIPERIDONES AND THE SYNTHESIS OF SIX 5-HOMOPIPERAZINONES[1]

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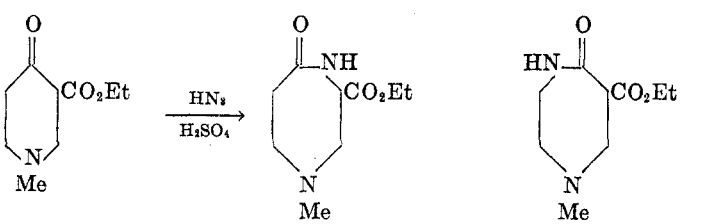
In the previous communication (1) of this series it was demonstrated that 4-piperidones undergo conversion during the Schmidt reaction to 5-homopiperazinones. This paper reports the application of the Schmidt reaction to 3-ethoxycarbonyl-4-piperidones and the synthesis of six hitherto unreported homopiperazinones.

All of the investigated piperidones with one exception are known compounds and were prepared by procedures which did not differ significantly from those previously reported. The one exception is 1,5-dimethyl-3-ethoxycarbonyl-4-piperidone (V) which appears to have been unreported although Howton (2) has described the methyl ester. The ethyl esters, numbered (I) and (II) in the experimental, which were used for the preparation of V appear to be in a similar category.

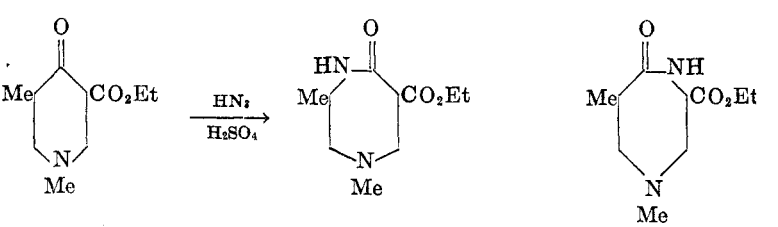
The acid-catalyzed reaction of *beta*-keto esters with hydrazoic acid was first reported by Schmidt (3), who applied the reaction to ethyl acetoacetate and various *alpha*-alkylated derivatives. Subsequently Adamson (4) prepared ornithine and lysine from 2-ethoxycarbonylcyclopentanone and 2-ethoxycarbonylcyclohexanone respectively. In all cases only products formed by the migration of the alkoxycarbonylalkyl group were isolated.

1.



III IV IV′

2.



V VI VI′

[1] An abstract of a thesis submitted by A. J. Besozzi to the Faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1951.

The accompanying equations 1 and 2 illustrate the Schmidt reaction with the 3-ethoxycarbonyl-4-piperidones III and V. The products of these reactions are formulated as the homopiperazinones IV and VI. The structures of the isomeric homopiperazinones IV′ and VI′, whose presence also was indicated, are included for comparison.

The homopiperazinones IV and VI were isolated in yields of about 30 %. Since the crude product gave a negative ferric chloride test the low yield cannot be attributed to incomplete reaction. No carbon dioxide was evolved during the reaction which precludes decarboxylation before or after formation of the amide linkage. Possible explanations of the low yield are an acid-catalyzed aldol condensation and/or the formation of acids by cleavage of the piperidone or homopiperazinone ring.

Evidence for structures IV and VI was obtained by hydrolytic degradation. For example, pyruvic acid and a volatile base were isolated after prolonged acid hydrolysis of the product produced from III. The probable intermediate source of these substances is indicated in equation 3. It has been assumed that *beta* elimination accompanied hydrolysis of the ester and amide linkages. No search was made for acrylic acid and methylamine could not be separated from the small amount of volatile base isolated. Ammonia was detected by means of a spot test.

3. $$\text{IV} \xrightarrow[H_2O]{HCl} CH_3NHCH_2CH(NH_2)CO_2H \rightarrow CH_3NH_2 + NH_3 + CH_3COCO_2H + CH_2{=}CHCO_2H$$

In addition a slow evolution of carbon dioxide was observed. This observation is not in agreement with structure IV but can be attributed to the presence of pyruvic acid. Under these conditions IV′ might be expected to yield N-methylethylenediamine and acrylic acid accompanied by rapid evolution of carbon dioxide. When the product from the Schmidt reaction on V was degraded in like fashion, 2-amino-1-methylaminopropane was isolated as indicated in equation 4. Early and vigorous evolution of carbon dioxide was observed. The isomeric homopiperazinone VI′ might be expected to yield pyruvic acid, ammonia, methylamine and methacrylic acid but not a diamine.

4. $$\text{VI} \xrightarrow[H_2O]{HCl} CH_3NHCH_2CH(NH_2)CH_3 + CO_2 + CH_2{=}CHCO_2H$$

In order to determine whether any of the isomeric homopiperazinones IV′ and VI′ were formed both of the reaction products were hydrolyzed before any purification. From crude homopiperazinone prepared from III there was obtained N-methylethylenediamine in addition to the products previously mentioned; while from V, pyruvic acid and ammonia were isolated in addition to 2-amino-1-methylaminopropane. These results demonstrated the presence of both isomers and simultaneously established this technique as a method of structure determination.

Although the yields of the homopiperazinones IV and VI were low some comment concerning the correlation of these data with the presently accepted

mechanism of the Schmidt reaction is appropriate since the isolation of VI represents the first evidence for appreciable migration of alkyl group rather than the ethoxycarbonylalkyl group in a *beta*-keto ester. In 1948 Smith (5) proposed that the Schmidt reaction with carbonyl compounds proceeded by a carbonium ion mechanism and involved a *trans* migration concurrent with loss of nitrogen. Subsequently Smith and Horwitz (6) studied a series of *para*-substituted benzophenones and concluded that the steric factor is of greater importance than any migratory aptitude. The formation of VI by migration of an alkyl group rather than the ethoxycarbonylalkyl group appears to us to constitute further evidence for the importance of steric factors in the Schmidt reaction. Fischer-Hirschfelder models were constructed for the Smith-Horwitz intermediate derivable from V. From these models it was deduced that the methyl group *alpha* to the carbonyl exerted at least as great a steric effect as the ethoxycarbonyl group.

Four other symmetrically substituted 4-piperidones were converted to 5-homopiperazinones by the Schmidt reaction. The names of these compounds and pertinent data are summarized in Tables I and II. The assignment of structures to these cyclic amides was based on hydrolytic degradation to previously reported ethylenediamines. A comparison of the melting points of dihydrochlorides or dipicrates, and dibenzoyl derivatives is given in Table III. The dibenzoyl derivative of 2-methylaminophenethylamine was previously unreported. No attempt was made to isolate acrylic acid after any of these hydrolyses but cinnamic acid was obtained in good yield from 1-methyl-2,7-diphenyl-5-homopiperazinone (X).

TABLE I

5-HOMOPIPERAZINONES

Cp'd Number	5-Homopiperazinone	Yield, %	m.p., °C.	Formula	Analyses					
					C		H		N	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
VII	1-Phenyl-	71	117–118	$C_{11}H_{14}N_2O$	69.4	69.4	7.4	7.2	14.7	14.8
VIII	1-Benzyl-	74	128–129	$C_{12}H_{16}N_2O$	70.6	70.9	7.9	7.8	13.7	13.9
IX	1-Phenethyl-	74	137–138	$C_{13}H_{18}N_2O$	71.5	71.5	8.3	8.0	12.9	13.2
X	1-Methyl-2,7-diphenyl-	95	183.5–184	$C_{18}H_{20}N_2O$	77.1	77.1	7.2	7.3	10.0	9.8

TABLE II

PICRATES OR HYDROCHLORIDES OF THE 5-HOMOPIPERAZINONES

5-Homopiperazinone	Derivative	m.p., °C.	Formula	Analysis N	
				Calc'd	Found
1-Phenyl-	Picrate	164–165	$C_{17}H_{17}N_5O_8$	16.7	16.8
1-Benzyl-	Hydrochloride	227–228	$C_{12}H_{17}ClN_2O$[a]	11.6	11.7
1-Phenethyl-	Picrate	177–178	$C_{19}H_{21}N_5O_8$	15.7	15.9
1-Methyl-2,7-diphenyl-	Picrate	213–214	$C_{24}H_{23}N_5O_8$	13.7	13.9

[a] Cl *Anal.* Calc'd: 14.7. Found: 14.6.

TABLE III

DIAMINES FROM 5-HOMOPIPERAZINONES

5-Homopiperazinones	Diamine	Yield, %	Dihydrochloride m.p., °C		N,N'-Dibenzoyldiamine m.p., °C	
			Found	Reported	Found	Reported
1-Phenyl-	N-Phenylethylene-diamine	46	[a]		150–151	147.5 (8)
1-Benzyl-	N-Benzylethylene-diamine	44	251–252	253 (9)	186.5–187	188 (10)
1-Phenethyl-	N-Phenethylethyl-enediamine	31	238–246d	245 (11)	124–125	124 (12)
1-Methyl-2,7-diphenyl-	2-Methylamino-phenethylamine	62	231–232	230 (13)	179.5–180	[b]

[a] *Dipicrate:* m.p. 179–180°; reported 179–180° (7). [b] Previously unreported; analysis in experimental.

The use of homopiperazinones as a source of homopiperazines was demonstrated by the reduction with lithium aluminum hydride of 1-benzyl-5-homopiperazinone (VIII) to 1-benzylhomopiperazine in excellent yield.

EXPERIMENTAL

All melting points are corrected. Microanalyses performed by W. Manser, Zürich. The acrylates used in the synthesis of starting materials were generously contributed by the Rohm and Hass Co.

Ethyl 3-methylamino-2-methylpropanoate (I) *and oxalate.* An absolute ethanol (110 g.) solution of ethyl methacrylate (182.4 g., 1.25 moles) was added with cooling over a period of one half hour to an ethanol (125 g.) solution of methylamine (32.7 g., 1.07 moles). After the stoppered reaction vessel was allowed to stand at room temperature for three days, the alcohol was removed under reduced pressure and the fraction boiling at 53–54° at 7 mm. was collected, $n_D^{26°}$ 1.4258. The yield was 78% (120 g.).

Anal. Calc'd for $C_7H_{15}NO_2$: C, 57.9; H, 10.4; N, 9.7.
Found: C, 58.0; H, 10.2; N, 9.6.

The *acid oxalate* was prepared by adding a saturated isopropyl ether solution of oxalic acid to an isopropyl ether solution of the amino ester and was obtained from ethanol as colorless plates of m.p. 149.5–150°.

Anal. Calc'd for $C_9H_{17}NO_6$: C, 45.9; H, 7.3; N, 6.0.
Found: C, 45.9; H, 7.2; N, 6.2.

Methyl(2-ethoxycarbonylethyl)(2-ethoxycarbonylpropyl)amine (II) *and oxalate.* Ethyl acrylate (83 g., 0.83 mole) was added with cooling over a period of 20 minutes to the amino ester I (120.4 g., 0.83 mole). After the stoppered flask was allowed to stand at room temperature for five days, the volatile materials were removed at the water-pump at a bath temperature of 50–60°. Distillation was continued and the fraction boiling at 108–109° at 2 mm. was collected, $n_D^{22°}$ 1.4362. The yield was 78% (146.5 g.).

Anal. Calc'd for $C_{12}H_{23}NO_4$: C, 58.8; H, 9.4.
Found: C, 58.8; H, 9.4.

Acid oxalate: colorless plates from ethanol, m.p. 116.5–117.5°.

Anal. Calc'd for $C_{14}H_{25}NO_8$: C, 50.1; H, 7.5; N, 4.2.
Found: C, 50.4; H, 7.7; N, 4.5.

1,5-Dimethyl-3-ethoxycarbonyl-4-piperidone hydrochloride (V). This compound was prepared from II by the procedure described by Howton (2) for the methyl ester. Re-

crystallization of the hydrochloride from a mixture of absolute ethanol and ethyl ether afforded V as a colorless, microcrystalline powder of m.p. 97–100°d.

Anal. Calc'd for $C_{10}H_{15}ClNO_3$: N, 5.9. Found: N, 5.6.

1,3-Dimethyl-4-piperidone hydrochloride. This compound was prepared from V as described by Howton (2) as a check on the identity of V, m.p. 192–193°d. Howton reported a m.p. of 194.5–195.3°.

1-Methyl-3-ethoxycarbonyl-5-homopiperazinone (IV). A chloroform solution of hydrazoic acid was prepared and the titer determined as described in *Organic Reactions* (3). To 15–20 ml. of this chloroform solution containing 0.43 g. (0.01 mole) of hydrazoic acid was added 2.21 g. (0.01 mole) of 1-methyl-3-ethoxycarbonyl-4-piperidone hydrochloride (III) (14, 15). This chloroform solution was added dropwise to conc'd sulfuric acid (7 ml.) in a three-necked flask equipped with a mechanical stirrer and a condenser. A temperature close to 0° was maintained by external cooling. The evolved gas was analyzed for carbon dioxide by passage through barium hydroxide solution and the volume of nitrogen was measured by collection over water. No carbon dioxide was detected. At the end of two to three hours when the volume of nitrogen collected approximated the theoretical amount the reaction mixture was poured into ice-water and solid potassium carbonate was added, with external cooling, until a sludge was produced. This sludge was extracted with fifteen 50-ml. portions of an ethyl ether, chloroform mixture (3-2). The combined extracts were dried over potassium carbonate and brought to dryness under reduced pressure to yield 1.6 g. of a yellow oil which gave a negative ferric chloride test. Crystallization was accomplished from an isopropyl ether, chloroform mixture (10–1), yield 29% (0.58 g.). Recrystallization from purified ligroin gave IV as colorless plates of m.p. 85–86°.

Anal. Calc'd for $C_9H_{16}N_2O_3$: C, 54.0; H, 8.1; N, 13.9.
Found: C, 54.2; H, 7.9; N, 14.0.

1,3-Dimethyl-6-ethoxycarbonyl-5-homopiperazinone (VI) *and picrate.* The procedure employed for the preparation of this compound was identical with that used for IV. Again carbon dioxide was not evolved during the reaction. From 2.35 g. (0.01 mole) of V there was obtained 1.93 g. of a yellow oil which slowly crystallized. A ferric chloride test was negative. Recrystallization from isopropyl ether, chloroform (10–1) gave VI as feathery needles, yield 36% (0.76 g.). After an additional recrystallization from purified ligroin with 88% recovery VI melted at 101–102°.

Anal. Calc'd for $C_{10}H_{18}N_2O_3$: C, 56.1; H, 8.5; N, 13.1.
Found: C, 56.0; H, 8.4; N, 13.2.

The *picrate* was prepared in water and recrystallized from ethanol, m.p. 160–161°.

Anal. Calc'd for $C_{16}H_{21}N_5O_{10}$: N, 15.8. Found: N, 16.0.

Degradation of 1-methyl-3-ethoxycarbonyl-5-homopiperazinone (IV). This homopiperazinone IV (0.40 g., 2 millimoles) was dissolved in 5 ml. of 20% hydrochloric acid and the solution was refluxed. Any evolved gases were passed through a barium hydroxide solution protected from the atmosphere by an Ascarite tube. Evolution of carbon dioxide was first detected about one hour after refluxing had commenced. After six hours the solution gave a yellow precipitate with 2,4-dinitrophenylhydrazine. Recrystallization from acetic acid gave fluffy yellow needles of m.p. 217–218° which showed no depression of m.p. when mixed with an authentic sample of pyruvic acid 2,4-dinitrophenylhydrazone.

After a total of five days of refluxing the then colored solution was concentrated almost to dryness. The method of Mulliken (16) for the separation of volatile from non-volatile amines was applied to the residue with the following results: no non-volatile amine could be detected while the volatile base, obtained as the hydrochloride, appeared to be ammonia, yield 33%. Identification was accomplished by a positive Riegler test (17) and failure to separate any methylamine hydrochloride from a number of combined volatile amine fractions by extraction with anhydrous butanol.

Degradation of 1,3-dimethyl-6-ethoxycarbonyl-5-homopiperazinone (VI). The homopiperazinone VI (1.00 g., 4.6 millimoles) was dissolved in 15 ml. of 20% hydrochloric acid and the solution was treated as just described. Evolution of carbon dioxide was observed

as soon as refluxing commenced. Neither pyruvic acid nor volatile amine were detected but a non-volatile amine, *2-amino-1-methylaminopropane*, was isolated as the *dihydrochloride*, yield 34% (0.25 g.), m.p. 175–176°; reported (18) 175–176°. The *dibenzoyl* derivative melted at 138.5°; reported (18) 138–138.5°.

Degradation of crude IV *and crude* VI. Crude IV (1.83 g.), obtained directly without purification from the piperidone III as previously described, was dissolved in hydrochloric acid and the solution was treated as described under the heading *Degradation* IV. The results were as follows: initial and subsequent evolution of carbon dioxide, isolation of pyruvic acid 2,4-dinitrophenylhydrazone, isolation of ammonium chloride (71 mg.), and isolation of the non-volatile amine *N-methylethylenediamine dihydrochloride* (54 mg.), m.p. 130–132°; reported (19) 130–132°. The *dipicrate* of N-methylethylenediamine was also prepared, m.p. 220–222°; reported (19) 220–222°.

Crude VI (1.83 g.) obtained from the piperidone V and treated in the same manner as crude IV gave carbon dioxide, pyruvic acid 2,4-dinitrophenylhydrazone, ammonium chloride (71 mg.), and 2-amino-1-methylaminopropane dihydrochloride (0.663 g.).

Preparation of the 4-piperidones. 1-Phenyl-4-piperidone was prepared by previously reported (20) reactions from ethyl 3-phenylaminopropanoate which was synthesized in 71% yield from aniline and ethyl acrylate by the procedure employed by Southwick and Seivard (21) for the preparation of the methyl ester.

1-Benzyl-4-piperidone was prepared as described by Stock and McElvain (22).

1-Phenethyl-4-piperidone was synthesized as described by Bolyard and McElvain (23) from bis-(2-ethoxycarbonylethyl)phenethylamine. The latter compound was prepared in 70% yield from phenethylamine and ethyl acrylate.

1-Methyl-2,6-diphenyl-4-piperidone was prepared essentially as described by Riedel (24 in the patent literature, m.p. 150–151°. Riedel reported 152–153°.

General procedure for the preparation of the 5-homopiperazinones VII, VIII, IX, and X. A chloroform solution of the 4-piperidone hydrochloride or free base (0.01 mole) was cooled in an ice-bath and stirred as conc'd sulfuric acid (10 ml.) was added dropwise. Then solid sodium azide (0.025 mole) was added over a period of one hour. The stirring was continued for an additional 30 minutes and the various reaction mixtures were worked up by the procedure previously described for the esters. Each of these 5-homopiperazinones was recrystallized from a mixture of benzene and purified ligroin. Further data on these compounds are reported in Table I. Picrates or hydrochlorides were prepared in the usual manner with the data given in Table II.

Degradation of the 5-homopiperazinones VII, VIII, and IX. The 5-homopiperazinone was refluxed with hydrochloric acid (20%) for 50 hours and the solution was decolorized as necessary. Evaporation of the solvent under reduced pressure gave the dihydrochloride of the appropriate diamine. These data are reported in Table III.

Degradation of 1-methyl-2,7-diphenyl-5-homopiperazinone (X). *Isolation of cinnamic acid. Preparation of N,N'-dibenzoyl-2-methylaminophenethylamine.* The homopiperazinone X was dissolved in hydrochloric acid (20%) and the solution alternately was refluxed and extracted with ethyl ether until no more solid separated from the cold reaction mixture. Evaporation of the ether extracts gave a colorless solid which showed no depression in m.p. when mixed with an authentic sample of cinnamic acid, yield 84%.

The aqueous fraction was evaporated to yield 2-methylaminophenethylamine dihydrochloride, see Table III. The hitherto unreported dibenzoyl derivative, N,N'-dibenzoyl-2-methylaminophenethylamine, was prepared in the usual way and was obtained as colorless needles from ethanol, m.p. 179.5–180°.

Anal. Calc'd for $C_{23}H_{22}N_2O_2$: N, 8.0. Found: N, 8.2.

1-Benzylhomopiperazine oxalate and picrate. Lithium aluminum hydride (0.35 g., 9.2 millimoles) was added to 40 ml. of anhydrous tetrahydrofuran and the mixture was refluxed for several hours. To the resulting solution and suspension was added 1-benzyl-5-homopiperazinone (VIII) (0.852 g., 4.2 millimoles) dissolved in 40 ml. of tetrahydrofuran. After refluxing for seven hours the reaction mixture was cooled and the excess lithium aluminum hydride destroyed with water. The tetrahydrofuran layer was separated and 100 ml. of a

20% solution of sodium potassium tartrate was added to the aqueous suspension which then was extracted with three 50-ml. portions of an ethyl ether, chloroform mixture (3–2). The combined extracts were dried over potassium carbonate and the solvents were evaporated. The yield of yellow oil amounted to 0.75 g. or 94%. The *acid oxalate* was obtained as a colorless microcrystalline powder of m.p. 201–202°d.

Anal. Calc'd for $C_{16}H_{22}N_2O_8$: C, 51.9; H, 6.0; N, 7.6.
Found: C, 52.3; H, 5.9; N, 7.7.

The *dipicrate* was obtained as a yellow microcrystalline solid of m.p. 212–213°d.

Anal. Calc'd for $C_{24}H_{24}N_8O_{14}$: C, 44.5; H, 3.7; N, 16.9.
Found: C, 44.4; H, 3.8; N, 17.3.

SUMMARY

Two *beta*-keto esters, III and V, (1-methyl- and 1,5-dimethyl-3-ethoxycarbonyl-4-piperidone respectively) have been found to undergo the Schmidt reaction. The presence of both possible structural isomers in the reaction product has been demonstrated but only a single pure product was isolated in each case. From III there was obtained a 5-homopiperazinone resulting from migration of the ethoxycarbonylalkyl group while from V there was found a 5-homopiperazinone produced by migration of the alkyl group. These results are considered to be in agreement with the concept of a syn-anti intermediate in the Schmidt reaction.

Four other 4-piperidones have been converted to 5-homopiperazinones and the structure of each 5-homopiperazinone has been verified by degradation.

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