[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

STUDIES IN PIPERIDONE CHEMISTRY. I. A SYNTHESIS OF 5-HOMOPIPERAZINONES

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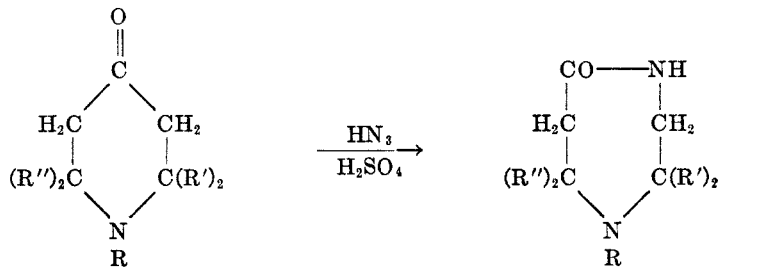
The extension of either the well-known Schmidt reaction (1) or the Beckmann rearrangement (2) to 4-piperidones or their oximes should result in the synthesis of 5-homopiperazinones.

Triacetonamine or 2,2,6,6-tetramethyl-4-piperidone (I) was prepared from phorone by the procedure described by Guareschi (3). When the amino ketone, I, was treated with hydrazoic and sulfuric acids, 2,2,7,7-tetramethyl-5-homopiperazinone (II) was formed in a yield of 88%. The following equation illustrates this and subsequent Schmidt reactions:



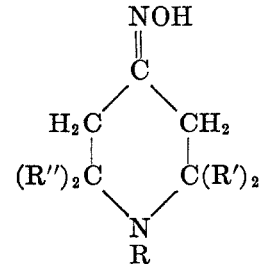
I. R = H, R′ = R″ = CH_3
VI. R = CH_3, R′ = R″ = H
XIII. R = R′ = R″ = H

II. R = H, R′ = R″ = CH_3
VII. R = CH_3, R′ = R″ = H
XVII. R = R′ = R″ = H

The cyclic amide, II, was hydrolyzed with dilute hydrochloric acid. The only product isolated was 1,2-diamino-2-methylpropane dihydrochloride (III). Therefore it would appear that cleavage of the amide linkage n II was accompanied by β-deamination. The diamine, III, was identified by cionversion to the diacetyl derivative and comparison with an authentic sample.

In order to further substantiate the homopiperazinone structure, the presence of a secondary amino group was demonstrated by converting the cyclic amide, II, to 1-nitroso-2,2,7,7-tetramethyl-5-homopiperazinone (IV). This neutral nitroso derivative, IV, gave a positive Liebermann test (4).

A Beckmann rearrangement of triacetonamine oxime (V) should afford another method of synthesis of the cyclic amide, II.



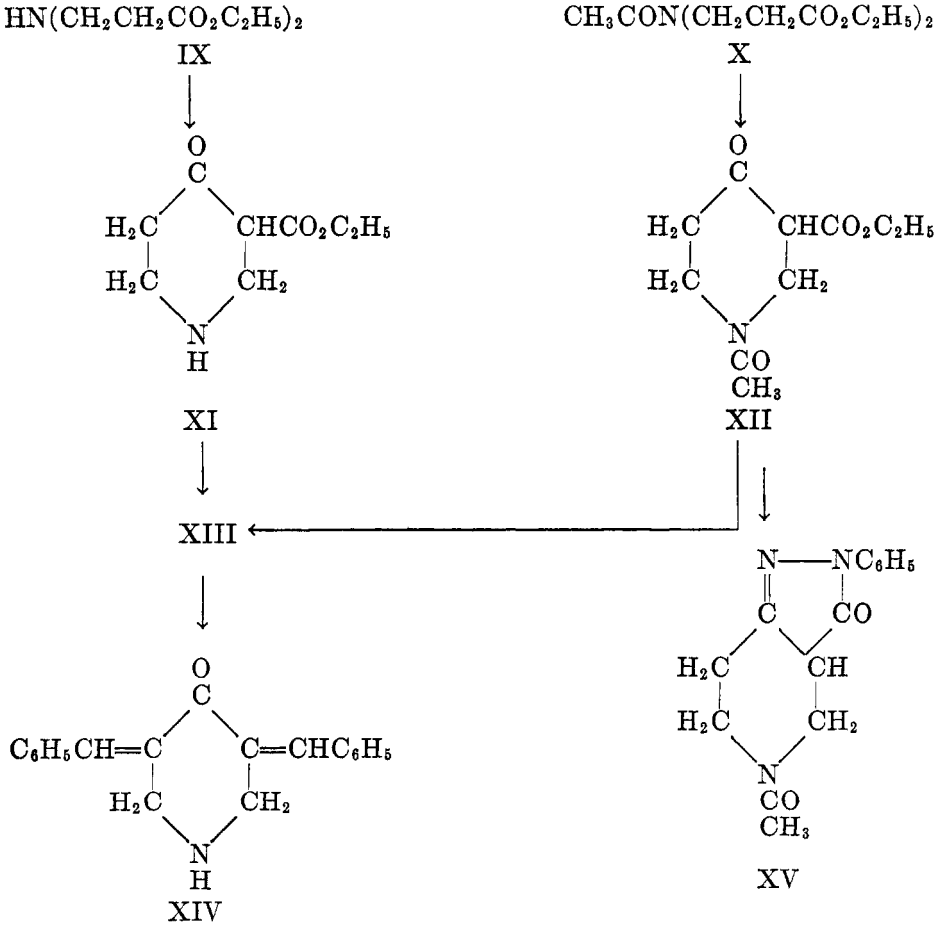
V. R = H, R′ = R″ = CH_3
VIII. R = CH_3, R′ = R″ = H
XVI. R = R′ = R″ = H

The common reagents for this rearrangement, phosphorus pentachloride and sulfuric acid, were tried unsuccessfully. However, thionyl chloride did bring about conversion of the oxime, V, to the amide, II, although in poor yield.

Since it seemed advisable to include an N-alkylamino ketone in this investigation, 1-methyl-4-piperidone (VI) was prepared by known (5, 6) methods. This ketone, VI, was readily converted to 1-methyl-5-homopiperazinone (VII) with hydrazoic and sulfuric acids in 53% yield.

The compounds, 1-methyl-4-piperidone oxime (VIII) and its hydrochloride were also prepared. These hitherto unreported compounds have some value as crystalline derivatives of the ketone, VI, but were synthesized with the hope that one would undergo a Beckmann rearrangement to the amide, VII. However, thionyl chloride and other acidic reagents produced only intractable red oils.

The last amino ketone selected for this investigation was 4-piperidone (XIII). Although this ketone, XIII, had been previously reported (8, 9, 10), certain difficulties and discrepancies were encountered in its synthesis. The accompanying diagram illustrates the method used by previous workers and the modification employed in this research.



The amino ester, di-(β-carbethoxyethyl)amine (IX) was synthesized from di(β-cyanoethyl)amine by a procedure outlined in the patent literature (7).

Ruzicka and co-workers (8, 9) first prepared 4-piperidone but were unable to isolate crystalline hydrochlorides of 3-carbethoxy-4-piperidone (XI) or 4-piperidone (XIII) nor could they distill either of these amines. They demonstrated the presence of 4-piperidone by preparing 3,5-dibenzal-4-piperidone hydrochloride (XIV). Some years later Kuettel and McElvain (10) isolated the keto ester, XI, as a crystalline hydrochloride and obtained two crystalline modifications of 4-piperidone hydrochloride. These hydrochlorides were assigned monohydrate and sesqui-ethanolate structures on the basis of ionic chloride determinations.[1]

The synthesis of Kuettel and McElvain (10) was repeated with the hope that the yield of 11% in the Dieckmann condensation could be improved. The ester, XI, was isolated but with no improvement in yield. Therefore the secondary amino group in the amino ester, IX, was blocked with an acetyl group. After N-acetyldi-(β-carbethoxyethyl)amine (X) had been synthesized in the course of this research, McElvain and Stork (11) reported the preparation of this compound. Furthermore, they reported that they attempted a Dieckmann condensation of the acetylated ester, X, but isolated only a trace of an oil which was not further investigated. This condensation was repeated with some changes in conditions and isolation procedure and 1-acetyl-3-carbethoxy-4-piperidone (XII) was isolated in 72% yield. The β-keto ester, XII, gave a vivid color with ferric chloride and formed a pyrazolone, XV, when heated with phenylhydrazine.

Hydrolysis of the acetamino-ester, XII, with dilute hydrochloric acid and crystallization from ethanol gave 4-piperidone hydrochloride sesqui-ethanolate as reported by Kuettel and McElvain (10).

The sesqui-ethanolate of 4-piperidone hydrochloride was converted to the monohydrate. After recrystallization, we found 4-piperidone hydrochloride monohydrate to melt from 140–145° with decomposition while Kuettel and McElvain (10) have reported a melting point of 92–94°. Because of this discrepancy in melting points, samples of 4-piperidone hydrochloride which had been prepared from the amino ester, XI, and the acetamino ester, XII, respectively, were converted to the known 3,5-dibenzal-4-piperidone hydrochloride (XIV) and the hitherto unknown derivative, 1-nitroso-4-piperidone (XV). Identical derivatives were obtained from both samples.

Further confirmatory evidence was obtained by the preparation of 4-piperidone oxime (XVI) and hydrochloride.

Finally, 4-piperidone hydrochloride monohydrate was converted to 5-homopiperazinone (XVII) with hydrazoic and sulfuric acids. One attempt to demonstrate the presence of a secondary amino group by the preparation of an N-nitroso derivative failed, and lack of material prevented repetition of the reac-

[1] (added in press) In a recent paper dealing with 4-piperidone and derivatives, McElvain and McMahon [*J. Am. Chem. Soc.* **71**, 901 (1949)] now formulate 4-piperidone hydrochloride sesqui-ethanolate as a diethyl ketal. We had considered this a likely possibility but our analyses did not indicate this structure.

tion. Therefore, the structure of compound XVII is formulated by analogy with previous Schmidt reaction products and should be regarded as tentative.

Further work on these compounds and other applications of the Schmidt reaction in this field are in progress in these laboratories.

EXPERIMENTAL[2, 3]

2,2,6,6-Tetramethyl-4-piperidone (*I*) was prepared by the method of Guareschi (3) from technical grade 42% phorone, which was used without purification, in a yield of 34%. Recrystallization from wet isopropyl ether gave the monohydrate of I; m.p. 58–60°.

2,2,7,7-Tetramethyl-5-homopiperazinone (*II*) was prepared by a Schmidt reaction as follows: A solution of 1.73 g. (0.01 mole) of 2,2,6,6-tetramethyl-4-piperidone monohydrate in 10 ml. of chloroform was dried over potassium carbonate, filtered into an eight-inch test tube, and cooled in an ice-bath. To this cold, vigorously stirred, solution was added dropwise 8 ml. of concentrated sulfuric acid. Sodium azide (1.62 g. = 0.025 mole) was then added in small portions, over a period of thirty minutes, through a small funnel of such shape that the solid dropped directly into the mixture. The stirring was continued for another fifteen minutes. The mixture was then diluted with 45 ml. of ice and water. This diluted solution was saturated with solid potassium carbonate and extracted with eight 50-ml. portions of ether. The combined ether extracts were dried over potassium carbonate, filtered, and brought, under reduced pressure, to dryness. The yield of almost white crude product amounted to 1.52 g. (88%); m.p. 140–145°. Recrystallization from dry benzene gave thick, white plates that melted at 147.5–148°.

Anal. Calc'd for $C_9H_{17}N_2O$: C, 63.5; H, 10.7; N, 16.5; Neut. equiv., 170.
Found: C, 63.1; H, 10.1; N, 16.3; Neut. equiv., 169.

The *hydrochloride* of I was prepared in absolute ethanol with alcoholic hydrogen chloride; recrystallized from ethanol; m.p. 295–300° with dec.

Anal. Calc'd for $C_9H_{18}ClN_2O$: N, 13.6. Found: N, 13.6, 13.4

Hydolysis of the amide, II was accomplished by refluxing in 20% hydrochloric acid for 40 hrs. Some unreacted amide, II, was recovered and the corrected yield of 1,2-diamino-2-methylpropane dihydrochloride (III) amounted to 71%; m.p. 290–300° with dec. [Mills and Quibell (12) reported 298–300° with dec.].

Anal. Calc'd for $C_4H_{14}Cl_2N_2$: N, 17.4. Found: N, 17.2.

The *diacetyl* derivative of III melted at 97–99°, while a mixture of this derivative and 1,2-diacetamino-2-methylpropane, prepared according to Drew and Head (13), melted at 97–99°. [They (13) reported a melting point of 100° for this compound.]

1-Nitroso-2,2,7,7-tetramethyl-5-homopiperazinone (*IV*) was prepared by heating a water solution of 108 mg. of II hydrochloride and 41 mg. of sodium nitrite on the steam-bath for an hour. The yellowish-green solution was adjusted to *p*H 2–4 with one drop of dilute hydrochloride acid, and extracted with several portions of ether. The combined ether extracts were brought to dryness and the residue recrystallized from a mixture of benzene and ligroin (70–90°). IV was obtained in 58% yield as pale yellow needles that melted at 150.5–151.0°. IV gave a positive Liebermann test (4).

Anal. Calc'd for $C_9H_{17}N_3O_2$: N, 21.1. Found: N, 21.0.

2,2,6,6-Tetramethyl-4-piperidone oxime (*V*) *hydrochloride* was prepared in 90% yield by refluxing an aqueous ethanol solution of the ketone, I, and hydroxylamine hydrochloride; white plates; m.p. about 300° with dec.

Anal. Calc'd for $C_9H_{19}ClN_2O$: Cl, 17.2: N, 13.6. Found Cl, 17.0; N, 13.7.

2,2,7,7-Tetramethyl-5-homopiperazinone (*II*) was prepared by a Beckmann rearrangement as follows: 1.00 g. of the hydrochloride of II was dissolved in 10 ml. of cold, freshly

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[2] All melting points are corrected; boiling points are uncorrected.

[3] The authors wish to thank E. J. Moriconi and A. J. Besozzi for performing some of the microanalyses.

distilled, thionyl chloride. The initially colorless solution turned yellow and gradually deposited a red oil. After standing for 14 hrs. at room temp., the excess thionyl chloride was removed under reduced pressure. The dark red oil that remained was dissolved in 5 ml. of ice-water, decolorized with Norit and again brought to dryness under reduced pressure to yield a red oil that crystallized when triturated with absolute ethanol. This crude hycrochloride was converted to the free base with aqueous potassium carbonate and extracted with benzene. The residue obtained by the evaporation of the combined benzene extracts was recrystallized six times from isopropyl ether. II was obtained as white plates that melted at 144.5–146.0°. The mixed melting point with the oxime, V, was 110–125° and with the amide, II, prepared by the Schmidt reaction, 146–147°.

1-Methyl-5-homopiperazinone (*VII*) was prepared by a procedure analogous to that used for II; however, chloroform was used to extract VII from the saturated potassium carbonate solution. From 1.50 g. (0.010 mole) of 1-methyl-4-piperidone hydrochloride, prepared by known methods (5, 6), and 0.78 g. (0.012 mole) of sodium azide, VII was obtained in 53% yield; recrystallized from petroleum ether (30–60°) as hygroscopic white needles of m.p. 83–84°.

Anal. Calc'd for $C_6H_{12}N_2O$: N, 21.9; Neut. equiv., 128.
Found: N, 21.6; Neut. equiv., 129.

The *hydrochloride* of VII was prepared in absolute ethanol with alcoholic hydrogen chloride; recrystallized from ethanol was a white, hygroscopic, microcrystalline solid; m.p. 209–210°.

Anal. Calc'd for $C_6H_{13}ClN_2O$: Cl, 21.6. Found: Cl, 21.6.

1-Methyl-4-piperidone oxime (*VIII*) *hydrochloride* was prepared in 85% yield by refluxing an aqueous ethanol solution of the ketone, VI, (b.p. 51.0–52.5° at 8 mm.) [43.5–44.1° at 6 mm. and 56–58° at 8 mm. have been reported (6, 14)] and hydroxylamine hydrochloride; white needles, m.p. 243–244° with dec.

Anal. Calc'd for $C_6H_{13}ClN_2O$: N, 17.0. Found: N, 16.8.

The hydrochloride was converted to the amine, VIII, with ethereal ammonia; recrystallized from dry benzene. *1-Methyl-4-piperidone oxime* (*VIII*) was obtained as white needles, m.p. 129.5–130.0°.

Anal. Calc'd for $C_6H_{12}N_2O$: N, 21.9; Neut. equiv., 128.
Found: N, 21.6; Neut. equiv., 127.

Di-(β-carbethoxyethyl)amine (*IX*) was prepared by the method outlined in the patent literature (7) and a procedure adapted from Organic Syntheses (15) for a similar reaction. Di-(β-cyanoethyl)amine, 24.6 g. (0.20 mole) was converted to 28.0 g. (64%) of IX; b.p. 108–110° at 0.1 mm. [The b.p. of IX, prepared by another method has been reported (11) as 119–125° at 1–2 mm.]

1-Acetyl-3-carbethoxy-4-piperidone (*XI*) was prepared from N-acetyldi-(β-carbethoxyethyl)amine; b.p. 151–155° at 0.1 mm.; n_D^{27} 1.4612. [McElvain and Stork (11) reported b.p. 183–185° at 5 mm.] To a suspension of 4.6 g. (0.2 g. atom) of sodium-sand in 200 ml. of dry xylene was added 51.8 g. (0.2 mole) of X and 0.5 ml. of absolute ethanol. The mixture was then stirred and heated until the xylene just began to reflux when a vigorous reaction, that required cooling, took place and the reaction product separated as a yellow solid. After the initial reaction had subsided, the mixture was heated and stirred for another hour. After cooling, the solid was filtered off and washed with several portions of petroleum ether. The yield of crude sodium salt amounted to 42.0 g. A solution of 23.5 g. of this sodium salt in 35 ml. of water was extracted with two 25-ml. portions of chloroform, cooled in an ice-bath and acidified with conc'd hydrochloric acid. This acidic solution was saturated with sodium chloride and extracted with seven 25-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, filtered, and brought under reduced pressure to a pale yellow oil that crystallized on standing overnight to waxy needles; yield 17.3 g., or 72% from X. The keto-ester melted from 30–40° and could not be distilled under oil-pump vacuum; nor could it be recrystallized. It gave a vivid reddish-purple color with 10% ferric chloride. It was vacuum dried over phosphorus pentoxide before analysis.

Anal. Calc'd for $C_{10}H_{15}NO_4$: C, 56.3; H, 7.1.
Found: C, 56.1; H, 7.0.

6-Acetylpiperidino(4',3'-c)-2-phenyl-3-pyrazolone (*XIII*) was prepared as follows: 1-acetyl-3-carbethoxy-4-piperidone (XI) (0.483 g.) and phenylhydrazine (0.269 g.) were dissolved in 10 ml. of 50% ethanol, and the solution heated on a steam-bath for six hours. The viscous yellow oil, that remained, crystallized on standing overnight. The product was washed with ether and recrystallized from ethanol. The yield of XIII amounted to 84%; the microcrystalline, white powder melted at 191–192° with dec.

Anal. Calc'd for $C_{14}H_{15}N_3O_2$: C, 65.3; H, 5.9; N, 16.3.
Found: C, 65.2; H, 6.0; N, 16.4.

4-Piperidone (*XIII*) *hydrochloride* was prepared by two methods as follows:

(a) 3-Carbethoxy-4-piperidone (XI) hydrochloride was synthesized and converted to XIII as described by Kuettel and McElvain (10). 4-Piperidone hydrochloride sesqui-ethanolate was isolated in 67% yield; m.p. 120–130° with dec. [K. and M. (10) reported a yield of 48% of material melting at 139–140° with dec.]

(b) 1-Acetyl-3-carbethoxy-4-piperidone (XI) (16.3 g.) was refluxed for seven hours with 250 ml. of 6 *N* hydrochloric acid. After decolorizing with 0.5 g. of Norit, the solution was filtered and evaporated under reduced pressure to a syrup that crystallized when triturated with absolute ethanol; recrystallized from absolute ethanol and ether. The yield of white needles of 4-piperidone hydrochloride sesqui-ethanolate amounted to 9.0 g. (58%); m.p. 120–130° with dec. After two more recrystallizations it melted at 136–138° with dec. [K. and M. (10) reported 139–141° with dec.]

Anal. Calc'd for $C_5H_9NO \cdot HCl \cdot C_2H_5OH$: C, 46.3; H, 9.9; Cl, 19.5; N, 7.7.
Calc'd for $C_5H_9NO \cdot HCl \cdot 1.5\ C_2H_5OH$; C, 47.0; H, 9.4; Cl 17.3; N, 6.8.
Found: C, 46.7, 46.8; H, 9.3, 9.6; Cl, 17.5; N, 6.8.

4-Piperidone hydrochloride sesqui-ethanolate was converted to the hydrate by refluxing with 5% hydrochloric acid for thirty minutes followed by removal of the water and acid under reduced pressure. 4-Piperidone hydrochloride monohydrate was isolated as white granules of m.p. 140–145° with dec. After recrystallization from a mixture of acetone and water, the hydrate was obtained as transparent nuggets that again melted at 140–145° with dec. [K. and M. (10) have reported a melting point of 92–94°.]

Anal. Calc'd for $C_5H_9NO \cdot HCl \cdot H_2O$: C, 39.1; H, 7.9; Cl, 23.0; N, 9.1.
Found: C, 39.3; H, 7.8; Cl, 23.1; N, 9.0.

3,5-Dibenzal-4-piperidone hydrochloride (*XIV*) was prepared as described by Kuettel and McElvain (10) from two samples of the sequi-ethanolate obtained from XI and XII. Both preparations of the dibenzal derivative were obtained as yellow needles that melted separately or mixed from 250–278° with some dec. from 250–270° and vigorous dec. from 270–278°. The decomposition point was taken by placing the sample on the cold block and raising the temp. as rapidly as possible to 230°, then at a rate of 5° per minute [other reported decomposition points are 275–277° (8) and 276–277° (10)].

Anal. Calc'd for $C_{19}H_{18}ClNO$: Cl, 11.4; N, 4.5.
Found: Cl, 11.3, N, 4.6.

1-Nitroso-4-piperidone (*XV*) was prepared from the two samples of 4-piperidone hydrochloride sesqui-ethanolate obtained from XI and XII by the procedure use for IV. The yield, in both cases, of pale yellow needles of m.p. 61–62° amounted to 60%; mixed m.p. 61–62°. Both samples of this nitrosamine gave a positive Liebermann test (4).

Anal. Calc'd for $C_5H_8N_2O_2$: N, 21.9. Found: N, 22.1.

4-Piperidone oxime (*XVI*) was prepared as follows: 4-piperidone hydrochloride monohydrate (0.250 g.), hydroxylamine hydrochloride (0.136 g.), and sodium bicarbonate (0.165 g.) were dissolved in 2 ml. of water. After standing overnight, the solution was saturated with anhydrous potassium carbonate and extracted with five 5-ml. portions of chloroform. The combined extracts were dried over potassium carbonate and brought to dryness under reduced pressure. The yield of crystalline crude product amounted to 0.139 g. (75%); recrystallized from dry benzene to yield white, somewhat hygroscopic needles, m.p. 117–118°.

Anal. Calc'd for $C_5H_{10}N_2O$: N, 24.5; Neut. equiv., 114.
Found: N, 24.7; Neut. equiv., 113.

A portion of XVI in absolute ethanol was converted to the hydrochloride with ethanolic hydrogen chloride. The product crystallized from absolute ethanol as long, silky needles, m.p. 233–235° with dec.

Anal. Calc'd for $C_5H_{11}ClN_2O$: Cl, 23.5. Found: Cl, 23.4.

5-Homopiperazinone (XVII) was prepared from 0.515 g. of 4-piperidone hydrochloride monohydrate by a procedure analogous to that used for the preparation of II. Removal of the ether yielded a red oil that showed no tendency toward crystallization and was, therefore, converted to the hydrochloride with ethanolic hydrogen chloride. After crystallization from ethanol, 0.269 g. (51%) of *XVII hydrochloride* was obtained as white, hygroscopic needles, m.p. *223–225°*.

Anal. Calc'd for $C_5H_{11}ClN_2O$: C, 39.9; H, 7.4, N, 18.6.
Found: C, 40.0; H, 7.3; N, 18.6.

SUMMARY

1. The Schmidt reaction has been extended to three piperidones, 2,2,6,6-tetramethyl-4-piperidone, 1-methyl-4-piperidone, and 4-piperidone.

2. At least two homopiperazinones have been isolated and characterized.

3. Contrary to a literature report, N-acetyl-di-(β-carbethoxyethyl)amine has been found to undergo a Dieckmann condensation.

4. A literature method of synthesis of 4-piperidone has been modified with some improvement in yield.

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