[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Piperidine Derivatives. XVIII. The Condensation of Aromatic Aldehydes with 1-Methyl-4-piperidone

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The preparation of 3-substituted-4-piperidones via the condensation of aromatic aldehydes with 1-methyl-4-piperidone (I) was the purpose of the work here reported. Only two examples of such a condensation appear in the literature: benzaldehyde with 4-piperidone[2] and 1-methyl-4-piperidone.[3] Both of these condensations, however, yielded only the corresponding 3,5-dibenzal-4-piperidones.[4]

When 1-methyl-4-piperidone was treated with benzaldehyde in a 4% solution of potassium hydroxide in 40% ethanol–water (which was just sufficient alcohol to keep the reaction mixture homogeneous) a rapid reaction occurred, but none of the monobenzal derivative (IV) was found among the several reaction products. The main reaction product was 1-methyl-3,5-dibenzal-4-piperidone (VIII) which precipitated from the reaction mixture; in addition to this compound phenyl-bis-3-(1-methyl-4-ketopiperidyl)-methane (X) and two apparently similar products with wide melting ranges, which were separated by their solubility differences in dilute ethanol, were obtained by dilution of the reaction mixture with water. In contrast to the dibenzalpiperidone (VIII), the ethylenic bonds of which are rapidly and completely hydrogenated over Adams platinum oxide catalyst, these latter two products absorb hydrogen slowly and incompletely for one ethylenic bond per molecule. Elemental analyses indicate that one of these products, A, is a mixture of the monobenzalpiperidone (IV) and the carbinol (III) and that the other product, B, is a mixture of the monobenzalpiperidone (IV) and the dicarbinol (VI) *or* a mixture of the carbinol (III) and the benzalcarbinol (VII).

In one of the first experiments with this procedure two products, having elemental analyses corresponding to the carbinol (III), were isolated at the point where mixtures A and B appeared in subsequent experiments. These were, undoubtedly, the two racemic forms of III, but neither could be isolated completely free of the other.

When benzaldehyde was allowed to react with 1-methyl-4-piperidone in a 4% solution of potassium hydroxide in 55–60% ethanol–water solvent, 1-methyl-3-benzal-4-piperidone (IV) *slowly* precipitated from the solution.[5] It was the sole product of the reaction and was obtained in 61% yield.

Since the dibenzalpiperidone (VIII) was rapidly precipitated from a 40% ethanol–water solvent in which it is insoluble and not formed in the 60% ethanol–water solvent in which it is quite soluble, it appears that the reaction of the piperidone (I) with benzaldehyde in the presence of alkali is best represented by a series of equilibria from which either the mono- or dibenzal derivative may be obtained, depending on the solubility of the product in the reaction solvent. This conclusion is further indicated by the fact that either of the carbinol mixtures A and B, the two racemic forms of III, as well as the dibenzal derivative (VIII), which were formed in 40% ethanol–water solvent, were converted to the monobenzal derivative (IV) when allowed to stand in a 4% potassium hydroxide solution in 60% ethanol–water. The conversion of VIII to IV amounts to 78%.

It is a curious fact that the monobenzal derivative IV does not precipitate from the 40% ethanol–water solvent in which it is as insoluble as is the dibenzal derivative VIII. The most obvious explanation of this fact is that the series of equilibria involved in the transformation of II (or IIa) → VIII are attained more rapidly than that of II → IV. This is indicated by the rapid (see Table I) precipitation of VIII from the 40% ethanol–water solvent and the consequent shift of the reaction in this direction; when VIII is kept in solution by the 60% ethanol–water solvent, there is opportunity for the slower change of II (or IIa) into IV and the latter compound precipitates over a period of several days (see Table I). The mixtures of IV with the carbinols, which are present in the 40% ethanol–water solvent and are precipitated by dilution with water, may be molecular complexes that prevent the precipitation of IV.

It seems likely that the benzal derivatives IV and VIII are formed from the ions IIa and VIIa rather than from the direct dehydration of the carbinols III and VI. The carbinol mixtures were completely resistant to dehydration with hydrogen chloride in absolute ethanol, and when refluxed with acetic anhydride in pyridine, or with acetic anhydride containing *p*-toluenesulfonic acid, were converted to a product, the analyses and molecular weight of which approximates the structure IX, and which corresponds to the dodecahydrotriphenylene formed from cyclohexanone[6]

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[1] Eli Lilly and Company Fellow, 1945–1947.

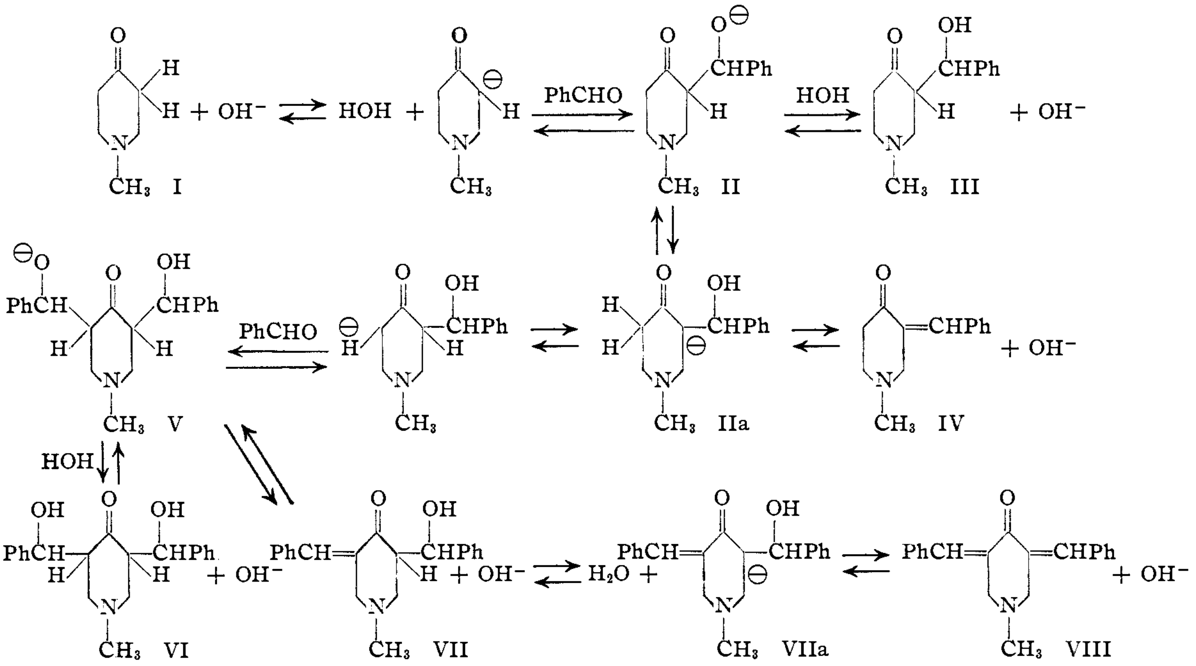
[2] Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 806 (1920); Kuettel and McElvain, This Journal, **53**, 2692 (1931).

[3] Howton, *J. Org. Chem.*, **10**, 279 (1945).

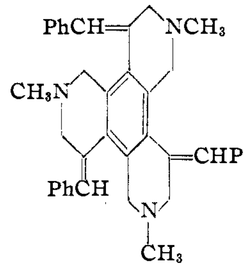
[4] Similarly tropinone has yielded the dipiperonal derivative [Robinson, *J. Chem. Soc.*, 111, 762 (1917)] and the dibenzal derivative despite numerous attempts to prepare the monobenzal derivative [Willstätter, *Ber.*, **30**, 731, 2681, 2716 (1897)].

[5] Poggi and Gaustella, *Gazz. chim. ital.*, **61**, 405 (1931), have reported the formation of 2-benzalcyclohexanone from benzaldehyde and cyclohexanone in a 4% aqueous solution of potassium hydroxide.

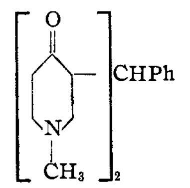
[6] Mannich, *Ber.*, **40**, 154 (1907); Kunze, *ibid.*, **59**, 2086 (1926); Triebs, *ibid.*, **61**, 684 (1928).



and to the *sym*-tris-2,3-thiocoumaronobenzene formed from thioindoxyl by the action of acetic anhydride with zinc chloride.[7]



IX



X

The fourth product X isolated from the base-catalyzed condensation of benzaldehyde with the piperidone I is the result of the condensation of two moles of the piperidone with one of the aldehyde. The yields of X vary with the ratio of reactants as may be seen from Table I, which summarizes the results of typical runs in a 4% potassium hydroxide solution in various solvents.

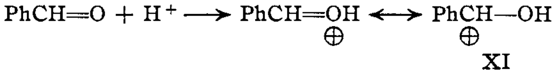
TABLE I

BASE-CATALYZED REACTION OF BENZALDEHYDE WITH 1-METHYL-4-PIPERIDONE (I)

PhCHO/I, moles	Solvent	Yield of VIII, %	Yield of mixtures A + B, %	Yield of IV, %	Yield of X, %
1.0	40% EtOH	44[a]	36	...	8
2.0	40% EtOH	66	28	...	0.3
1.0	60% EtOH	...	..	61[b]	..
0.12	12% EtOH	45	16	...	11
1.0	Water[c]	25	30	...	19

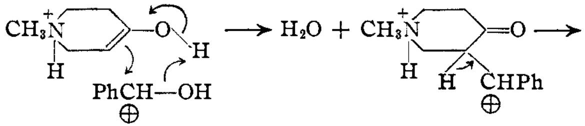
[a] Precipitated in fifteen minutes; the weaker base, sodium bicarbonate, gave similar yields but required several days to produce them. [b] About five days required for this amount of IV to precipitate. [c] Benzaldehyde added dropwise over a period of 2.5 hours to an aqueous solution of potassium hydroxide and the piperidone.

The condensation of benzaldehyde with the piperidone (I) may also be effected by acid catalysis. This reaction was carried out in absolute ethanol saturated with hydrogen chloride and the sole product was the hydrochloride of VIII, which precipitated in 86% yield over a period of three days. In this case it seems certain that the carbinols III or VI ***are not*** intermediates in the formation of VIII, because the mixtures (A and B from the base-catalyzed reaction) containing these carbinols remain unchanged in the medium used for the acid-catalyzed reaction. The reaction mechanism, therefore, cannot permit the formation of a carbinol. The simultaneous coupling and loss of water between the enolic form[8] of the piperidone and the carbonium ion (XI) to produce the car-



$$\mathrm{PhCH{=}O} + \mathrm{H}^+ \longrightarrow \underset{\oplus}{\mathrm{PhCH{=}OH}} \longleftrightarrow \underset{\oplus}{\mathrm{PhCH{-}OH}}$$

XI



XII

$\overset{+}{\mathrm{H}} + \mathrm{IV{\cdot}HCl} \longrightarrow$ etc. to VIII·HCl

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[7] Dalgliesh and Mann, *J. Chem. Soc.*, 910 (1945).

[8] Although the amount of the enolic form of the ketone as well as the rate of its formation may be increased by the acidic medium [*cf.* Hauser and Breslow, THIS JOURNAL, **62**, 2391 (1940)]; Schwarzenbach and Wittwer, *Helv. Chim. Acta*, **30**, 659 (1947); Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, p. 237], the concentration of the enolic form may well be the limiting factor that determines the over-all rate of reaction.

bonium ion XII, which then passes into a benzal derivative, would seem to rationalize the acid-catalyzed condensation of benzaldehyde with I.

The solubilities of the hydrochlorides of IV and VIII in absolute ethanol are the reverse of those of IV and VIII in the 60% ethanol–water medium used in the base-catalyzed reaction. The hydrochloride of IV is soluble in absolute ethanol while the hydrochloride of VIII is quite insoluble. If a solvent in which the hydrochloride of I is soluble and the hydrochloride of IV is insoluble could be found, it might be possible to prepare IV by an acid-catalyzed reaction; as yet such a solvent has not been found.

Condensation of Other Aldehydes with I.—The study of the condensation of benzaldehyde with I was intended to serve as a model for the determination of the proper conditions for the condensation of other aldehydes, particularly the quinoline aldehydes, with this piperidone. Actually the benzaldehyde condensation proved to be the most complex from the standpoint of the number of reaction products. With the other aldehydes only those products corresponding to the mono- and dibenzal derivatives IV and VIII were obtained; none of the carbinols or the bispiperidylarylmethanes, corresponding to X, were found.

The course of the condensation of quinoline-2 and 4-aldehydes with I showed a curious dependence on the amount of alkali used to catalyze the reaction. In a 4% solution of potassium hydroxide in ethanol–water, in which the molar ratio of alkali to I was 3.5:1, the 2-aldehyde gave a dark oil from which only a 9% yield of the diquinolinal derivative could be isolated. However, when a 0.25% solution of the alkali, containing an alkali to piperidone ratio of 0.54 was used, a 39% yield of the diquinolinol derivative and a trace of the monoquinolinol derivative were obtained. The quinoline-4-aldehyde yielded either the mono- or diquinolinol derivative depending on the amount of alkali used. Both of these quinoline aldehydes gave useless brown tars when hydrogen chloride in absolute ethanol was used as the reaction medium.

TABLE II

CONDENSATION OF CERTAIN ALDEHYDES, ArCHO, WITH 1-METHYL-4-PIPERIDONE (I)

Ar is	ArCHO/ I, moles	KOH/I, moles	Yield of mono—al, %	Yield of di—al, %[b]
2-Quinolyl	2	3.55	0	9
2-Quinolyl	2	0.54	Some[a]	39
4-Quinolyl	1	1.37	95	..
4-Quinolyl	2	0.73	Some[a]	79
α-Naphthyl	1	1.78	Some[a]	80
α-Naphthyl	1	0.27	Some[a]	88
o-Chlorophenyl	1	1.42	Some[a]	74
o-Chlorophenyl	2	1.78	0	90
o-Chlorophenyl	1	0.27	Some[a]	82

[a] Percentage yield not given since this product was not obtained pure; analyses indicated it to be mainly the mono—al derivative. [b] Yield based on amount of aldehyde used.

Neither benzaldehyde, *o*-chlorobenzaldehyde or α-naphthaldehyde showed any variations in reaction products with variations in the amount of alkali used to effect the condensations.

The condensations of these aldehydes with I in the presence of varying amounts of potassium hydroxide are summarized in Table II. In each case water containing sufficient ethanol to make the initial reaction mixture homogenous was used as the solvent.

Experimental

Methyl-di-(β-carbethoxyethyl)-amine.—A cooled one-liter reaction bomb was filled with 432 ml. (400 g.) of ethyl acrylate (containing 0.25% hydroquinone inhibitor) and 86 ml. (62 g.) of liquefied methylamine. Crystallization occurred upon stirring these chilled reactants. The cover was quickly secured since the temperature rose to around 80° within five minutes. The reaction vessel was heated in a water-bath at 60–70° for one hour. The bomb was cooled, opened, and the reaction mixture distilled. The fraction boiling at 110–119° (mainly at 118–119°) at 0.5 mm. was methyl-di(β-carbethoxyethyl)-amine; it weighed 367 g.

1-Methyl-3-carbethoxy-4-piperidone Hydrochloride.—Although this compound could be prepared in good yields (80%) by the cyclization of methyl-di-(β-carbethoxyethyl)-amine with sodium ethoxide,[9] the following procedure using sodium hydride was found more satisfactory.

Into a three-liter, three-necked flask equipped with a Hershberg stirrer, dropping funnel, and a reflux condenser, were placed 800 ml. of dry thiophene-free benzene and 54 g. of sodium hydride. After flushing the apparatus with nitrogen, 30 g. of methyl-di-(β-carbethoxyethyl)-amine was added to the vigorously stirred suspension of sodium hydride in benzene.

Five minutes after adding two milliliters of absolute ethanol the reaction started as evidenced by the evolution of hydrogen. When, after five minutes more, the reaction mixture was noticeably warm, 201 g. of methyl-di-(β-carbethoxyethyl)-amine was added at such a rate as to keep the mixture refluxing briskly. During this addition of the di-ester the appearance of the reaction mixture gradually changed from a dark-gray fluid to an almost white paste. To facilitate stirring an additional 250 ml. of benzene was added after addition of the di-ester was completed. The mixture then was stirred and refluxed with external heating until no more hydrogen was evolved.

A crock of crushed ice was placed under the reaction flask to cool the mixture while 135 g. of glacial acetic acid was added. To this very slightly acid solution, cooled to 5°, 123 ml. of water was added to precipitate sodium acetate trihydrate. This salt was filtered off and washed with 350 ml. of benzene.

The combined filtrates were distilled to remove ethanol and water. After 600 ml. of distillate had been collected, a refractive index showed that pure benzene was distilling over. The residual solution of 1-methyl-3-carbethoxy-4-piperidone in benzene was diluted with 500 ml. of absolute ether. This solution then was cooled in an ice-salt-bath and treated with dry hydrogen chloride until the 1-methyl-3-carbethoxy-4-piperidone hydrochloride had precipitated. The yield of product softening at 115°, melting at 125–128°, was 201 g. (91%).

1-Methyl-4-piperidone (I).—To a one-liter flask containing 350 ml. of 20% hydrochloric acid was added 86.0 g. of 1-methyl-3-carbethoxy-4-piperidone hydrochloride. After refluxing for one hour, the ferric chloride reagent gave no coloration. The solution was evaporated to dryness on a steam-bath at 10 mm. pressure. The solid product, heated at 100° for four hours at 0.1 mm. and further dried over solid potassium hydroxide for twenty-four hours, weighed 57.7 g., m. p. 80–120°. Although this

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[9] Prill and McElvain, This Journal, 55, 1233 (1933).

melting range goes above that of the pure compound, 0.45 g. of crude material dissolved in 90 ml. of hot acetone gave 0.40 g. of pure compound melting at 93–95°. Other samples of the crude piperidone hydrochloride showed even higher upper limits of the melting points than that mentioned above, yet this apparently impure material always gave good yields of sharp melting product when recrystallized. Thus the crude material can be used successfully for further work without recrystallization.

To 37.0 g. of crude 1-methyl-4-piperidone hydrochloride dissolved in 50 ml. water was added 14 g. of solid potassium hydroxide. Then 20 g. of potassium carbonate was added to salt out the free amine. This basic solution was extracted with seven 100-ml. portions of ether. The ethereal solution was dried overnight with anhydrous sodium sulfate and the ether distilled. The higher boiling residue was distilled at 19 mm. pressure. A forerun weighing 1.7 g. was collected to 67°. The 1-methyl-4-piperidone fraction boiled from 67–69° and weighed 18.7 g.

The phenylhydrazone of this piperidone melted at 100–104°.[10]

The semicarbazone, prepared in the usual manner, did not precipitate from the reaction medium until salted out with potassium carbonate. After filtering and washing with a small amount of ice water it melted at 182–184°; recrystallization from ethyl acetate did not raise this m. p.

Anal. Calcd. for $C_7H_{14}N_4O$: C, 49.39; H, 8.29. Found: C, 48.85; H, 8.04.

The 2,4-dinitrophenylhydrazone hydrochloride was also made, m. p. 249° d. The free base was obtained by dissolving 1.0 g. of the hydrochloride in 75 ml. water, neutralizing with sodium bicarbonate, filtering, and recrystallizing from ethyl acetate. The orange prisms melted 172.0–173.5°.

Anal. Calcd. for $C_{12}H_{15}N_5O_4$: N, 23.88. Found: N, 24.0.

The Condensation of Benzaldehyde with the Piperidone (I) in 40% Ethanol.—To a solution of 7.5 g. of 1-methyl-4-piperidone and 7.0 g. of freshly distilled benzaldehyde in 69 ml. of 40% ethanol was added 3.0 g. of potassium hydroxide. The flask was then stoppered and shaken for fifteen minutes. The yellow solid that precipitated then was filtered off and the filtrate diluted with 75 ml. water. The white precipitate from the diluted reaction medium was labeled mixture A. It weighed 1.31 g. and melted at 115–150° dec.

Anal. Found: C, 76.42; H, 7.15; N, 6.59.

These analytical data indicate mixture A to be composed of the carbinol (III) and the monobenzal derivative (IV) (see below for the elemental content of these compounds).

The yellow solid which had been filtered from the 40% ethanol solution was dissolved in 250 ml. of hot 5% hydrochloric acid. Upon cooling 4.93 g. of fine yellow needles of **1-methyl-3,5-dibenzal-4-piperidone hydrochloride,** m. p. 243.5–244.5°, was obtained. This compound has been reported to melt at 240–241°.[3]

Anal. Calcd. for $C_{20}H_{20}ClNO$: Cl, 10.9. Found: Cl, 10.8.

The 1-methyl-3,5-dibenzal-4-piperidone was obtained in quantitative yield from its hydrochloride by dissolving the salt in hot 50% ethanol, adding sufficient sodium bicarbonate solution to neutralize the hydrogen chloride, cooling and filtering. After two recrystallizations from dilute alcohol, the canary-yellow **1-methyl-3,5-dibenzal-4-piperidone** melted at 116.5–117.5°.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.04; H, 6.39; N, 4.76.

This compound has been previously reported by Howton[3,11] to melt 117.2–118.2°.

The acidic filtrate from which the dibenzal piperidone hydrochloride had been obtained was neutralized with sodium bicarbonate to precipitate 2.92 g. of the white mixture B, m. p. 115–160° dec.

Anal. Found: C, 75.16; H, 6.93; N, 5.85.

These analytical data indicate mixture B to be composed of IV (see below) and the dicarbinol (VI) (calcd. C, 73.9%; H, 7.1%; N, 4.3%) *or* of the carbinol (III) (see below) and the benzalcarbinol (VII) (calcd. C, 78.3%; H, 6.88%; N, 4.53%).

The dilute alkaline reaction mixture from which mixture A had been obtained deposited massive white rosettes on standing three days.[12] The amount increased until after two weeks 0.82 g. of **phenyl-bis-3-(1-methyl-4-keto-piperidyl)-methane,** m. p. 221–225°, was filtered off. After two recrystallizations from dilute ethanol an analytical sample melted 233–234°.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34. Found: C, 72.23; H, 7.95.

Phenyl-3-(1-methyl-4-keto-piperidyl)-carbinol (III).—One of the first reactions carried out as described above yielded a product the analysis of which corresponded to phenyl-3-(1-methyl-4-keto-piperidyl)-carbinol. Instead of mixture A, 1.90 g. of white solid, m. p. 115–126°, was obtained. On attempted recrystallization from dilute ethanol, it repeatedly precipitated as an oil.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 71.03; H, 7.42.

The hydrochloride of this compound was made by dissolving it in a small quantity of absolute ethanol, diluting with absolute ether, and treating the solution with hydrogen chloride. After decanting the supernatant liquid from the precipitated salt, it was redissolved in ethanol and reprecipitated with ether. This was repeated twice to obtain an analytical sample melting at 230–235° dec.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: Cl, 13.9. Found: Cl, 14.1.

At the place where mixture B was obtained in the previously described reaction, 3.09 g. of a product melting at 90–120° d. precipitated. The hydrochloride, made as described above, melted at 243–245° dec.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; Cl, 13.9. Found: C, 60.80; H, 7.14; Cl, 14.0.

The melting point of a mixture of the carbinol hydrochloride melting at 243–245° with that melting at 230–235° was 110–160° dec. It was concluded that these carbinols are the two racemic forms, each contaminated with a small amount of the other.

None of the later experiments yielded either of these carbinols; only the mixtures A and B, with analyses approximating those given above, were obtained.

Neither of these carbinols were affected when allowed to stand in solution in absolute ethanol saturated with hydrogen chloride. Both yielded the same product, m. p. 187–189° d., with acetic anhydride as that obtained in the following experiment with mixture B.

A solution of 4.83 g. of mixture B in 32 ml. of pyridine and 35 ml. of acetic anhydride was refluxed five hours. The brown solution then was poured into 400 ml. of ice-water to hydrolyze the acetic anhydride. Upon neutralization with sodium bicarbonate a dark, tacky oil precipitated. After standing four days, the oil solidified so that it could be filtered off. The crystalline material weighed 1.07 g. It was recrystallized four times from dilute ethanol to give 0.81 g. of a white solid, m. p. 187–189° dec. This compound rapidly darkened on exposure to light and air.

The elemental content and molecular weight of this product approximated that of the cyclic dehydration trimer (IX) of the benzalpiperidone.

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[10] *Cf.* Cook and Reed, *J. Chem. Soc.*, 401 (1945).

[11] Although Howton reported correct nitrogen and hydrogen analyses for his 1-methyl-3,5-dibenzal-4-piperidone, the carbon values were consistently 2% lower than the theoretical value.

[12] On the two occasions that a very small amount of 1-methyl-3-benzal-4-piperidone was obtained from such a reaction, it crystallized from the dilute alkaline reaction medium one day after filtering off mixture A. The monobenzal derivative was thus removed before the dipiperidyl methane started to precipitate.

Anal. Calcd. for $C_{39}H_{39}N_3$: C, 85.21; H, 7.15; mol. wt., 550. Found: C, 84.87; H, 6.72; mol. wt., 504 (Rast).

Mixture A, when refluxed with acetic anhydride and pyridine as described above, gave a 15% yield of this product, m. p. 187–189° dec.

The Condensation of Benzaldehyde with the Piperidone (I) in 60% Ethanol. 1-Methyl-3-benzal-4-piperidone (IV).—To a solution of 1.06 g. (0.01 mole) of benzaldehyde and 1.13 g. (0.01 mole) of 1-methyl-4-piperidone in 45 ml. of 60% ethanol was added 0.3 g. of potassium hydroxide. The solution became yellow almost at once. After standing one day a very small quantity of oil appeared. The solution was heated slightly to dissolve this oil which did not reappear on cooling. No further visible reaction occurred until a seed of 1-methyl-3-benzal-4-piperidone was added. Two days after adding this seed 0.78 g. of 1-methyl-3-benzal-4-piperidone, m. p. 213–215°, was filtered off. On successive days three additional crops totaling 0.27 g., and melting at 214–217° were obtained. The mother liquor then was diluted with 18 ml. of water and decanted from 0.16 g. of oil. This oil, when it solidified, melted at 85–105° and could not be recrystallized from dilute ethanol. One day after the oil had been removed from the diluted reaction mixture another 0.17 g. of product, m. p. 216–219° was obtained. The total yield of crystalline product was 1.32 g. (61%). An analytical sample, twice recrystallized from water-ethanol solvent, m. p. 224–225°, had a faint yellow color.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.30; H, 7.38.

The benzalpiperidone (IV) was also obtained from mixtures A and B, and from the dibenzalpiperidone (VIII) in the following manner.

To 0.36 g. of mixture A in 17.5 ml. of 54% ethanol was added 0.2 g. of potassium hydroxide. Within one day crystals began to deposit. After standing for two weeks at room temperature 0.18 g. (53%) of IV, m. p. 215–218°, was obtained.

A solution of 0.50 g. of mixture B and 0.2 g. of potassium hydroxide in 17.5 ml. 60% ethanol stood for one week at room temperature without precipitating the monobenzal piperidone. The solution was then heated at reflux for ten minutes and allowed to stand at room temperature again. A week after heating the mixture, crystals of IV began to separate. After one month 0.13 g. (28%) of monobenzalpiperidone, m. p. 214–216°, was obtained.

A solution of 0.48 g. of pure 1-methyl-3,5-dibenzal-4-piperidone (VIII), 0.19 g. of 1-methyl-4-piperidone and 1.0 g. of potassium hydroxide in 26 ml. of 60% ethanol was prepared. After standing for three days the solution was refluxed for five minutes while 4.0 ml. of hot water was added. After seventeen days of standing at room temperature 0.23 g. of IV, m. p. 211–215°, was filtered off. A second crop weighing 0.07 g. was obtained eighteen days after the first crop was filtered off. The total yield was 45% of that theoretically possible from the dibenzalpiperidone and the added 1-methyl-4-piperidone. However, the yield is 78% of theoretical, if based on the decomposition of dibenzalpiperidone only.

The Condensation of Benzaldehyde with the Piperidone I with Ethanolic Hydrogen Chloride.—Benzaldehyde (1.06 g.) and 1-methyl-4-piperidone (1.13 g.) were dissolved in 15 ml. of absolute alcohol. Anhydrous hydrogen chloride was passed in until the solution was saturated. The flask was allowed to stand at room temperature for two days during which time a crystalline deposit slowly formed. The hydrochloride of the dibenzal derivative so obtained melted 234–240° and weighed 1.40 g. (86%) (see above for analytical data of this salt).

1-Methyl-3,5-dibenzyl-4-piperidone.—In an apparatus for hydrogenation at atmospheric pressure[13] 5.14 g. of 1-methyl-3,5-dibenzal-4-piperidone hydrochloride in 60 ml. of ethanol was hydrogenated over 0.48 g. of Adams platinum oxide catalyst. Although the dibenzalpiperidone was not completely soluble in the ethanol, the hydrogenated product was and, consequently, the insoluble material disappeared, as the hydrogenation proceeded. After the theoretical amount of hydrogen was taken up (fifteen minutes), the catalyst was filtered off, the solvent evaporated, and the product neutralized with sodium bicarbonate. The brown, oily product did not crystallize and was dissolved in petroleum ether (b. p. 60–68°)-benzene solution (three volumes of benzene to two volumes of petroleum ether) and filtered through a twenty-five centimeter column of activated aluminum oxide. Upon evaporation of the filtrate 2.45 g. of oily, white crystals was obtained. Since these crystals were soluble at room temperature in all common organic solvents, they were triturated with 10 ml. of ice-cold petroleum ether (b. p. 40–60°) to give 1.31 g. of product m. p. 76–79°. An analytical sample was obtained by dissolving the crystals in a minimum amount of petroleum ether (b. p. 40–60°), then cooling the solution to $-10°$. After three such recrystallizations the melting point of 1-methyl-3,5-dibenzyl-4-piperidone was 84.0–85.5°.

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 82.12; H, 7.62.

The Condensation of Other Aldehydes with I. Quinoline-2-aldehyde.—To 1.58 g. (0.01 mole) of quinoline-2-aldehyde[14] and 0.56 g. (0.005 mole) of 1-methyl-4-piperidone dissolved in 51 ml. of 30% aqueous ethanol, 0.15 g. (0.002 mole) of potassium hydroxide was added. The solution became yellow immediately and a precipitate appeared within one minute. After shaking the solution for twenty-five minutes, a single lump of semi-solid product was removed. When dried this yellow material weighed 1.87 g. and melted at 143–147°. The residual reaction liquid was diluted with 60 ml. of water to obtain a second crop (0.04 g.) of yellow solid, m. p. 140–146°. This reaction product was recrystallized from 80 ml. of 95% ethanol to give 0.72 g.[15] of long slender yellow needles of **1-methyl-3,5-di-(2-quinolinal)-4-piperidone**, m. p. 153–154°. A thrice recrystallized sample, m. p. 158–159°, was used for analyses.

Anal. Calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41. Found: C, 79.72; H, 5.24.

The filtrate from this recrystallization was evaporated to dryness and the residue redissolved in 30 ml. of benzene. Hot petroleum ether (b. p. 60–68°) was added to the boiling benzene and the solution was cooled. In this manner 0.54 g. of tan powder, m. p. 150–160°, was obtained. The purity of this product was not improved by recrystallization, since the contaminant seemed to be as soluble in various solvents as the main portion. Furthermore, recrystallization was discouraged by the heat-sensitivity of the product. An elemental analysis suggested that it was mainly a mono-quinolinal piperidone.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 76.32; H, 5.28.

Quinoline-4-aldehyde.—To 5.73 g. (0.03 mole) of quinoline-4-aldehyde hydrate[16] and 3.70 (0.03 mole) of 1-methyl-4-piperidone, dissolved in 75 ml. of 67% aqueous ethanol, 2.5 g. (0.05 mole) of solid potassium hydroxide was added. This solution was shaken for fifteen minutes, diluted with 200 ml. of water, then shaken for twenty minutes and diluted with another 200 ml. of water. After a final ten minutes of shaking the light-tan solid was filtered and dried. It weighed 7.36 g. (95%) and melted at 190–203°. A 6.05-g. sample of this crude product was triturated with a few ml. of cold benzene,

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(13) Fieser and Hershberg, This Journal, **60**, 944 (1938).

(14) Kaplan, *ibid.*, **63**, 2654 (1941).

(15) This large loss on recrystallization is due partly to decomposition. For example, when 0.58 g. of pure 1-methyl-4,5-di-(2-quinolinal)-4-piperidone was recrystallized from 45 ml. of 95% ethanol only 0.46 g. was recovered. The filtrate, when evaporated to dryness, gave 0.09 g. of a brown powder which was much more ethanol-soluble and higher-melting than the di-quinolinalpiperidone.

(16) Kwartler and Lindwall, This Journal, **59**, 524 (1937).

filtered, and dried. The **1-methyl-3-(4-quinolinal)-4-piperidone** thus obtained weighed 5.96 g. and melted 222-225° dec. For an analytical sample this triturated product was recrystallized from 95% ethanol. It melted at 250-252° dec. when heated from room temperature; when introduced at a bath temperature of 240°, however, it melted at 252-253°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 76.06; H, 6.04.

A mixture of 0.42 g. (0.0037 mole) of 1-methyl-4-piperidone, 1.30 g. (0.0074 mole) of quinoline-4-aldehyde, and 0.15 g. (0.002 mole) of potassium hydroxide in 50 ml. of 30% aqueous ethanol was shaken for twenty minutes. The yellow solid which formed was filtered off and recrystallized from hot methanol. The first crop of long yellow needles of **1-methyl-3,5-di-(4-quinolinal)-4-piperidone** weighed 0.94 g., m. p. 198-200°. A second crop (0.20 g.) of this same product, m. p. 193-196°, was obtained by diluting the ethanol filtrate with a few ml. of water. On further dilution a third crop of crystals weighing 0.09 g. was obtained. The latter product softened at 190° but the major portion did not melt until 245°. This behavior indicates this product to be mainly the mono-4-quinolinal derivative described above.

An analytical sample of **1-methyl-3,5-di-(4-quinolinal)-4-piperidone**, m. p. 199-200°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41. Found: C, 79.85; H, 5.41.

***o*-Chlorobenzaldehyde.**—To 1.75 g. (0.01 mole) of freshly distilled *o*-chlorobenzaldehyde and 1.40 g. (0.012 mole) of 1-methyl-4-piperidone in 26 ml. of 62% aqueous ethanol was added 1.0 g. of solid potassium hydroxide. After shaking for fifteen minutes the crude, yellow **1-methyl-3,5-di-(*o*-chlorobenzal)-4-piperidone** was filtered off. Recrystallization from ethanol gave 1.63 g. (73%) of yellow needles, m. p. 152-155°. A thrice recrystallized sample, m. p. 152-154°, was used for analytical purposes.

Anal. Calcd. for $C_{20}H_{17}Cl_2NO$: C, 67.04; H, 4.78. Found: C, 67.25; H, 4.73.

The **hydrochloride** of 1-methyl-3,5-di-(*o*-chlorobenzal)-4-piperidone, after recrystallization from an ethanol-ether mixture, melted at 227-229° d.

Anal. Calcd. for $C_{20}H_{17}Cl_2NO \cdot HCl$: ionic Cl, 9.0. Found: ionic Cl, 9.0.

The reaction mixture from which the dibenzal derivative had been filtered was diluted with 60 ml. of water to precipitate 0.764 g. of an almost white powder, m. p. 120-135°. After five recrystallizations from ethanol-water, this product melted at 150-155°. An elemental analysis indicated that this somewhat impure sample was mainly **1-methyl-3-(*o*-chlorobenzal)-4-piperidone.**

Anal. Calcd. for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99. Found: C, 65.93; H, 5.34.

α-Naphthaldehyde.—The condensation of this aldehyde with the piperidone I was carried out in a manner similar to that of *o*-chlorobenzaldehyde. The crude, yellow dinaphthal derivative, m. p. 160-170°, was obtained in 80% yield. Recrystallization from ethanol gave an analytical sample of **1-methyl-3,5-di-(α-naphthal)-4-piperidone**, m. p. 173-175°.

Anal. Calcd. for $C_{28}H_{23}NO$: C, 86.34; H, 6.09. Found: C, 86.74; H, 6.22.

A small amount of an ivory-colored powder, m. p. 177-181°, the analyses of which indicated it to be an impure mononaphthal derivative, also was obtained. Variations in the relative amounts of potassium hydroxide used in the condensations of *o*-chlorobenzaldehyde and α-naphthaldehyde did not materially affect the nature of the reaction products (see Table II).

Summary

The base-catalyzed condensation of benzaldehyde with 1-methyl-4-piperidone has been found to yield either the mono or the dibenzal derivative depending on the nature of the solvent used for the reaction. In addition to these products, other materials corresponding to the phenylpiperidyl carbinols and mixtures of these types with the benzal derivative, as well as bis-dipiperidylphenylmethane, have been isolated.

The base-catalyzed condensation is shown to be reversible by the conversion of the carbinol-containing mixtures, as well as the dibenzal derivative, into the monobenzal derivative.

The acid-catalyzed condensation of benzaldehyde and the piperidone yields only the dibenzal derivative. The carbinol is shown not to be an intermediate in this condensation.

Quinoline-4-aldehyde yields either the mono- or diquinolinal derivative of the piperidone depending on the amount of alkali used to effect the condensation. *o*-Chlorobenzaldehyde and α-naphthaldehyde yields only the dibenzal derivative regardless of the amount of alkali used. Similarly quinoline-2-aldehyde yields mainly a rather unstable diquinolinal derivative.

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