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

Piperidine Derivatives. XXI. 4-Piperidone, 4-Piperidinol and Certain of their Derivatives

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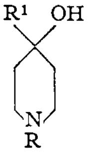
The preparation of 4-piperidinol (II) in 30% yield by the reduction of 4-hydroxypyridine with sodium in alcohol was reported[2] in 1915. A similar reduction of 4-methoxypyridine gave mainly piperidine together with a small amount of 4-methoxy-1,2,5,6-tetrahydropyridine, which was converted by hydrochloric acid to the hydrochloride of 4-piperidone (I).[2b] This piperidone could not be distilled, and on standing gradually underwent self-condensation to yield an odorless, amorphous solid.

Later a low yield of a crude hydrochloride of I was obtained by hydrolysis and decarboxylation of the reaction mixture resulting from the Dieckmann cyclization of di-(β-carbethoxyethyl)-amine.[3] This hydrochloride was characterized as its 3,5-dibenzal derivative. Analyses of the self-condensation product of the free base (I) indicated that the condensation had involved a loss of water between amino hydrogen and the carbonyl oxygen, and the conclusion was drawn that the stability of such well known derivatives of I as nortropine (2,6-dimethylene), triacetoneamine (2,2,6,6-tetramethyl) and vinyldiacetoneamine (2,2,6-trimethyl) is the result of the steric inhibition of the reactivity of the secondary amino group by the 2,6-substituents.[3]

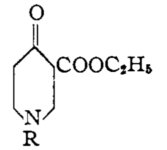
The Dieckmann cyclization of III with sodium ethoxide was later shown to yield only 10% of the 3-carbethoxy-4-piperidone (IV) and in view of the high yields of the 1-alkyl-3-carbethoxy-4-piperidones from IIIa, the low yield of IV was attributed to the high reactivity of the secondary amino group of III and/or its condensation product IV.[4]

I, R = H
Ia, R = C_6H_5CO



II, R = R[1] = H
IIa, R = C_6H_5CO
R[1] = H
IIb, R = H
R[1] = C_6H_5
IIc, R = C_6H_5CO
R[1] = $CH_2COOC_2H_5$

$RN(CH_2CH_2COOC_2H_5)_2$
III, R = H
IIIa, R = alkyl
IIIb, R = C_6H_5CO



IV, R = H
IVa, R = C_6H_5CO

The recently reported[5] preparation of IIIb in high yield and its cyclization to IVa, which in the present work was found to proceed with sodium hydride in 92% yield, offered readily available material for the preparation and study of I and II and their derivatives.

Hydrolysis and decarboxylation of IVa yields the hydrochloride of I, which was reported[4] to crystallize from an alcohol–ether mixture with 1.5 molecules of alcohol of crystallization; this conclusion was based on the chloride analyses of the salt. However, the hydrogenation behavior of this salt in the present work indicated it to be the hydrochloride of the diethylketal of I, which, incidentally, has a chlorine content comparable to that originally found.[4] Analyses for the other elements of this molecule confirmed the ketal structure.[6]

This ketal hydrochloride could not be hydrogenated in alcohol solution over a platinum catalyst, but in an aqueous solution containing a trace of hydrochloric acid it was readily hydrogenated to the hydrochloride of II. The latter salt also was obtained by the hydrolysis of 1-benzoyl-4-piperidinol (IIa) resulting from the hydrogenation of Ia.

The 4-piperidone (I) was readily N-acylated, *e. g.*, the benzoyl derivative (Ia) was obtained in 70% yield from IVa *via* I. All attempts to remove the 3-carbethoxy group of IVa without simultaneously removing the 1-benzoyl group were not very successful. Mild hydrolysis of IVa with 2% aqueous potassium hydroxide followed by decarboxylation gave only a 30% yield of Ia; heating IVa with benzoic acid and a trace of *p*-toluenesulfonic acid gave a quantitative yield of carbon dioxide, but only 23% of Ia could be isolated from the resulting mixture.

In view of the experience with the condensation of 1-methyl-4-piperidone and a variety of aromatic aldehydes,[7] it seemed of interest to determine the behavior of Ia in such reactions. In an alcoholic solution of hydrogen chloride Ia reacted with two equivalents of benzaldehyde to give a quantitative yield of the 3,5-dibenzal derivative (VI), as did the corresponding 1-methyl derivative.[7] Alcoholysis of VI with alcoholic hydrogen chloride gave the hydrochloride of the diben-

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[1] Eli Lilly and Company Fellow, 1947–1948.

[2] (a) Koenigs and Neumann, *Ber.*, **48**, 956 (1915); (b) Emmert and Dorn, *ibid.*, **48**, 688 (1915).

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

[4] Kuettel and McElvain, THIS JOURNAL, **53**, 2692 (1931).

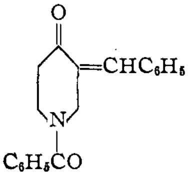
[5] McElvain and Stork, *ibid.*, **68**, 1049 (1946).

[6] It is of interest to note that the chlorine content reported for the hydrochloride of 1-phenylethyl-4-piperidone (Bolyard and McElvain, THIS JOURNAL, **51**, 922 (1929)) also corresponds to that of the hydrochloride of the diethylketal.

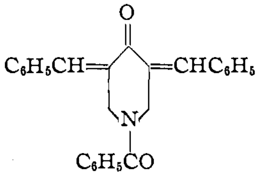
[7] McElvain and Rorig, *ibid.*, **70**, 1820 (1948).

zal derivative of I,[3,4] which on treatment with dilute alkali gave a stable free base. Apparently the 3,5-dibenzal substituents inhibit the reactivity of the carbonyl group of I as the previously noted[8] 2,6-substituents do for the amino group.

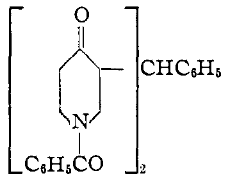
The course of the reaction of Ia with benzaldehyde in basic solution appeared even more complex than that of the 1-methyl analog.[7] A variety of conditions were tried and the procedure that produced the least complex mixture of reaction products is described in the experimental part. The products isolated from this condensation were: 16% of the monobenzal derivative (V), 29% of the phenyldipiperidylmethane (VII) and a trace of VI. The products V and VII precipitated from this reaction mixture as a complex that could not be separated by recrystallization from methanol. However, a solution of the complex in boiling ethyl acetate yielded the two components, *neither* of which would redissolve in this solvent.



V



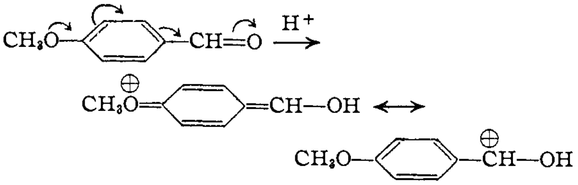
VI



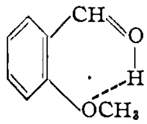
VII

To determine whether a weaker base would produce a less complex mixture of reaction products, sodium benzoate instead of potassium hydroxide was used to effect the condensation. The reaction was very slow: after a month, crystals of VI began to separate; they were removed periodically and after ten months a 65% yield of pure VI was obtained. A similar reaction mixture without the sodium benzoate gave no product.

If the proposed mechanisms[7] for the condensation of aromatic aldehydes with 1-methyl-4-piperidone in acidic and basic medium are valid, substituents in the aldehyde would be expected to show a more pronounced effect on the rate of the acid-catalyzed condensation than on the base-catalyzed reaction. A series of condensations of a variety of substituted benzaldehydes with Ia confirmed this conclusion. In acidic medium a tremendous variation in reaction rate (see Table I) was noted: anisaldehyde and piperonal reacted more rapidly than benzaldehyde, which showed a greater reactivity than *p*-chlorobenzaldehyde and a very much greater reactivity than *m*- and *p*-nitrobenzaldehydes; *o*-chloro- and *o*-methoxybenzaldehydes gave no reaction whatsoever. In each case the dibenzylidene derivatives corresponding to VI were the sole reaction products. It appears, therefore, that a group, *e. g.*, *p*-methoxy, capable of increasing the electron density around the carbonyl oxygen facilitates the coördination of the proton at this point and the consequent formation of the reactive (and resonance-stabilized) carbonium ion

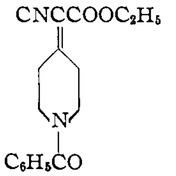


The failure of the *o*-substituted aldehydes, particularly the *o*-methoxy-benzaldehyde, to show any reaction is noteworthy and is probably related to the chelation (hydrogen bonding) between the oxonium hydroxyl and the adjacent methoxy group, which prevents formation of the carbonium ion necessary for the reaction

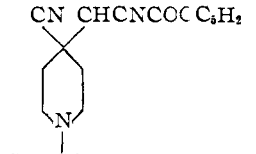


In contrast to their behavior in acidic medium, each of these aldehydes reacted quite rapidly with Ia in alkaline solution (see Table II). The small variations in the observed reaction rates indicate that those electron attracting substituents, *e. g.*, nitro and chloro, which have a retarding effect in acidic medium, definitely accelerate the reaction in basic solution. This behavior shows that the base-catalyzed condensation is relatively independent of the structure of the aldehyde, as the postulated mechanism[7] would indicate.

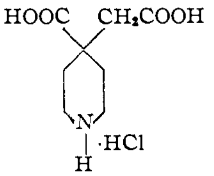
The condensation of the piperidone Ia with cyanoacetic ester[8] gave a 76% yield of the piperidylidene derivative VIII, the structure of which was shown by its reaction with aqueous potassium cyanide solution to form the dinitrile IX in 93% yield. The latter product was further characterized by hydrolysis to the dicarboxylic acid X.



VIII



IX



X

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[8] Stork and McElvain, This Journal, 68, 1053 (1946).

The α,β-unsaturated cyanoester (VIII) reacted immediately with phenylmagnesium bromide to give a precipitate which appeared to be the magnesium enolate of VIII (with β,γ-unsaturation) as shown by the fact that 76% of the reaction product, after decomposition with acid, dissolved in cold, aqueous potassium cyanide; from another run 71% of VIII was recovered by adsorption on alumina. That portion of the reaction product which was insoluble in the cyanide solution could be evaporatively distilled, but the product so obtained did not give analytical data corresponding to those calculated for the product resulting from the 1,4-addition of the Grignard reagent to VIII. Methylmagnesium bromide gave even more of the enolate of VIII; 93% of this reaction product dissolved in aqueous potassium cyanide.[9]

Phenylmagnesium bromide reacted with the piperidone Ia to give the corresponding 4-phenyl-4-piperidinol, which was converted by alkaline hydrolysis to the piperidinol IIb.

The piperidone Ia and ethyl bromoacetate in the Reformatsky reaction gave a good yield of the piperidinol IIc, which proved to be remarkably resistant to dehydration: it was distilled without appreciable decomposition and also was recovered unchanged after heating in refluxing 90% formic acid.

Experimental

1-Benzoyl-3-carbethoxy-4-piperidone (IVa).—A 3-liter three-neck flask was fitted with dropping funnel, a mercury-seal stirrer and a water-cooled condenser with a gas trap connected to the top. After filling the apparatus with nitrogen, the condenser was removed momentarily and 29.7 g. (1.24 mole) of sodium hydride added through a powder funnel; from the other neck of the flask 800 ml. of thiophene-free benzene was added through the dropping funnel.[10] After again flushing the system with nitrogen, stirring was started and 200 g. (0.62 mole) of N-benzoyl-di-(β-carbethoxyethyl)-amine[5] (IIIb) was added. When 2 ml. of absolute alcohol was added, the reaction mixture became green in color and evolution of hydrogen started immediately. The rapidly stirred suspension was heated gently on a steam-bath for two and one-half hours, after which time it was cooled in an ice-bath and treated consecutively with 74.5 g. (1.24 moles) of glacial acetic acid and 67.0 g. (3.72 moles) of water. After the reaction mixture had stood for fifteen minutes, the crystalline sodium acetate trihydrate was removed by filtration and the filter cake washed with an additional 500 ml. of benzene.

The combined benzene filtrates were placed in a round-bottom flask and heated on a steam-bath at water-pump pressure until all of the solvent had been removed. The residue was 157 g. (92%) of IVa, a reddish oil, which crystallized after standing several days to give a solid melting at 56–59°.

1-Benzoyl-4-piperidone (Ia).—A mixture of 100 g. of IVa and 400 ml. of 6 *N* hydrochloric acid was refluxed for two hours. Extraction of the benzoic acid from the cooled reaction mixture with ether, followed by evaporation of the aqueous solution to dryness, gave the crude hydrochloride of I as a semi-solid mass. This material was dissolved in 30 ml. of water and to this stirred solution were added 50 g. of potassium carbonate, 500 ml. of chloroform, and then to this 51 g. of benzoyl chloride at a sufficient rate to maintain gentle reflux. The mixture was heated for four hours, after which time 30 ml. of alcohol was added and heating continued for an additional one-half hour. Then sufficient water to dissolve the precipitated salts was added to the cooled reaction mixture. The chloroform layer was separated and washed with 5% potassium carbonate solution, water, 5% hydrochloric acid, and with a saturated salt solution. After drying, the chloroform was removed by distillation and the residue distilled under reduced pressure to give 51 g. (70%) of Ia as a colorless liquid, b. p. 158–160° (0.2 mm.). Part of the product was allowed to stand in a closed flask and after several months it crystallized to a white solid, m. p. 49–52°. The succeeding batches of Ia could be crystallized readily by seeding with these crystals.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45. Found: C, 71.17; H, 6.41.

The semicarbazone, which was prepared and crystallized from an ethyl acetate–ethyl alcohol mixture, melted at 193.5–195°,

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: N, 21.55. Found: N, 21.77.

The 2,4-dinitrophenylhydrazone, after crystallization from methanol, melted at 196–198°.

Anal. Calcd. for $C_{18}H_{17}N_5O_5$: C, 56.39; H, 4.47. Found: C, 56.23; H, 4.48.

1-Diphenylacetyl-4-piperidone.—This compound was prepared by the procedure for Ia, except that diphenylacetyl chloride was substituted for benzoyl chloride. Recrystallization of the product from benzene gave fluffy white needles, m. p. 135–136°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.80; H, 6.62.

The 2,4-dinitrophenylhydrazone melted at 185–187°.

Anal. Calcd. for $C_{25}H_{23}N_5O_5$: C, 63.42; H, 4.90. Found: C, 63.18; H, 4.89.

1-Acetyl-4-piperidone.—The crude hydrochloride of I from 75 g. of IVa was dissolved in 250 ml. of glacial acetic acid and a solution of 22.4 g. of sodium acetate in 150 ml. of glacial acetic acid added with stirring. Following this, 36 g. of acetic anhydride was added and the reaction mixture heated with stirring on a steam-bath for ninety minutes, after which time 10 ml. of methanol was added and heating continued for fifteen minutes. The precipitated salt was filtered off and the acetic acid removed by distillation. The residue was fractionally distilled under reduced pressure through a short (15 mm.) Vigreux column to give 18.6 g. (49%) of 1-acetyl-4-piperidone as a water-white liquid; b. p. 124–128° (0.2 mm.); $n^{25}{}_{\rm D}$ 1.5023; $d^{25}{}_4$ 1.144, and $M_{\rm D}$ 36.4 (calcd. 36.3). This compound is completely miscible with water, but insoluble in ether.

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.43; H, 7.99.

The 2,4-dinitrophenylhydrazone, after crystallization from ethanol, melted at 212–213°.

Anal. Calcd. for $C_{13}H_{15}N_5O_5$: C, 48.59; H, 4.71. Found: C, 48.40; H, 4.95.

4,4-Diethoxypiperidine (4-Piperidone Diethylketal) Hydrochloride.—The crude hydrochloride of I, obtained from 50 g. of IVa was recrystallized three times from an absolute alcohol–ether mixture to give 8.0 g. (21%) of 4,4-diethoxypiperidine hydrochloride; m. p. 138–140° (Kuettel and McElvain[4] reported 138–140° for the hydrochloride of I·1.5C_2H_5OH).

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(9) In contrast to these results, Kohler and collaborators (*Am. Chem. J.*, **33**, 21, 153 and 333 (1905); **35**, 386 (1906); **38**, 511 (1907)) reported the 1,4-addition of Grignard reagents to a variety of α,β-unsaturated nitriles, aldehydes, ketones and esters. Birch and Robinson (*J. Chem. Soc.*, 501 (1943)) reported 1,4-addition of methylmagnesium bromide to ethyl cyclohexylidenecyanoacetate to the extent of 45%. More recently Widequist (*C. A.*, **41**, 1615 (1947)) reported good yields of the 1,4-addition products from isopropylidenemalonic ester and both methylmagnesium iodide and butylmagnesium bromide).

(10) These two materials were added from opposite necks of the flask to minimize the danger of fire, which once resulted from the sparking of a granule of sodium hydride when it and the benzene were added through the same neck.

Table I

Rates of Formation, Yields, Melting Points and Analyses of Various 3,5-Di-arylidene (RCH=) Derivatives of 1-Benzoyl-4-Piperidone

	Time (hr.) for initial precipitation.	Yield (%) in					M. p., °C.	Formula	Analyses, %			
									Calcd.		Found	
R is		5	24	72	340	670 hrs.			C	H	C	H
C_6H_5	6	..	75[a]	97	...	..	165–167	$C_{26}H_{21}NO_2$	82.29	5.58	82.02	5.47
p-$CH_3OC_6H_4$	1	76	85	91	...	..	177–178	$C_{28}H_{25}NO_4$	76.52	5.73	76.27	5.78
o-$CH_3OC_6H_4$	...				None							
3,4-$OCH_2OC_6H_3$	0.5	76	89	99	...	..	196–197	$C_{28}H_{21}NO_6$	71.94	4.53	71.90	4.53
p-ClC_6H_4	11	..	18	73	...	..	194–195	$C_{26}H_{19}Cl_2NO_2$	69.65	4.27	69.73	4.43
o-ClC_6H_4	...				None							
m-$NO_2C_6H_4$	120	..	..	..	30	61	205–207	$C_{26}H_{19}N_3O_6$	66.52	4.08	66.57	4.24
p-$NO_2C_6H_4$	168	..	..	..	30	52	226–228	$C_{26}H_{19}N_3O_6$	66.52	4.08	66.43	4.38

[a] After twelve hours the yield was 27%.

Anal. Calcd. for $C_9H_{20}ClNO_2$: C, 51.54; H, 9.61; Cl, 16.9; OC_2H_5, 43.0. Found: C, 51.37; H, 9.64; Cl, 16.9; OC_2H_5, 43.2.

A higher melting form of this ketal salt was obtained as follows: 2 g. of the above salt, m. p. 138–140°, was dissolved in 50 ml. of alcohol and the solution stirred for several hours in a hydrogenation apparatus with hydrogen over previously reduced platinum oxide catalyst (Adams). At the end of this time there had been no appreciable uptake of hydrogen. The catalyst was removed by filtration, the filtrate warmed and dry ether added. After standing overnight, 1.0 g. of white crystals melting at 150° separated. Upon cooling and remelting this salt, a melting point of 140–141° was obtained. A mixed melting point with the salt, m. p. 138–140°, was 147–148°. Upon cooling and remelting, this mixture melted at 140–141°.

Anal. Found: C, 51.25; H, 9.44; Cl, 16.9.

1-Benzoyl-4-piperidinol (IIa).—In the glass liner of the hydrogenation bomb was placed 20 g. of 1-benzoyl-4-piperidone (Ia), 2 g. of Raney nickel and 80 ml. of alcohol. The liner was placed in the bomb and the latter filled with hydrogen to a pressure of 2200 p. s. i. After hydrogenation at 75° for two hours, the bomb was opened, the catalyst removed by filtration and the filtrate evaporated to dryness to give a quantitative yield of IIa as a colorless oil, which crystallized to a solid, m. p. 70–73°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 69.85; H, 7.42.

This compound also was prepared by reduction of Ia with Adams platinum-oxide catalyst.

1-Benzoyl-4-piperidyl N-phenylcarbamate was prepared by the action of phenyl isocyanate on IIa. After recrystallization from petroleum ether, it melted at 184–185°.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22. Found: C, 70.26; H, 6.37.

4-Piperidinol (II) Hydrochloride.—Ten grams of 1-benzoyl-4-piperidinol (IIa) was refluxed with 100 ml. of 20% aqueous hydrochloric acid for one hour and the resulting solution cooled to room temperature. The benzoic acid, some of which had crystallized, was removed by extraction with benzene and the aqueous solution evaporated to dryness. The crude hydrochloride thus obtained was recrystallized from alcohol–ether to give 3.4 g. (50%) of 4-piperidinol hydrochloride; m. p. 151–153° (reported,[2b] 146–148°).

Anal. Calcd. for $C_5H_{12}ClNO$: C, 43.63; H, 8.79; Cl, 25.8. Found: C, 43.48; H, 8.43; Cl, 25.3.

This compound was also prepared by the hydrogenation of the hydrochloride of 4,4-diethoxypiperidine over Adams platinum oxide catalyst in an aqueous solution containing a few drops of hydrochloric acid; twenty-four hours were required to hydrolyze and reduce 1 g. of the ketal. The product was recovered by filtering off the catalyst, evaporating to dryness and recrystallizing the crude hydrochloride from an alcohol–ether mixture. The yield of II, m. p. 148–149°, was 0.4 g. (43%)

The Acid-catalyzed Condensation of 1-Benzoyl-4-piperidone (Ia) with Aromatic Aldehydes.—The procedure used in these condensations is illustrated by the following preparation of 1-benzoyl-3,5-dibenzal-4-piperidone (VI). A solution of 0.5 g. of Ia and 0.52 g. (2 equivalents) of benzaldehyde in 30 ml. of absolute alcohol was cooled in an ice-bath and saturated with hydrogen chloride. The solution soon became very dark in color and after six hours crystals began to form. After one day of standing, the bright-yellow crystals were filtered off and dried. The yield was 0.70 g. (75%) of large yellow crystals, m. p. 162–164°. After two more days, 0.2 g. of a second crop, m. p. 162–163°, was obtained, bringing the total yield to 0.90 g. (97%). The melting point of this product was raised to 165–167° by recrystallization from either methyl or ethyl alcohol. It, as well as the other diarylidene derivatives listed in Table I, has extremely low solubilities in methyl and ethyl alcohols, acetone, ether, petroleum ether and benzene.

The rates of formation, yields, melting points and analyses of the various 3,5-diarylidene derivatives of Ia are summarized in Table I.

The dibenzal derivative (VI) was also prepared in the following manner. In 15 ml. of 65% aqueous alcohol were dissolved 1.0 g. of Ia, 1.06 g. of benzaldehyde and 0.30 g. of sodium benzoate, and the solution was allowed to stand. Crystals started to form after one month. The product was filtered off at intervals to give, after ten months, 1.2 g. (65%) of VI, m. p. 164–166°.

1-Benzoyl-3,5-dibenzyl-4-piperidone.—In 100 ml. of ethanol was suspended 2.0 g. of VI and 150 mg. of Adams catalyst. This suspension was stirred with hydrogen until two moles had been absorbed (two hours). The catalyst was removed by filtration and the filtrate evaporated to dryness to give a viscous oil. This oil was dissolved in petroleum ether (b. p. 90–100°); from this solution 0.8 g. (40%) of a 1-benzoyl-3,5-dibenzyl-4-piperidone, m. p. 127–129° separated. Further recrystallization from the same solvent raised the melting point to 130–131°.

Anal. Calcd. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57. Found: C, 81.33; H, 6.49.

The semicarbazone, after recrystallization from alcohol-water, was obtained as white needles, m. p. 162–165°.

Anal. Calcd. for $C_{27}H_{28}N_4O_2$: N, 12.72. Found: N, 12.96.

1-Benzoyl-3,5-dibenzyl-4-piperidinol.—In 100 ml. of ethyl alcohol was suspended 2.0 g. of VI and 150 mg. of Adams catalyst and the mixture was stirred in the hydrogenation apparatus until no more hydrogen was absorbed (three hours). After removing the catalyst the solution was evaporated to dryness to give a colorless, viscous oil. Three successive crystallizations of this material from petroleum ether (90–100°) gave 0.7 g. (45%) of a product, m. p. 111–114°.

Anal. Calcd. for $C_{26}H_{27}NO_2$: C, 81.00; H, 7.06. Found: C, 80.98; H, 7.23.

3,5-Dibenzal-4-piperidone Hydrochloride.—A solution of 0.5 g. of VI in 40 ml. of absolute alcohol was saturated with hydrogen chloride and the mixture refluxed two hours. Upon cooling, 0.25 g. (62%) of fluffy yellow crystals, m. p. 270–273°, separated. Recrystallization from alcohol raised the melting point to 274–276° (reported, 276–277°[4]; 275–277°[3]).

3,5-Dibenzal-4-piperidone.—In 25 ml. of 5% potassium carbonate was suspended 0.5 g. of 3,5-dibenzal-4-piperidone hydrochloride and the mixture was stirred at room temperature for two hours to insure complete reaction. The free base (0.45 g.) was filtered off and dried, m. p. 183–185°; recrystallization from alcohol gave lustrous, pale yellow crystals, m. p. 183–184°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 82.82; H, 6.49.

3,5-Dibenzyl-4-piperidinol Hydrochloride.—In 80 ml. of alcohol was suspended 1.5 g. of 3,5-dibenzal-4-piperidone hydrochloride and 100 mg. of Adams catalyst. This suspension was stirred with hydrogen until hydrogen absorption ceased (4 hours), during which time, 105% of the theoretical amount of hydrogen was taken up. The catalyst was removed by filtration and the product recovered by evaporating the solution to a volume of 40 ml. and adding ether to start crystallization; 1.1 g. (73%) of **3,5-dibenzyl-4-piperidinol hydrochloride**, m. p. 288–291°, was obtained.

Anal. Calcd. for $C_{19}H_{24}ClNO$: C, 71.83; H, 7.62; Cl, 11.2. Found: C, 71.94; H, 7.53; Cl, 11.1.

The Base-catalyzed Reaction of 1-Benzoyl-4-piperidone (Ia) with Benzaldehyde.—In 130 ml. of 95% ethyl alcohol were dissolved 10.0 g. of Ia, 5.3 g. (one equivalent) of freshly distilled benzaldehyde and 1.0 g. of potassium hydroxide pellets. After standing for several days, a crop of yellow crystals started to form. After two weeks, these were removed by filtration, found to weigh 3.6 g., and to melt at 165–175°. This material was recrystallized from methanol to give 2.8 g. of lustrous, white crystals, m. p. 205–210°. Further recrystallization from methanol did not raise the melting point above 210–214°.

This material gave a red color with concentrated sulfuric acid, decolorized dilute potassium permanganate solution, and was found to contain 77.58% carbon and 6.04% hydrogen. It was dissolved readily in hot ethyl acetate; upon cooling, a crop of white crystals separated. These were removed by filtration, dried and found to weigh 2.6 g., m. p. 205–207°. When treated with hot ethyl acetate as before, most of the material was insoluble. The insoluble material (2.3 g.) was **1-benzoyl-3-benzal-4-piperidone (V)**, m. p. 236–240°.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.52; H, 5.92; N, 4.32.

From the ethyl acetate filtrates was obtained a second crop of crystals weighing 0.2 g. and melting at 228–240°. This material was recrystallized several times from ethanol to give **phenyl-bis-(1-benzoyl-4-keto-3-piperidyl)-methane** (VII) as a white powder, m. p. 272–274°. This compound gave no coloration with concentrated sulfuric acid and did not reduce dilute permanganate solution.

Anal. Calcd. for $C_{31}H_{30}N_2O_4$: C, 75.28; H, 6.11. Found: C, 75.07; H, 6.10.

After the original reaction mixture had stood an additional three weeks, a second crop of crystals, weighing 3.4 g., m. p. 215–230°, separated. Purification of this material showed it to be VII, bringing the total yield of this compound to 3.6 g. (29%).

From the mother liquors from the first recrystallization of both the first and the second crops of crystals from the original reaction mixture was obtained a trace (0.05 g.) of the dibenzal derivative (VI).

The Rates of the Base-catalyzed Reaction of 1-Benzoyl-4-piperidone with Aromatic Aldehydes.—In 6 ml. of 55% alcohol was dissolved 0.25 g. of Ia, two equivalents of the aldehyde and 0.05 g. of potassum hydroxide. The time required for the initial separation of a reaction product was noted; after two days the dry weight of this product was determined and expressed as the per cent. of the combined weight of the reactants. The results are summarized in Table II. No attempt was made to identify the reaction products.

TABLE II

BASE-CATALYZED CONDENSATIONS OF Ia AND AROMATIC ALDEHYDES, RCHO

R	Time, (min.) for initial precipitation	Yield, % of combined wt. of reactants in 2 days	Nature of product
C_6H_5	11	28	Oil
o-ClC_6H_4	0.25	83	Oil
p-ClC_6H_4	2	92	Oil
m-$NO_2C_6H_4$[a]	0.25	89	Oil
p-$NO_2C_6H_4$[b]	1	97	Yellow solid, m. p. 133–142°
o-$CH_3OC_6H_4$	3	92	Oil
p-$CH_3OC_6H_4$	40	77	Yellow solid, m. p. 115–123°

[a] Because of insolubility of aldehyde 65% alcohol was used. [b] Because of insolubility of aldehyde 75% alcohol was used.

Ethyl (1-Benzoyl-4-piperidylidene)-cyanoacetate (VIII).—In a 50-ml. round-bottom flask were placed 10.0 g. of 1-benzoyl-4-piperidone (Ia), 5.65 g. of cyanoacetic ester, 1 g. of anhydrous ammonium acetate, 3 ml. of glacial acetic acid, 20 ml. of dry benzene and a porcelain chip. The flask, after attachment to a Cope separator[11] filled with benzene, was heated in an oil-bath for one hour at 125°. Titration of the resultant water layer in the separator with standard base showed that it contained 0.4 g. of acetic acid; the yield of water amounted to 0.8 g. (calcd. 0.9 g.).

The reaction mixture was diluted with benzene, extracted with water and saturated sodium bicarbonate solution, and the benzene solution dried. The solvent was removed from the dried solution to give 14.0 g. of a dark-red oil. This oil was extracted with a total of 300 ml. of boiling ether to give, after evaporation of the solvent and drying the residue at 80° under 0.5 mm. pressure, 9.4 g. of **ethyl (1-benzoyl-4-piperidylidene)-cyanoacetate (VIII)** as a pale-yellow oil. A benzene solution of the ether-insoluble material was treated with ether until no further precipitate formed; the resultant suspension was filtered and the filtrate evaporated to dryness. The residual red oil was extracted with ether to give an additional 1.7 g. of VIII, bringing the total yield to 11.1 g. (76%). After standing overnight, the product crystallized to a white solid melting at 84–86°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08. Found: C, 68.49; H, 6.23.

Ethyl (1-Benzoyl-4-cyano-4-piperidyl)-cyanoacetate (IX).—The compound was made from VIII by the two following procedures.

(a)[12] A solution of 2.0 g. of VIII in 15 ml. of alcohol was treated with a solution of 0.87 g. of potassium cyanide in 5 ml. of water and the yellow solution cooled in an ice-bath. To this solution was added a mixture of 1.2 ml. of concentrated hydrochloric acid and 1 ml. of water and the reaction mixture allowed to stand twenty-five minutes at room temperature, before pouring into 50 ml. of cold 5% hydrochloric acid. The oily product that separated was taken up in benzene. After removal of the residual hydrogen cyanide by several extractions with water, the benzene was removed by distillation to give, after drying, 2.2 g. (96%) of IX as a colorless liquid, which crystallized

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(11) Cope, *et al.*, THIS JOURNAL, **63**, 3452 (1941).

(12) *Cf.* Hope and Sheldon, *J. Chem. Soc.*, **121**, 2223 (1922).

to a solid melting at 110–113°. Recrystallization from benzene and petroleum ether (60–68°) gave white rosettes, m. p. 119–121°.

(b) A mixture of 10 ml. of 10% aqueous potassium cyanide solution and 0.2 g. of VIII was shaken for one-half hour and the resulting solution then carefully neutralized with 10% hydrochloric acid. Extraction with benzene gave 0.20 g. (93%) of IX after the benzene was removed and the residue dried.

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89. Found: C, 66.62; H, 6.02.

4-(4-Carboxypiperidyl)-acetic Acid Hydrochloride (X).—A solution of 1 g. of IX in 25 ml. of 25% hydrochloric acid was refluxed for twenty-four hours. After cooling, the benzoic acid was extracted with benzene. The aqueous solution was evaporated to dryness, the residue treated with an excess of 30% potassium hydroxide and the solution heated until the evolution of ammonia ceased. The alkaline solution was acidified with concentrated hydrochloric acid and evaporated to dryness.

The residue of sodium chloride and the salt (X) was treated with two 50-ml. portions of boiling absolute alcohol. The alcohol solutions were combined, filtered, evaporated to 40 ml. and treated with dry ether to the point of cloudiness. The flocculent precipitate which formed was removed by filtration and the filtrate placed in the refrigerator overnight. The product (X) that separated was removed by filtration, dried and found to weigh 0.51 g. (76%). Its melting point, 207–212°, was raised to 217–219° by two recrystallizations from alcohol-ether.

Anal. Calcd. for $C_8H_{14}ClNO_4$: C, 42.96; H, 6.31; Cl, 15.9. Found: C, 42.63; H, 6.54; Cl, 15.7.

The Reaction of VIII with Phenylmagnesium Bromide.—A solution of 4.5 g. (0.015 mole) of VIII in a mixture of 25 ml. of dry benzene and 75 ml. of dry ether was placed in a three-neck flask equipped with stirrer, condenser and dropping funnel. After filling the system with dry nitrogen 0.016 mole of phenylmagnesium bromide in 50 ml. of ether was added; an immediate precipitate formed. After refluxing for one-half hour, the reaction mixture was cooled, diluted with 100 ml. of ether and treated with cold 10% hydrochloric acid until the mixture cleared. The organic layer was removed, dried and evaporated to give 5.1 g. of a yellow gum. This gum was dissolved in 100 ml. of dry benzene and the resulting solution poured through a 20 cm. column of alumina. The column then was eluted with an additional 300 ml. of benzene and the combined eluates evaporated to dryness. The residue (3.3 g.) crystallized to a white solid, m. p. 78–80°; mixed m. p. with VIII 80–84°. By elution with chloroform 0.2 g. of a dark colored, saturated gum was obtained.

The yellow gum from another similar reaction was treated with 5 ml. of benzene and stirred overnight with 150 ml. of 10% aqueous potassium cyanide solution. The mixture then was extracted twice with 75-ml. portions of benzene to give, after evaporation of the solvent, 1.3 g. of a dark-colored gum which did not decolorize dilute permanganate solution. When this gum was evaporatively distilled, biphenyl first sublimed far up the tube and then, at 215–230° (0.4 mm.), a yellow oil was collected. A considerable quantity of carbonaceous material remained in the bottom of the tube. The yellow oil was separated from the rest of the material and again evaporatively distilled as a clear yellow oil at 215–225° (0.5 mm.). The analytical values (C, 75.57; H, 6.88; OC_2H_5, 8.1) obtained for this compound, however, did not check with those (C, 73.38; H, 6.43; OC_2H_5, 12.0) calculated for ethyl 1-benzoyl-4-phenyl-4-piperidylacetate.

Ethyl (1-Benzoyl-4-hydroxy-4-piperidyl)-acetate (IIc).—In a 500-ml. three-neck flask, equipped with condenser, stirrer and addition funnel were placed 5.0 g. of 1-benzoyl-4-piperidone (Ia), 5 g. of well-cleaned zinc foil, 20 ml. of dry ether and 20 ml. of dry benzene. After flushing the flask with a stream of nitrogen, 7.5 ml. of ethyl bromoacetate and a crystal of iodine were added. Stirring and heating caused the reaction to start immediately. The stirred reaction mixture was heated at gentle reflux for two and one-half hours, during which time an additional 5 g. of zinc was added.

After cooling the reaction mixture, 5 ml. of methyl alcohol and 5 ml. of acetic acid were added and the clear solution decanted into 50 ml. of water. The mixture was then acidified with acetic acid and extracted with 50 ml. of benzene. The organic layer was washed several times with dilute ammonia, dried and the solvent removed to give 6.6 g. (92%) of IIc as a dark-red oil. A small amount of this oil was subjected to evaporative distillation and it was found that practically all of the material distilled as a yellow oil at a jacket temperature of 205–215° (0.2 mm.).

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.48; H, 7.34.

4-Phenyl-4-hydroxypiperidine (IIb) Hydrochloride.—A solution of 12.0 g. (0.059 mole) of Ia in a mixture of 30 ml. of dry benzene and 60 ml. of dry ether was treated with a solution of 0.067 mole of phenylmagnesium bromide in 100 ml. of ether. After the addition, the mixture was refluxed for one hour, with stirring. The cooled mixture then was treated with saturated ammonium chloride solution until it cleared. The organic layer was removed by decantation, the salt washed with ether and the combined ether solutions evaporated to dryness.

The yellow gum thus obtained was refluxed for three hours with a solution of 8 g. of potassium hydroxide in a mixture of 40 ml. of alcohol and 60 ml. of water. After removal of most of the alcohol by distillation, 100 ml. of water was added and the resulting mixture extracted with a total of 750 ml. of ether. After drying the ether extract with anhydrous potassium carbonate and Drierite, it was treated with hydrogen chloride. This gave 5.2 g. (41%) of a brown solid melting at 180–185°. Recrystallization from alcohol–ether gave 2.0 g. (16%) of the hydrochloride of IIb as a white solid, m. p. 202–204°.

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.55; Cl, 16.6. Found: C, 61.73; H, 7.86; Cl, 16.4.

Summary

A variety of derivatives of 4-piperidone and 4-piperidinol have been prepared from 1-benzoyl-4-piperidone and their properties reported.

The product obtained from the crystallization of 4-piperidone hydrochloride from alcohol is shown to be the ketal, 4,4-diethoxypiperidine hydrochloride.

The rates of the reactions of 1-benzoyl-4-piperidone with certain substituted benzaldehydes in acidic and basic media confirm the previously postulated mechanisms for such reactions.

The application of the Knoevenagel, Reformatsky and Grignard reactions to 1-benzoyl-4-piperidone are described. The product of the former reaction, ethyl (1-benzoyl-4-piperidylidene)-cyanoacetate, does not give significant amounts of 1,4-addition products with Grignard reagents, but reacts primarily as an acid to form a magnesium enolate.

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