β-Condensation Reactions of Cyclic Amines with Benzaldehyde: Evidence for the Enamine Pathway

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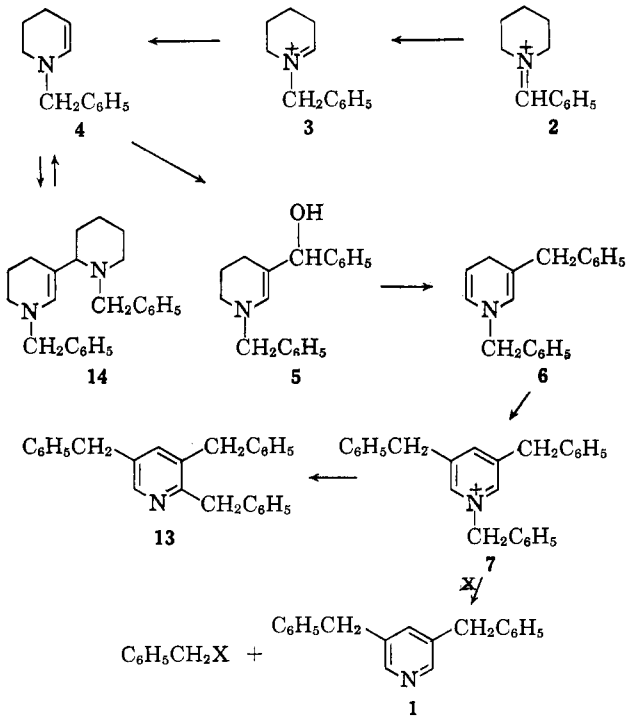
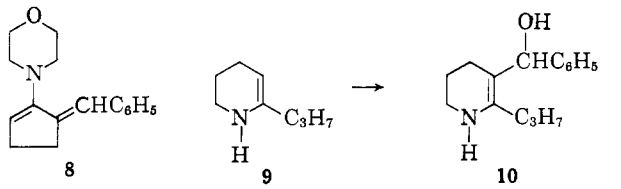
The mechanism of condensation of benzaldehyde with piperidine to give 3,5-dibenzylpyridine (**1**) is discussed, and evidence is presented that N-benzyl-Δ^2-tetrahydropyridine (**4**) is an intermediate. Reactions of benzaldehyde with 6-chloro-1,2,3,4-tetrahydroquinoline and with 1,2,3,4-tetrahydroisoquinoline have been shown to give 3-benzyl-6-chloroquinoline (**16**) and 4-benzylisoquinoline (**17**), respectively.

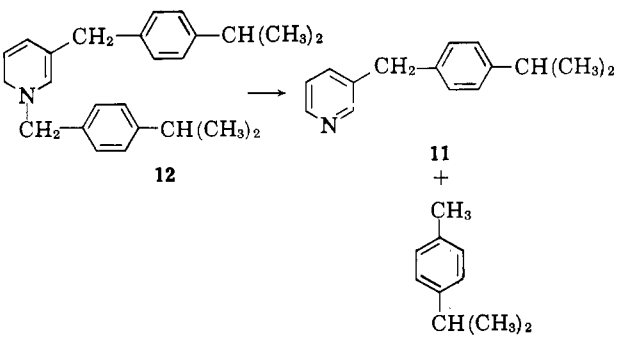
Seventy years ago Rügheimer reported that benzaldehyde condenses with N-benzoylpiperidine at high temperature to give 3,5-dibenzylpyridine (**1**).[2] This work was confirmed and extended recently by Poirer, Morin, McKim, and Bearse,[3] and by the present authors,[4] who found that the acetic acid-catalyzed reaction of piperidine and benzaldehyde in refluxing toluene gives the same product. From these results structures could be assigned to the unknown products of some similar reactions.[5,6] Piperidine or N-benzoylpiperidine has been shown to condense as well with *o*-, *m*-, and *p*-tolualdehyde,[7] *p*-cuminaldehyde,[8] *p*-dimethylamino-[3,6] and *p*-diethylaminobenzaldehyde,[6] anisaldehyde,[3] and 3- and 4-pyridinealdehyde.[3]

In the earlier paper we proposed that this transformation involves rearrangement of the initially formed Schiff cation (**2**) *via* a second Schiff cation (**3**) to the enamine (**4**) followed by condensation at the β-position with benzaldehyde to give the adduct **5**. Dehydration of **5** would give a second enamine (**6**) which on addition of benzaldehyde and loss of hydroxide would produce the 1,3,5-tribenzylpyridinium ion **7**. Displacement by a suitable nucleophile such as acetate ion, water, or piperidine would then give 3,5-dibenzylpyridine.[9] We further suggested that Rügheimer's reaction proceeds by the same mechanism, except that water formed during the condensation is consumed in hydrolysis of N-benzoylpiperidine. We now report evidence in favor of the enamine pathway.



Addition of benzaldehyde to enamines and subsequent dehydration in the manner proposed finds support in the recent literature. Thus Birkofer, Kim, and Engels have prepared compounds such as **8** by reaction of cyclic ketones with benzaldehyde in refluxing benzene.[10] Although tetrahydropyridines have not been studied in this respect, it seems likely that the undefined 1:1 adduct of γ-coniceine (**9**) and benzaldehyde[11] is the 3-phenylhydroxymethyl derivative (**10**), similar to **5**. From the reaction of N-benzoylpiperidine and *p*-cuminaldehyde Rügheimer and Herzfeld isolated, besides the dicuminylpyridine, 3-*p*-cuminylpyridine (**11**) and *p*-cymene.[8] The latter are most readily visualized as products of pyrolysis of the second enamine (**12**, corresponding to **6**).





Concerning the last step of the reaction, decomposition of the pyridinium ion **7**, Poirier, *et al.*, have shown

(1) Inquiries may be addressed to W. D. B. at Room 2-304, M.I.T.

(2)(a) L. Rügheimer, *Ber.*, **24**, 2186 (1891); (b) L. Rügheimer, *ibid.*, **25**, 2421 (1892); (c) L. Rügheimer, *Ann.*, **280**, 36 (1894); (d) L. Rügheimer and W. Kronthal, *ibid.*, **280**, 50, 51 (1894).

(3) R. H. Poirier, R. D. Morin, A. M. McKim, and A. E. Bearse, *J. Org. Chem.*, **26**, 4275 (1961).

(4) E. P. Burrows, R. F. Hutton, and W. D. Burrows, *ibid.*, **27**, 316 (1962).

(5) S. Skraup and K. Böhm, *Ber.*, **59**, 1015 (1926).

(6) E. D. Parker and A. Furst, *J. Org. Chem.*, **23**, 201 (1958).

(7) L. Rügheimer and K. Döring, *Ann.*, **280**, 74 (1894).

(8) L. Rügheimer and W. Herzfeld, *ibid.*, **280**, 60 (1894).

(9) Poirier, *et al.*, have outlined a similar pathway, but without specifically invoking enamine intermediates.

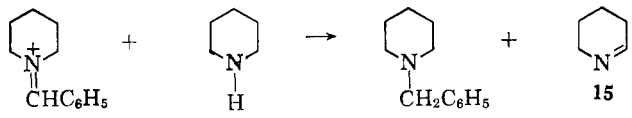
(10) L. Birkofer, S. M. Kim, and H. D. Engels, *Ber.*, **95**, 1495 (1962).

(11) J. von Braun and A. Steindorff, *ibid.*, **38**, 3094 (1905).

benzyl acetate to be present in the reaction mixture; however, stronger evidence that **7** is an intermediate is provided by Rügheimer's isolation (in low yield) of either 3,4,5- or 2,3,5-tribenzylpyridine (**13**),[2b] resulting most probably from Ladenburg rearrangement of the tribenzylpyridinium ion.[12]

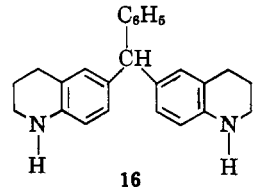
Although every step in this mechanism is plausible, it seemed advisable to test at least one intermediate, the most accessible being N-benzyl-Δ^2-tetrahydropyridine (**4**). Leonard and Hauck have shown that Δ^2-tetrahydropyridines lacking a substituent in the 2-position undergo dimerization to tetrahydroanabasine derivatives.[13] We prepared N,N′-dibenzyl-Δ^2-tetrahydroanabasine (**14**) according to their directions, anticipating that dimerization would be reversible under the β-condensation conditions. When the dimer was treated with benzaldehyde and acetic acid in refluxing toluene the product was indeed 3,5-dibenzylpyridine, in 16% yield.

There is, however, a serious objection to the first step of the piperidine reaction in which the Schiff cation **2** rearranges to **3**, for this is precisely the type of double bond migration shown not to occur in the closely related Sommelet reaction.[14] This introduces the possibility that the first step may be intermolecular hydride transfer from piperidine to the Schiff cation, producing N-benzylpiperidine and Δ^1-tetrahydropyridine (**15**). The latter could also give 3,5-dibenzylpyridine by a series of steps similar to those described above, although the Ladenburg product (**13**) would be more difficult to reconcile. The Sommelet-type mechanism would necessarily limit to 50% the yield of β-condensation product, but this, regrettably, is not disqualifying in any of the reactions we have studied.[15] Evidence eliminating this mechanism will be described later.



2 **15**

A number of other cyclic amines were treated with benzaldehyde. Neither 1,2,3,4-tetrahydroquinoline nor 6-methyl-1,2,3,4-tetrahydroquinoline gives a β-condensation product. In the former case the product is the same as that obtained by Einhorn from the zinc chloride-catalyzed reaction, probably 6,6′-benzalbistetrahydroquinoline (**16**).[16,17] In 6-chlorotetrahydroquinoline the aromatic ring is deactivated, and the β-condensation product, 3-benzyl-6-chloroquinoline (**17**), is formed in 20% yield. In 1,2,3,4-tetrahydroisoquinoline the problem of aromatic ring condensation is absent, and 4-benzylisoquinoline (**18**) is produced in 34% yield.[18] This being the cleanest reaction we encountered, it seemed best suited for testing the Sommelet-type mechanism, which requires that N-benzyl-1,2,3,4-tetrahydroisoquinoline (**19**) be formed in at least as great a yield as the isoquinoline. Infrared analysis of the reaction mixture showed that the N-benzyl derivative, if present at all, is produced in less than 3% yield. Since **19** was shown to be stable under the reaction conditions, the Sommelet mechanism may be discarded.



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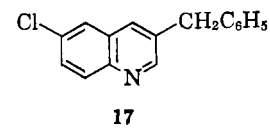

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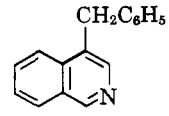

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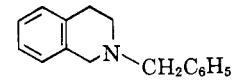

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Providing as it does access to the carbon skeleton of saturated amines, this reaction would appear to have important synthetic potential. At the onset of the work our sanguine expectation was that, within structural limitations, any aldehyde lacking a reactive α-hydrogen would undergo multiple alternate condensation with any amine, the most favorable prospects being those in which aromatic systems are created. We have not, however, succeeded in isolating pyridine derivatives from the reactions of pivalic or cinnamic aldehyde with piperidine, or from the reactions of benzaldehyde with 2-methyl- or 2,6-dimethylpiperidine, nor have we obtained a pyrrole from the condensation of benzaldehyde with pyrrolidine. In retrospect, these results are not inconsistent with the enamine mechanism, but they limit the preparative utility of β-condensation.

Experimental

3,5-Dibenzylpyridine from N,N′-Dibenzyl-Δ^2-tetrahydroanabasine.—The anabasine derivative was prepared in 38% yield by mercuric acetate oxidation of N-benzylpiperidine according to the directions of Leonard and Hauck,[13] except that solid sodium sulfide nonahydrate rather than hydrogen sulfide was used to precipitate the mercury salts after the reaction was complete. To 5.72 g. of the anabasine derivative in 100 ml. of dry toluene was added 7.5 g. of benzaldehyde and 3.0 ml. of glacial acetic acid. The solution was heated to reflux under a Dean–Stark trap. After 20 hr. about 1.5 ml. of aqueous phase had collected. The reaction mixture was cooled and the solvent was removed under reduced pressure, leaving 13.1 g. of dark, viscous oil. A 1.03-g. sample of the product was dissolved in benzene and chromatographed on 25 g. of Merck acid-washed alumina. Elution with ether (2–10% in benzene) yielded 0.106 g. of white crystalline material, m.p. 88–89° after recrystallization from ether. The infrared spectrum of this material (potassium bromide disk) was identical with that of 3,5-dibenzylpyridine,[4] and the mixture melting point with authentic material was undepressed.

3-Benzyl-6-chloroquinoline.—A solution of 8.18 g. of 6-chloroquinoline (Eastman White Label) in 200 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure using W-7 Raney nickel as catalyst. After 9 hr., 2430 ml. of

(12) H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 414.

(13) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(14) S. J. Angyal, *Org. Reactions*, **VIII**, 199 (1954). Dr. Hutton first called our attention to this point and suggested the alternative mechanism.

(15) Rügheimer reported a 70% yield of **1** from N-benzoylpiperidine.[2c] The yield of **1** claimed by Poirier, *et al.*, for the piperidine reaction is too high, being based on the wrong stoichiometry.

(16) A. Einhorn, *Ber.*, **19**, 1243 (1886).

(17) L. Rügheimer and W. Kronthal, *ibid.*, **28**, 1321 (1895), claimed that benzylquinolines were produced from N-benzoyltetrahydroquinoline and benzaldehyde, but provided no evidence in this or subsequent papers.

(18) For the similar condensation reactions of N-benzoyltetrahydroisoquinoline, *cf.* L. Rügheimer and B. Friling, *Ann.*, **326**, 261 (1903), and L. Rügheimer and E. Albrecht, *ibid.*, **326**, 297 (1903).

hydrogen had been taken up (2450 ml. corresponded to two molar equivalents of hydrogen), and further uptake was very slow. The catalyst was then separated and the filtrate was evaporated to dryness under reduced pressure, redissolved in acetone (25 ml.), and filtered to remove sodium hydroxide. Evaporation of the acetone gave 7.93 g. of crude crystalline 6-chloro-1,2,3,4-tetrahydroquinoline,[19] which was dissolved directly in 55 ml. of dry toluene. To this solution was added benzaldehyde (10.6 ml.) and glacial acetic acid (1 ml.), and the mixture was allowed to reflux 41 hr. under a Dean–Stark trap. The toluene was removed under reduced pressure and the residue was extracted with four 50-ml. portions of hot *n*-heptane. The heptane extracts yielded 9.56 g. of dark sirup, of which 1.03 g. was dissolved in benzene and chromatographed on 33 g. of Woelm alumina (activity I). From the later 1:10 ether–benzene fractions and the pure ether fractions 256 mg. of crude crystalline 3-benzyl-6-chloroquinoline was obtained. An analytical sample, recrystallized four times from ether, had m.p. 91.5–92°. The yield, based on the weight of 6-chlorotetrahydroquinoline, was 20%.

Anal. Calcd. for $C_{16}H_{12}NCl$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.90; H, 4.80; N, 5.57.[20]

The ultraviolet spectrum of the product [λ_{max} 265–270 (unresolved multiplet), 296, 302, 309, 315, 323 mμ, ϵ_{max} 4350, 3140, 2750, 4030, 3140, 5950] closely resembled that of 6-chloroquinoline [λ_{max} 272 (broad), 292, 298, 306, 312, 319 mμ, ϵ_{max} 4300, 2950, 2500, 3300, 2600, 4400].

4-Benzylisoquinoline.—A solution of 5.00 g. of 1,2,3,4-tetrahydroisoquinoline (Eastman White Label) and 1.5 ml. of acetic acid in 80 ml. of dry toluene was heated at reflux for 48 hr. under a Dean–Stark trap. About 2 ml. of aqueous phase collected. Removal of solvent under reduced pressure left 13.5 g. of thick red oil, which was extracted with five 50-ml. portions of hot heptane. The heptane extract was allowed to stand overnight, then decanted from precipitated gums and decolorized with charcoal. Evaporation under reduced pressure left 5.68 g. of yellow oil which partially crystallized. Crystalline material, washed with ether and recrystallized from acetone, had m.p. 119.5–120°. Authentic 4-benzylisoquinoline, prepared in 3.7% yield by a small-scale adaptation of the method of Avramoff and Sprinzak,[21] had m.p. 119.5–120° after three recrystallizations from acetone. A mixture melting point was undepressed, and the infrared spectra of the two samples potassium bromide disk) were superimposable.

The ultraviolet spectrum of 4-benzylisoquinoline had λ_{max} 265 (sh), 274, 285, 298, 310, 318, 323 mμ, ϵ_{max} 4480, 5130, 4270, 2070, 3910, 3870, 5480. A homogeneous sample of the decolorized reaction mixture exhibited the three longest wave length bands, from which it was determined that 4-benzylisoquinoline was produced in 34% yield from tetrahydroisoquinoline. About one third of the material was collected crystalline and ether-washed.

N-Benzyl-1,2,3,4-tetrahydroisoquinoline (3.87 g.), prepared from tetrahydroisoquinoline and benzyl chloride in pyridine solution, was treated with benzaldehyde (4 ml.) and acetic acid (1.5 ml.) in precisely the same manner as described above for tetrahydroisoquinoline. No water collected in the Dean–Stark trap, and recovery of the N-benzyl derivative was quantitative. The infrared spectrum of N-benzyltetrahydroisoquinoline (chloroform solution) exhibited a number of strong bands absent from the spectrum of 4-benzylisoquinoline. In particular, the band at 2800 cm.$^{-1}$ has intensity proportional to concentration. From this it was determined that N-benzyltetrahydroisoquinoline constituted no more than 6% of the noncrystalline portion of the decolorized reaction mixture of tetrahydroisoquinoline and benzaldehyde, and was thus formed in less than 3% yield in that reaction.

1,2,3,4-Tetrahydroquinoline and Benzaldehyde.—Treatment of tetrahydroquinoline with benzaldehyde under the conditions affording 4-benzylisoquinoline from tetrahydroisoquinoline gave only polymeric material. When the heating period was decreased to 15 hr. a small amount (less than 5% of the initial weight of tetrahydroquinoline) of crystalline material was isolated from the heptane extract. It was recrystallized from acetone and, on the basis of its melting point (151–152°) and infrared spectrum (N–H band at 3440 cm.$^{-1}$ in carbon tetrachloride solution) was assigned the same structure as Einhorn's compound[16] (6,6′-benzalbistetrahydroquinoline, m.p. 152–153°).

Spectra.—Ultraviolet spectra in 95% ethanol were determined using the Cary Model 14 recording spectrophotometer.

(19) J. von Braun, A. Petzold, and J. Seeman, *Ber.*, **55**, 3779 (1922).
(20) Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.
(21) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4090 (1956).

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The Reaction of Chloroacetaldehyde with Cyanide Ion in Aqueous Medium

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When an aqueous solution of chloroacetaldehyde (I) is added to an excess of aqueous sodium cyanide at 0°, 2-chloro-1-cyanoethyl acetate (II) is obtained in 90% yield. A study of this reaction indicates that the cyanohydrin of I dehydrohalogenates to acetyl cyanide, which then acetylates the conjugate base of more cyanohydrin to yield II.

Introduction

The reaction of an equimolar quantity of an aldehyde with cyanide ion in water normally will give the conjugate base of the corresponding aldehyde cyanohydrin. However, certain aldehydes have been shown to undergo reactions in the presence of cyanide ion which do not lead to cyanohydrins. The best known and most thoroughly studied example of what may be termed an atypical reaction of an aldehyde with cyanide ion is the benzoin condensation. In this reaction the cyanide ion sufficiently increases the acidity of the hydrogen of the —CHO group by converting the aldehyde to a mixture of cyanohydrin and its conjugate base so that this aldehydic hydrogen now alpha to a nitrile becomes easily removable in the presence of a base.[1] This appears to be a crucial step in the formation of a benzoin from the corresponding aldehyde.

The rearrangement of β-formyl acrylic acid to succinic acid has also been shown to be cyanide ion-catalyzed.[2] The proposed mechanism as in the benzoin condensation again incorporates the ability of the cyanide ion to increase greatly the acidity of the hydrogen of the —CHO group.

The interesting cyanide ion-catalyzed decomposition of β,β-dicarbethoxypropionaldehyde into diethyl malonate and ethyl acetate is another example of a reaction whose mechanistic explanation depends on the increased acidity of the aldehydic hydrogen. In this latter case the anion formed fragments to give a more stable anion; the aldehyde is converted to an ester.

(1) For pertinent references see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 257.
(2) V. Franzen and L. Fikentscher, *Ann.*, **623**, 68 (1959).