21-monoacetate-1,2-H^3 was put on the column as described above. From every three runs, four peak fractions containing the 1,2-H^3-aldosterone-21-monoacetate were pooled, and the total activity was about 1500 mc. The specific activity of the substance was determined and found to be 100 $\mu c/\mu g$.

Hydrolysis of the aldosterone-21-monoacetate-1,2-H^3. (a) *Enzymatic hydrolysis.* The solution of 10 ml. of 0.05*M* monohydrogen sodium orthophosphate was prepared and the *p*H adjusted to 7.0 with a few drops of acetic acid. Then 40 mg. of wheat germ lipase (Worthington Co., N. J.) was dissolved in that solution and warmed to 37° in a constant temperature oven. The solution of 200 mc of aldosterone-21-monoacetate-1,2-H^3 in 0.4 ml. propylene glycol was added to the enzyme solution in four portions with approximate 0.5 hr. intervals between additions. Incubation was continued for a total period of 4 hr. The incubation mixture was extracted with 4 × 15 ml. methylene dichloride. The combined solvent extract was washed with 2 ml. of water and taken down to dryness. It was further purified using a partition column made up with 28 g. Celite 545 in 14 ml. of the stationary phase.

The mobile phase (benzene) of the solvent system was equilibrated against the stationary phase [methanol-water (1:1 v./v.)]. Fractions of 5 ml. were collected and assayed for tritium using 5 λ from every fraction dissolved in the quenched scintillation liquid. The peak fractions 9, 10, and 11 containing aldosterone-1,2-H^3 were pooled and identity with standard aldosterone confirmed by paper chromatography, blue tetrazolium reaction, and soda fluorescence. The radiochemical purity of free compound and diacetate, prepared by acetylation with acetic anhydride and pyridine was determined as follows. Chromatography of a mixture of 1 μc of the 1,2-H^3-aldosterone and inert aldosterone (2 μg) in a Bush B_5 system gave a spot due to inert aldosterone, which was marked by pencil as observed in the ultraviolet light, and a strip (1.25 in. wide) of the chromatogram was scanned in a Vanguard automatic chromatogram scanner. It showed only one peak corresponding to the inert aldosterone; yield 100 mc. The specific activity of the aldosterone-1,2-H^3 was found to be 100 $\mu c/\mu g$.

A mixture of about 1 μc of the aldosterone-1,2-H^3 and 3 μg. inert aldosterone was acetylated with 0.15 ml. acetic anhydride and 0.3 ml. pyridine. The diacetate was run in the Bush B_3 system and scanned in a chromatogram scanner. Again only one sharp peak corresponding to the aldosterone diacete was observed thereby establishing the radiochemical purity of the aldosterone-1,2-H^3.

(b) *Alkaline hydrolysis.* Aldosterone 21-monoacetate-1,2-H^3 (220mc) was hydrolyzed according to the method of Simpson *et al.*[4] in a sealed tube. The reaction mixture was extracted with 4 × 15 ml. methylene dichloride; the total extract with 2 ml. of water and evaporated in dryness. It was purified by column chromatography and the fractions containing aldosterone-1,2-H^3 were identified. The radiochemical purity[11] of the product was established as described above in the case of aldosterone-1,2-H^3 obtained from the enzymatic hydrolysis; yield 66 mc. The specific activity was found to be 98 $\mu c/\mu g$.

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(11) It should be noted that no 17-isoaldosterone-1,2-H^3 could be detected (chromatography of a mixture of authentic aldosterone and its 17-isomer showed feasibility of its separation with a Bush B_5 system on paper, as well as on a Celite column).

β-Condensation Reactions of Piperidine with Aldehydes

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Saturated amines commonly exhibit nitrogen reactivity only. We wish to report a reaction in which piperidine is attacked on the carbon skeleton without loss of the nitrogen function. Skraup and Böhm in 1926 isolated from the reaction of benzaldehyde and piperidine a compound of unknown structure, m.p. 88–89°, to which they assigned the formula $C_{20}H_{19}N$.[4] In 1958 Parker and Furst reported that *p*-dimethyl- and diethylaminobenzaldehyde react with piperidine to give compounds $C_{23}H_{27}N_3$ and $C_{27}H_{35}N_3$, respectively.[5]

We have reinvestigated the reaction of benzaldehyde with piperidine and have shown the product to be 3,5-dibenzylpyridine (Ia). The NMR spectrum of the product exhibits a high field singlet (CH_2; $\tau = 6.17$), a broad, poorly resolved multiplet in the region for phenyl protons ($\tau = 2.90$) and a doublet (J = 1.7 c.p.s.) at such low field ($\tau = 1.82$) as to be attributable only to the 2,6-protons of a pyridine ring. The methiodide prepared from the free base was not sufficiently soluble in water for NMR analysis, and was converted by treatment with silver chloride to a hygroscopic methochloride (II). The 4-proton resonance, obscured by the phenyl multiplet in the spectrum of the free base, is shifted downfield by quaternization ($\delta = -3.32$ relative to DHO in deuterium oxide) and the intensity is half that of the 2,6-proton resonance ($\delta = -3.60$; the doublet is not resolved). Methylene ($\delta = 0.67$), *N*-methyl ($\delta = 0.57$) and phenyl ($\delta = -2.53$) protons have relative intensities in agreement with II. The doublet in the spectrum of the free base arises from spin coupling of the 2- and 4-protons of the pyridine nucleus. The coupling constant of 1.7 c.p.s. is close to the value of 1.9 c.p.s. calculated by Pople, Schneider, and Bernstein for the 2- and 4-protons of pyridine.[6] For 2,6-dibenzylpyridine, a mechanistically attractive alternative for Ia, coupling of the 3- and 4- protons should give splitting of about 8 c.p.s. by analogy

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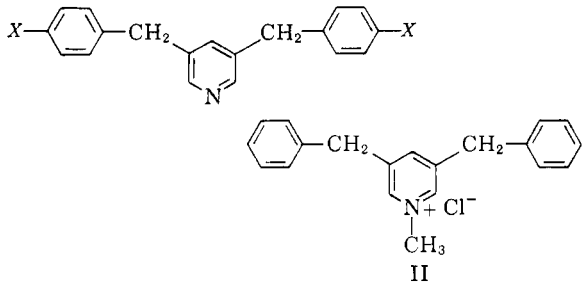
(4) S. Skraup and K. Böhm, *Ber.*, 59, 1015 (1926).

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

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959, p. 266.

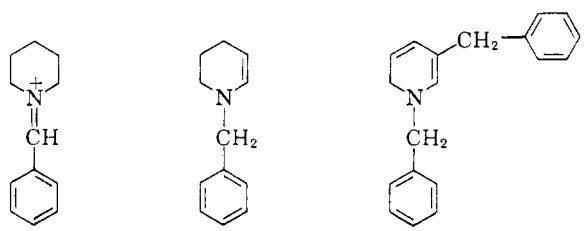
with 2,6-lutidine.[7] The ultraviolet spectrum of Ia (λ_{max} 262, 268, 276 mμ, ϵ_{max}. 4180, 4650, 3860) is strikingly similar to that of 3,5-lutidine.[8] The infrared spectrum is also consistent with Ia, as is the empirical formula, $C_{19}H_{17}N$.[9]



II

Ia. X = H
Ib. X = $N(CH_3)_2$
Ic. X = $N(C_2H_5)_2$

The molecular formulas and ultraviolet spectra reported by Parker and Furst are consistent with structures Ib and Ic.[10] The simplest mechanism for this transformation involves rearrangement of the initially formed Schiff cation III to the enamine IV followed by condensation with benzaldehyde, yielding the dibenzyldihydropyridine V. Condensation with a third molecule of benzaldehyde followed by displacement of the product from the *N*-benzyl group by piperidine gives 3,5-dibenzylpyridine.



III IV V

An analogous condensation was reported in 1891 by Rügheimer,[11] who isolated 3,5-dibenzylpyridine and benzoic acid from the reaction of benzaldehyde with *N*-benzoylpiperidine in a sealed tube, although his proof of structure was not conclusive. Our results suggest that benzaldehyde reacts with the free base rather than the benzamide, and that water so produced is consumed in hydrolysis of the benzamide. We are investigating other examples of this reaction.

(7) Pople, Schneider, and Bernstein, *op. cit.*, p. 128.
(8) R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *Trans. Faraday Soc.*, **50**, 918 (1954).
(9) The analysis given by Skraup and Böhm is only slightly better for $C_{20}H_{19}N$ than for $C_{19}H_{17}N$.
(10) R. H. Poirier *et al.* (paper presented before the St. Louis Meeting of the American Chemical Society, March, 1961, Abstracts 18-O) have also proposed these structures for the compounds of Parker and Furst.
(11) Rügheimer, *Ber.*, **24**, 2186 (1891); **25**, 2421 (1892); *Ann.*, **280**, 36 (1894).

EXPERIMENTAL

3,5-Dibenzylpyridine. A solution of 15 ml. of benzaldehyde, 5 ml. of piperidine, and a few drops of glacial acetic acid in 80 ml. of dry toluene was heated under reflux for 48 hr. under a Dean-Stark trap. The toluene was distilled *in vacuo* leaving 21 g. of dark syrupy residue of which 13.4 g. was dissolved in dry benzene and chromatographed on 550 g. of Merck acid-washed alumina. Non-crystalline material, total weight 5.3 g., was eluted with benzene, benzene-ether mixtures and finally ether. The last ether fractions were combined to give 2.14 g. of crude crystalline 3,5-dibenzylpyridine, m.p. 82–88°. (Thus the product isolated incorporated 25% by weight of the initial piperidine.) This material was recrystallized once from ether, then five times from acetone to give 394 mg., m.p. 90°.

Anal. Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found[12]: C, 87.98; H, 6.64; N, 5.43.

Portions of this sample were used for all spectral measurements and for the preparation of the methochloride.

3,5-Dibenzylpyridine methochloride. To a solution of 20 mg. of the free base in 0.2 ml. of carbon tetrachloride was added a slight excess of methyl iodide. The solution turned yellow immediately. After a few minutes the precipitated crystalline methiodide was removed by filtration and stirred with an aqueous slurry of freshly precipitated silver chloride. The suspension was filtered and the clear filtrate was lyophilized to give about 20 mg. of a white, hygroscopic solid. For NMR analysis the methochloride was dissolved in deuterium oxide, filtered, lyophilized to dryness and redissolved in deuterium oxide.

Spectra. NMR spectra were obtained for degassed 10% solutions using the Varian 60 mc. spectrometer. For the free base in carbon tetrachloride solution tetramethylsilane was the internal standard. For the methochloride in deuterium oxide adventitious water was the internal standard. Chemical shifts were measured by the conventional sideband technique. Methochloride samples were not spun,

The ultraviolet spectrum of the free base in 95% ethanol was determined using a Cary recording spectrophotometer.

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The Synthesis of 2,2-Diphenyltetrahydro-3-furonitrile

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In connection with another problem, it became desirable to prepare an authentic sample of the compound named in the title. A synthesis of this material was achieved in the following manner.

Lithium aluminum hydride reduction of ethyl γ,γ-diphenylparaconate[2] (Ia), prepared by a Re-

(1) This paper is abstracted from a thesis submitted by Sándor Barcza for the B.A. degree, Princeton University, 1960.
(2) W. Borsche, S. Kettner, M. Gilles, H. Kühn, and R. Manteuffel, *Ann.*, **526**, 1 (1936).