Diazotization Test.—A solution of one gram of β-naphthol dissolved in 25 ml. of 3 *N* sodium hydroxide was prepared. A small amount of sample to be tested was dissolved in 1 *N* sodium hydroxide and a little solid sodium nitrite added. To this solution was added an excess of dilute hydrochloric acid and then poured into a few ml. of alkaline β-naphthol. Positive test was characterized by formation of azure-red color; negative, yellow or brown color. This test was used throughout our work to confirm the conjugation of free amino groups.

Acknowledgment.—The authors wish to express their gratitude to Research Corporation for their grant in support of this investigation.

NEW ORLEANS, LOUISIANA

[CONTRIBUTION FROM NORTH TEXAS STATE COLLEGE]

Reductions of 1-(4-Nitrophenacyl)-4-(1-hexyl)-pyridinium Bromide

BY PRICE TRUITT, BOB HALL[1] AND BENNIE ARNWINE[1]

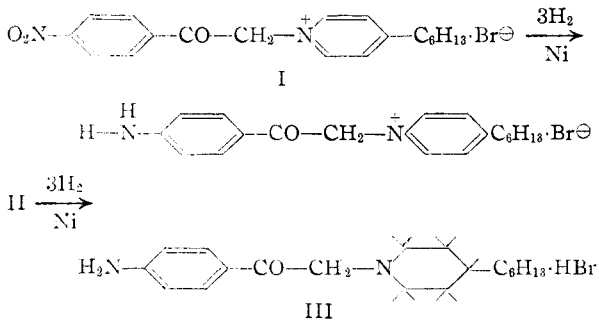
RECEIVED APRIL 8, 1952

The synthesis and reduction of 1-(4-nitrophenacyl)-4-(1-hexyl)-pyridinium bromide are reported. The catalytic hydrogenation of this compound occurs stepwise. The rates of hydrogenation with Adams catalyst indicate the pyridinium function is reduced first followed by the nitro group. The reverse order of reduction was noted with Raney nickel. The carbonyl group was not reduced under the conditions reported. The structures of these compounds have been proved by alternate syntheses.

The catalytic reduction of 1-phenacylpyridinium bromide at low temperature and low pressure in the presence of platinum gives 1-phenacylpiperidine hydrobromide.[2] Riegel and Wittcoff[3] were able to reduce preferentially the carbonyl group of this ketone at low temperature and high pressure (80 atmospheres) with Adams catalyst. However, they found[4] that this preferential hydrogenation was often impossible to accomplish when the benzene ring of the pyridinium ketone was substituted with hydroxyl groups. Truitt and coworkers[5] have found that substituents on the pyridine nucleus influence the catalytic hydrogenation of 1-phenacylpyridinium halides at low temperature and low pressure. A methyl or an ethyl group on the pyridinium portion of the molecule gave the corresponding 1-phenacyl-4-alkylpiperidine salt. However, when the alkyl group was C_5, C_6, C_8 or C_9 and in the 4-position of the pyridine ring the only reduction product which could be isolated was a 4-alkyl-1-(2-hydroxy-2-phenylethyl)-piperidine hydrohalide. This type compound resulted from the reduction of both reducible functions of the parent compound. It was impossible to isolate a product from these reductions where only one of the unsaturated groups had been reduced. The benzene ring was not altered under these conditions.

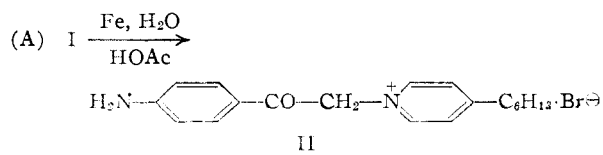
Our interest in compounds of this type for physiological studies necessitated our knowledge of the course of reduction of certain 1-(4-nitrophenacyl)-4-alkylpyridinium bromides. Since we were most interested in compounds in which the 4-alkyl group was rather large, we selected 1-(4-nitrophenacyl)-4-(1-hexyl)-pyridinium bromide for the present investigation.

The catalytic reduction of 1-(4-nitrophenyl)-4-(1-hexyl)-pyridinium bromide in the presence of Raney nickel at 50 p.s.i. and at room temperature proceeded stepwise as

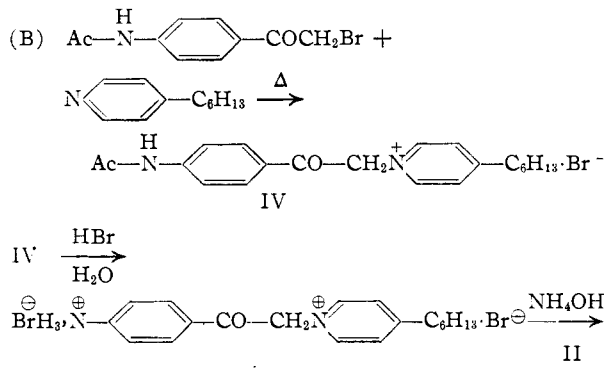


Compounds II and III were isolatable from this hydrogenation, but compound II predominated. Raney nickel would not catalyze the reduction of the carbonyl group under these conditions and the entire hydrogenation was very slow. Reduction of I with Adams catalyst at room temperature and 50 p.s.i. of hydrogen behaved very differently. The first three moles of hydrogen was absorbed very rapidly (about 5–15 minutes for a 10-g. sample of I) while several hours were required for the absorption of an additional three moles of hydrogen. No additional hydrogen was taken up even with prolonged shaking. Compound III was the main product, but a small amount of II could be isolated. They were easily separated by alcohol recrystallization.

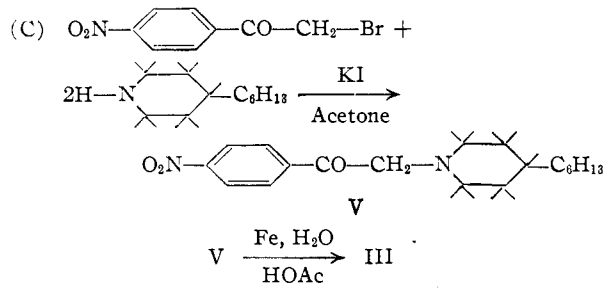
The structures of compounds II and III were determined with certainty by alternate modes of preparation and by study of their infrared spectra. Compounds I, II and III showed characteristic ketone absorption in the region of 6.2μ. The synthetic approaches to the reduction products are



(1) Parke, Davis and Company Research Fellows.
(2) F. Krohnke with K. Fasold, *Ber.*, **67**, 656 (1934).
(3) B. Riegel and H. Wittcoff, THIS JOURNAL, **68**, 1805 (1946).
(4) B. Riegel and H. Wittcoff, *ibid.*, **68**, 1913 (1946).
(5) Price Truitt, B. Bryant, W. E. Goode and B. Arnwine, *ibid.*, **74**, 2179 (1952).



Acetylation of II from procedure A also produced IV. A mixed melt of II from A and B did not show a depression in this value. Compound II by both procedures gave compound III when reduced catalytically with hydrogen.



Attempts to prepare III by condensing 4-acetylaminophenacyl bromide and 4-hexylpiperidine were unsuccessful in our hands.

The chemical evidence points to the reduction of the nitro group before the pyridinium function and very little reduction of the carbonyl group occurs during the hydrogenation of the other two. Small amounts of an unidentified product could be isolated from the hydrogenations and it may prove to result from the reduction of the carbon-to-oxygen double bond. The structure of this substance is under study at the present time.

Experimental

1-(4-Nitrophenacyl)-4-(1-hexyl)-pyridinium Bromide (I).—A solution of 24.4 g. (0.10 mole) of 4-nitrophenacyl bromide, 150 ml. of toluene and 17 g. (0.104 mole) of 4-(1-hexyl)-pyridine was allowed to stand until the dark oil which had immediately separated had changed to a yellow crystalline solid. The solid was removed and washed with ether. Recrystallization from an alcohol–ether mixture gave 25 g. (62%) of the yellow product, m.p. 144–145°.

Anal. Calcd. for $C_{19}H_{23}BrN_2O_3$: Br, 19.7; N, 6.91. Found: Br, 19.9; N, 7.07.

Hydrogenation of 1-(4-Nitrophenacyl)-4-(1-hexyl)-pyridinium Bromide (I) (with Raney Nickel).—A solution of 5 g. (0.0123 mole) of I in 100 ml. of 95% ethanol with 0.2 g. of Raney nickel was hydrogenated at room temperature and 50 p.s.i. hydrogen pressure until 0.047 mole of hydrogen had been absorbed. Twenty-six hours was required for this reaction.

The mixture was heated and filtered to remove the catalyst. The filtrate was cooled in the ice-box and filtered. The white crystals, which were very insoluble in alcohol, weighed 1.5 g. (23%) and melted with decomposition at 240°. The properties of this compound coincided with those of 1-(4-aminophenacyl)-4-(1-hexyl)-piperidine hydrobromide III which was prepared by two other methods in this investigation.

Anal. Calcd. for $C_{19}H_{31}BrN_2O$: C, 59.62; H, 8.17; Br, 20.88; N, 7.32. Found: C, 59.49; N, 8.28; Br, 21.1; N 7.26.

The free base was obtained from this salt by the action of ammonia upon a 50% aqueous ethanol solution of the hydrobromide, m.p. 95.5–97°.

Anal. Calcd. for $C_{19}H_{30}N_2O$: N, 9.28. Found: N, 9.35.

Ether was added to the filtrate from the isolation of III above and 2 g. (43%) of light yellow crystals, m.p. 170–181°, was garnered. The properties of this component were found to be those of 1-(4-aminophenacyl)-4-(1-hexyl)-pyridinium bromide which was prepared by two alternate methods in the present work.

Anal. Calcd. for $C_{19}H_{25}BrN_2O$: C, 59.50; H, 7.31; Br, 21.2; N, 7.43. Found: C, 59.44; H, 7.22; Br, 21.4; N, 7.57.

Hydrogenation of 1-(4-Nitrophenacyl)-4-(1-hexyl)-pyridinium Bromide (I) (Adams Catalyst).—A solution of 10 g. (0.0246 mole) of 1-(4-nitrophenacyl)-4-(1-hexyl)-pyridinium bromide in 100 ml. of 95% ethanol with 0.2 g. of platinum oxide was hydrogenated at room temperature and 50 p.s.i. of hydrogen until 0.1476 mole of hydrogen had been absorbed. It was noted that one-half of the hydrogen was taken up in about 15 minutes while 12 hours was required for the remainder. The precipitate was dissolved in 250 ml. of 95% ethanol and filtered to remove the catalyst. The clear solution was cooled and 3.4 g. (33%) of the desired product obtained. Concentration of the filtrate gave 4.2 g. The combined yield was 74%, m.p. 240° (dec.). This product corresponded to one of the products from the Raney nickel hydrogenation, III.

Anal. Calcd. for $C_{19}H_{31}BrN_2O$: N, 7.31. Found: N, 7.51.

1-(4-Acetylaminophenacyl)-4-(1-hexyl)-pyridinium Bromide (IV).—A mixture of 10 g. (0.039 mole) of 4-acetylaminophenacyl bromide, 6.5 g. (0.04 mole) of 4-(1-hexyl)-pyridine, 100 ml. of toluene and 100 ml. of *n*-amyl alcohol was refluxed for one hour and allowed to cool. The product separated as a yellow powder. Recrystallization from absolute alcohol gave 9.8 g. (60%) of yellow needles, m.p. 230–234° (dec.).

Anal. Calcd. for $C_{21}H_{27}BrN_2O_2$: Br, 19.04; N, 6.66. Found: Br, 19.31; N, 6.79.

1-(4-Aminophenacyl)-4-(1-hexyl)-pyridinium Bromide (II). A. (From Iron Reduction I).—A mixture of 15 g. of powdered iron, 0.1 ml. of glacial acetic acid, 100 ml. of water and 5 g. (0.0123 mole) of I was stirred at 80–85° for nine hours. The mixture was diluted with 200 ml. of water, heated to reflux and filtered. Yellow crystals separated from the filtrate. Recrystallization from alcohol gave 1.9 g. (41%) of the yellow needles, m.p. 180–181°.

Anal. Calcd. for $C_{19}H_{25}BrN_2O$: N, 7.43. Found: N, 7.49.

Acetylation of the above amine with acetyl chloride and γ-picoline gave 1-(4-acetylaminophenacyl)-4-(1-hexyl)-pyridinium bromide (IV) m.p. 230–240°. A mixture of this compound and an authentic sample of IV showed no depression in the melting point.

B. (From Hydrolysis of IV).—Three grams (0.00716 mole) of 1-(4-acetylaminophenacyl)-4-(1-hexyl)-pyridinium bromide (IV) was added to 75 ml. of 20% hydrobromic acid solution and the mixture was heated on a steam-bath until all of the solid dissolved. The acid solution was carefully neutralized with ammonium hydroxide. The tan colored precipitate was collected and recrystallized from absolute alcohol. The yield of yellow crystals was 1.4 g. (52%), m.p. 179–181°. A mixture of this material and a sample from procedure A above melted at 179–180°.

Anal. Calcd. for $C_{19}H_{25}BrN_2O$: N, 7.42. Found: N, 7.67.

Reduction of 1-(4-Aminophenacyl)-4-(1-hexyl)-pyridinium Bromide (IV).—A mixture of 0.6 g. (0.0016 mole) of 1-(4-aminophenacyl)-4-(1-hexyl)-pyridinium bromide, 20 ml. of 95% ethanol and a small amount of platinum oxide was hydrogenated at room temperature and 50 p.s.i. of hydrogen until about 0.0048 mole of hydrogen was absorbed. This required about five minutes. The product, which had precipitated, was dissolved in 60 ml. of alcohol and the catalyst removed. When the filtrate was cooled it gave 0.3 g. (50%) of the product II as white crystals, m.p. 240° (dec.).

Anal. Calcd. for $C_{19}H_{31}BrN_2O$: N, 7.31. Found: N, 7.48.

1-(4-Nitrophenacyl)-4-(1-hexyl)-piperidine (V).—Ten grams (0.0246 mole) of 4-nitrophenacyl bromide was dissolved in 100 ml. of acetone and a large crystal of potassium iodide added. The solution was cooled to −5° and 10 g. (0.0585 mole) of 4-(1-hexyl)-piperidine was added dropwise at such a rate as to keep the temperature below 0°. The solution was immediately placed in the ice-box and allowed to sit overnight. The reaction mixture was filtered, washed with water and then with a small amount of acetone and then ether. This procedure gave 1.5 g. (18%) of the desired product as a yellow powder, m.p. 134–136°.

Anal. Calcd. for $C_{19}H_{28}N_2O_3$: N, 8.43. Found: N, 8.29, 8.34.

Catalytic reduction of compound V gave compound III as the free base in 82% yield, m.p. 95–96°.

DENTON, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

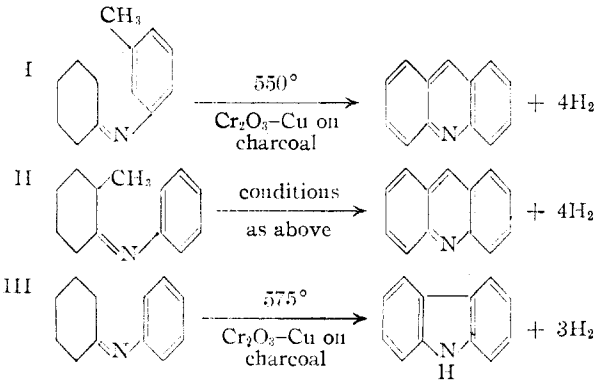
Catalytic Synthesis of Heterocycles. VII.[1] Dehydrocyclization of Anils to Acridine and Carbazole

BY CORWIN HANSCH, FELIX GSCHWEND AND JACK BAMESBERGER

RECEIVED MARCH 22, 1952

The preparation and vapor phase catalytic dehydrocyclization of N-2-methylcyclohexylideneaniline and N-cyclohexylidene-*o*-toluidine to acridine and of N-cyclohexylideneaniline to carbazole is described. The catalytic dehydrogenation of 2-methylcyclohexanol to 2-methylcyclohexanone is also discussed.

Recent work shows[2] that suitable aromatic anils may be easily dehydrocyclized to give nitrogen heterocycles. The work presented in this paper is an extension of this reaction to the synthesis of acridine and carbazole according to the equations



Although a large number of methods[3] have been devised for the synthesis of acridine and its derivatives, very little attention has been given to catalytic procedures. Graebe[4] reported the formation of some acridine and methylacridine by the pyrolysis of *o*-tolylaniline and di-*o*-tolylamine. It had been shown that N-benzylaniline[5] may be pyrolytically dehydrogenated to give acridine. The dehydrocyclization of anils appears to offer considerable advantage over that of the dehydrocyclization of the secondary aromatic amines in that mixed anils are more easily prepared than the mixed secondary amines. It is interesting to note in reactions I and II above that where the possibility for cyclization to occur either through a methyl group to a ring or directly from ring to ring, the bond forms preferentially through the methyl group, acridine being the product rather than methylcarbazole. In reaction III carbazole is the only possibility, but it is formed with greater difficulty and lower yield by ring to ring dehydrocyclization.

The 2-methylcyclohexanone used was found to be most smoothly prepared by the vapor phase dehydrogenation of the commercially available 2-methylcyclohexanol. This ketone was then condensed with aniline, using anhydrous $ZnCl_2$ as the catalyst, to give the anil.

Among the various methods for the preparation of carbazole one vapor phase catalytic method (using Pt-on-charcoal) has been reported[6] for the dehydrocyclization of diphenylamine. This same reaction has also been accomplished pyrolytically.[5,7]

Experimental

2-Methylcyclohexanone.—This substance was prepared by the dehydrogenation of 2-methylcyclohexanol. For the preparation of the dehydrogenation catalyst, the wire form of cupric oxide was reduced *in situ* with a slow stream of hydrogen at 150° for ½ hour. The temperature was then raised to 325° and the stream of hydrogen regulated so that the exothermic reduction did not raise the temperature of the catalyst above 350°. The catalyst was then reduced (about 45 minutes) until its temperature showed no tendency to rise in a fast stream of hydrogen. If the catalyst is reduced too long, or the reduction allowed to become too exothermic, the activity of the catalyst is greatly reduced.

In a typical run, 118 g. of 2-methylcyclohexanol was passed over 10 ml. of catalyst at space velocity of 866 (ml. vapor/ml. catalyst/hr. at normal temperature and pressure) at a temperature of 320°. This gave a yield of 86% 2-methylcyclohexanone as calculated from the hydrogen evolved. The gas evolved in this dehydrogenation was 97–98% hydrogen. The methylcyclohexanone was not separated from the unreacted alcohol, but used directly for the preparation of the anil.

N-2-Methylcyclohexylideneaniline.[8]—Crude 2-methylcyclohexanone from the above experiment, calculated to contain 94.5 g. of ketone was added to 80 g. of aniline and 1 g. of powdered anhydrous $ZnCl_2$ in 200 g. of toluene. The mixture was refluxed for 7 hours, the water being removed

(1) For the previous paper in this series see THIS JOURNAL, **73**, 3080 (1951).

(2) C. Hansch, D. G. Crosby, M. Sadoski, A. Leo and D. Percival, *ibid.*, **73**, 704 (1951).

(3) A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1946.

(4) C. Graebe, *Ber.*, **17**, 1370 (1884).

(5) H. Meyer and A. Hofmann, *Monatsh.*, **37**, 681 (1916).

(6) N. D. Zelinskii, I. N. Titz and M. Gaverdovskaia, *Ber.*, **59**, 2590 (1926).

(7) C. Graebe, *ibid.*, **5**, 377 (1872).

(8) This substance has been previously prepared (J. Hoch, *Compt. rend.*, **199**, 1428 (1934)) by the reaction of 1,1-diethoxymethylcyclohexane with aniline.