A STUDY OF THE REDUCTION PRODUCTS OF

N-(4-NITROPHENACYL)-4-(1-HEXYL)PYRIDINIUM BROMIDE

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THESIS

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By

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CHAPTER I

INTRODUCTION

Krönhke[1] has observed that certain N-substituted pyridine compounds possess both pressor and ergot like activity. Goode[2] and Bryant[3] investigated certain N-phenacyl-4-alkylpyridines and their reduction products. One of the reduction products, 1-phenyl-2-{1-[4-(5-nonyl)piperidine]}ethanol was found to be active *in vitro* against the tubercle bacillus. Herd[4] reported the synthesis of several N-(4-nitrophenacyl)-4-alkylpyridinium halides and their complete reduction products, the 1-(4-aminophenacyl)-2-[1-(4-alkylpiperidyl)] ethanols.

Because of the structural analogies between these compounds and several other physiologically active compounds, such as chloroamphenicol,[5] 4,4'-diaminodiphenyl sulfone,[6] and

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(1) F. Krönhke and K. Fasold, Ber., 67, 656 (1934).

(2) W. E. Goode, Unpublished M. S. thesis, Dept. of Chemistry, North Texas State College, 1947.

(3) B. E. Bryant, Unpublished M. S. thesis, Dept. of Chemistry, North Texas State College, 1950.

(4) R. Herd, Unpublished M. S. thesis, Dept. of Chemistry, North Texas State College, 1950.

(5) M. Rebstock, H. Crooks, Jr., J. Controulis, and Q. Bortz, J.A.C.S., 71, 2458 (1949).

(6) P. Truitt, R. Stead, L. Long, and W. Middleton, J.A.C.S., 71, 3512 (1949).

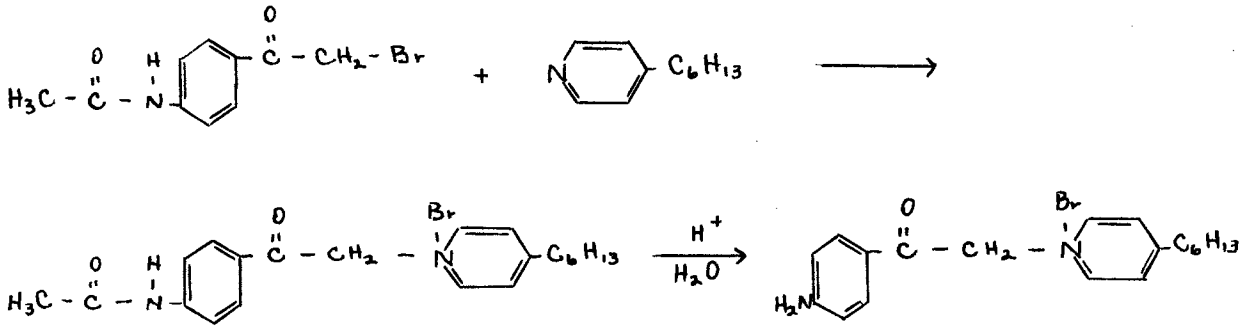
2,2-bis-(p-aminophenyl)-1,1,1-trichloroethane,[7] a more complete study of the reduction products and the sequence of catalytic reduction of N-(4-nitrophenacyl)-4-(1-hexyl)pyridinium bromide was made in this investigation. This compound was chosen for investigation as typical of the type since time did not permit a thorough study of all the reported N-(4-nitrophenacyl)-4-alkylpyridinium bromides.[4]

Samples of N-(4-nitrophenacyl)-4-(1-hexyl)pyridinium bromide were subjected to hydrogenation using platinum oxide and Raney Nickel catalysts and varying amounts of hydrogen.

Proof of structure of the compounds isolated in these hydrogenations was attempted in three ways: the preparation of derivatives, IR and UV analysis, and duplication by other means of synthesis.

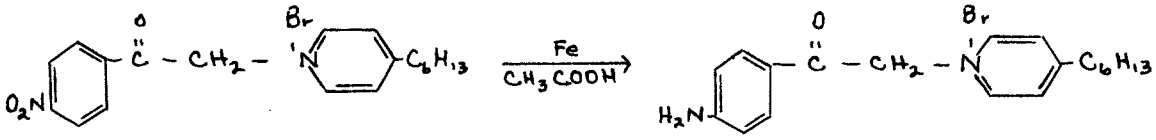
Four useful reactions which fall under the latter category are best shown by the equations below.

(1) Condensation of 4-acetylaminophenacyl bromide with 4-(1-hexyl)pyridine and acid hydrolysis of the adduct

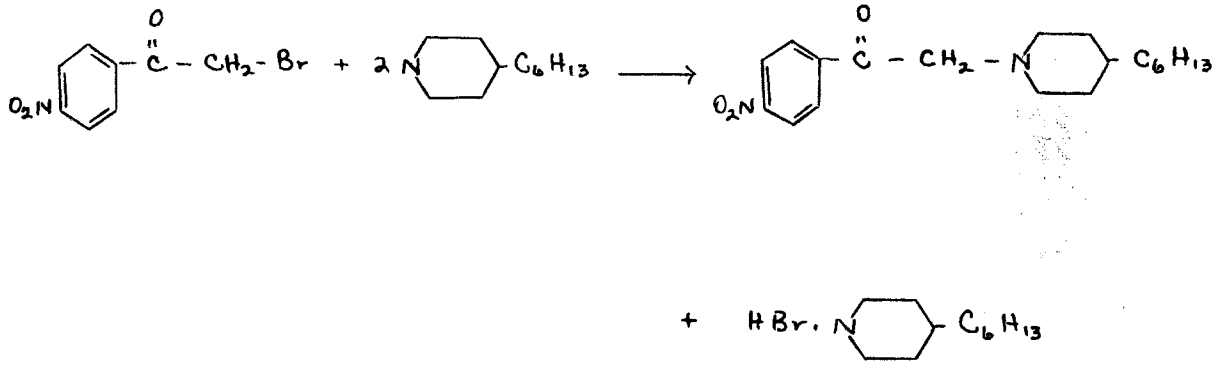


(7) S. Kirkwood, B. Phillips, and E. McCoy, J.A.C.S., 68, 2405 (1946).

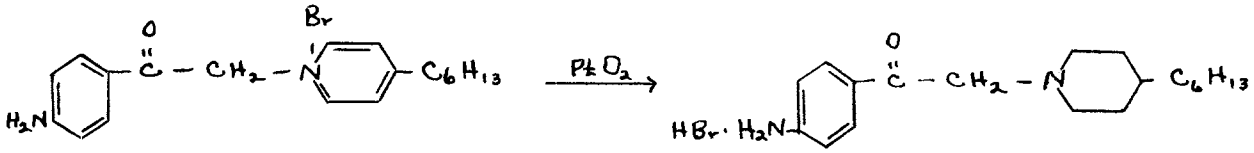
(2) Iron and acetic acid reduction of N-(4-nitrophenacyl)-4-(1-hexyl)pyridinium bromide



(3) Condensation of 4-nitrophenacyl bromide with 4-(1-hexyl)-piperidine



(4) Reduction of N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide with hydrogen in the presence of platinum oxide catalyst.



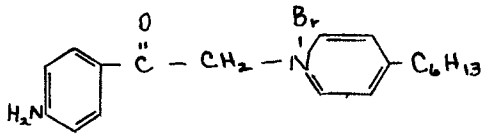
4-Nitrostyrene bromohydrin was made in the process of investigating the problem, and since it has not been reported in the literature, it is recorded in this paper.

N-(4-Nitrophenacyl)-4-methylpyridinium bromide is reported only as supplementary material to the investigation by Herd.[4]

CHAPTER II

EXPERIMENTAL

Raney Nickel Hydrogenation of N-(4-Nitrophenacyl)-4-(1-hexyl)pyridinium Bromide



Five grams (0.0123 mole) of N-(4-nitrophenacyl)-4-(1-hexyl)pyridinium bromide were dissolved in 100 ml. of 95% ethanol and about 0.2 g. of Raney Nickel catalyst was added. The reaction mixture was hydrogenated at room temperature at low pressure (50 p.s.i.) until 0.047 moles of hydrogen had been absorbed. Twenty-six hours were required for this absorption. Since a certain amount of product was in the form of a precipitate, the reaction mixture was diluted with more ethanol and heated until all the products were in solution. The catalyst was removed by filtration and the filtrate was placed in the ice-box. The cooled filtrate gave 1.5 g. (23%) of white crystals which were almost insoluble in ethanol. This product was removed by filtration, washed

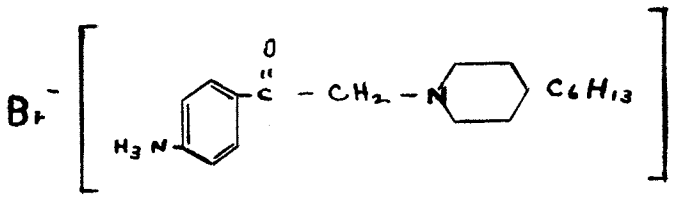
with cold ethanol and dried. This material decomposes above 240°. The properties of this product coincide with those of N-(4-aminophenacyl)-4-(1-hexyl)piperidinium hydrobromide which was prepared by at least two other methods in this investigation.

Anal. Calcd. for $C_{19}H_{25}BrN_2O$: N, 7.42. Found: N, 7.57.

Ether was added to the filtrate left after removal of the above mentioned product and 2 g. (43%) of light yellow crystals, m. p. 179-181°, were precipitated. The properties of this product were found to coincide with the properties of N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide which was prepared by two other methods in this investigation.

Anal. Calcd. for $C_{19}H_{25}BrN_2O$: N, 7.42. Found: N, 7.57.

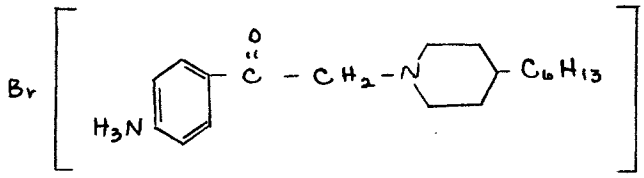
N-(4-Ammoniumphenacyl)-4-(1-hexyl)piperidine Bromide



Ten grams (0.0246 mole) of N-(4-nitrophenacyl)-4-(1-hexyl)pyridinium bromide were dissolved in 100 ml. of 95% ethanol and 0.2 g. of platinum oxide catalyst was added to this solution. The reaction mixture was hydrogenated at room temperature until the theoretical amount (0.1476 mole) of hydrogen had been absorbed. It was noted that half of the hydrogen was taken up quickly while the other half was absorbed only after hydrogenating for twelve hours. The precipitate was dissolved in 250 ml. of 95% ethanol and the catalyst removed by filtration. The clear filtrate was cooled and 3.4 g. (33%) of the desired product were obtained, m. p. 240° (dec.).

Anal. Calcd. for $C_{19}H_{31}BrN_2O$: N, 7.31. Found: N, 7.61.

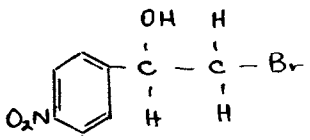
N-(4-Ammoniumphenacyl)-4-(1-hexyl)piperidinium Bromide



A mixture of 0.6 g. (0.0016 mole) of N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide, 20 ml. of 95% ethanol and a small amount of platinum oxide catalyst was placed in the low pressure hydrogenator at room temperature and allowed to remain until about 0.0048 mole of hydrogen had been absorbed. The time required for this absorption was only five minutes. The product, which had precipitated, was dissolved in a total of 60 ml. of alcohol and the catalyst was removed by filtration. When this filtrate was cooled it gave 0.3 g. (50%) of the product. These white crystals decomposed above 240°.

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

4-Nitrostyrene Bromohydrin[8]



Ten and one-half grams of 4-nitrostyrene and 500 ml. of water were placed in a 1-l., three-necked flask equipped with a dropping funnel, a mercury-sealed stirrer, and a thermometer. A solution which was 10% with respect to KBr and 7% with respect to bromine was added dropwise with stirring at 95° until the brown color of bromine persisted. When the reaction mixture was cooled, the product separated as a yellow solid. Recrystallization of this yellow material from CCl_4 gave 12 g. (69%) of the 4-nitrostyrene bromohydrin as yellow needles, m. p. 83-85°.

Anal. Calcd. for $C_8H_8BrNO_3$: N, 5.69. Found: N, 5.97.

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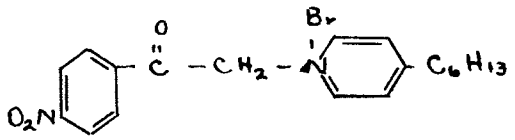
(8) R. W. Strassburg, R. A. Gregg, and C. Walling, J.A.C.S., 69, 2142 (1947).

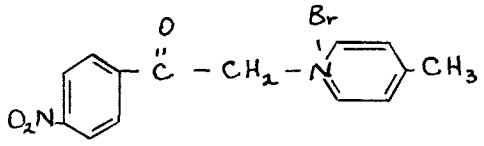
N-(4-Nitrophenacyl)-4-(1-hexyl)pyridinium Bromide



A solution of 24.4 g. (0.10 mole) of 4-nitrophenacyl bromide and 150 ml. of toluene was treated with 17 g. (0.104 mole) of 4-(1-hexyl)pyridine and an almost immediate reaction was noted by the formation of a dark oil. The reaction mixture was allowed to stand at room temperature for two hours, and at the end of this interval of time the oil had changed to a yellow crystalline solid. The yellow solid was removed from the reaction mixture by filtration and washed with anhydrous ether. Recrystallization from an alcohol-ether mixture gave 25 g. (62%) of the product as yellow crystals, m. p. 143-144°.

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

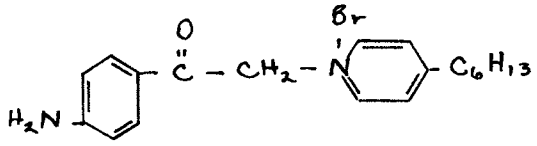
N-(4-Nitrophenacyl)-4-methylpyridinium Bromide



To a solution of 24.4 g. (0.10 mole) of 4-nitrophenacyl bromide and 150 ml. of toluene was added 10.5 g. (slightly in excess of 0.10 mole) of 4-methylpyridine. The reaction began almost immediately with the formation of a dark oil. The reaction mixture was allowed to stand at room temperature for twenty-four hours, and at the end of this interval of time the oil had changed to a brown, crystalline solid. The brown solid was removed from the reaction mixture by filtration and much of the brown color was removed by washing with anhydrous ether. Recrystallization from an alcohol-ether mixture gave 29 g. (86%) of the desired product as orange needles, m. p. 214-215°.

Anal. Calcd. for $C_{14}H_{13}BrN_2O_3$: N, 8.31. Found: N, 8.47.

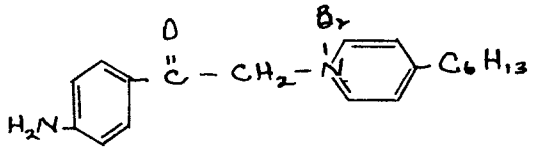
N-(4-Aminophenacyl)-4-(1-hexyl)pyridinium Bromide



Three grams (0.00716 mole) of N-(4-acetylaminophenacyl)-4-(1-hexyl)pyridinium bromide were placed in 75 ml. of 20% hydrogen bromide solution and heated over a steam bath until all of the solid had dissolved. The acid solution was then carefully neutralized with ammonium hydroxide and a tan precipitate formed. Recrystallization from absolute alcohol gave 1.4 g. (52%) of yellow crystals, m. p. 179-181°.

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

N-(4-Aminophenacyl)-4-(1-hexyl)pyridinium Bromide

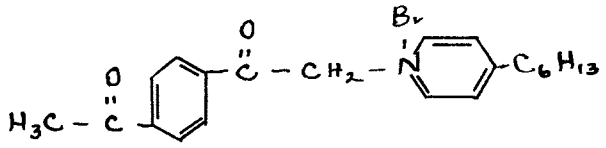


Fifteen grams of powdered iron, 0.1 ml. of glacial acetic acid, 100 ml. of water and 5 g. (0.0123 mole) of N-(4-nitrophenacyl)-4-(1-hexyl)pyridinium bromide were mixed in a 500-ml., three-necked flask equipped with a mechanical stirrer, a reflux condenser and a thermometer. The reaction mixture was stirred at 80-85° for nine hours, diluted with 200 ml. of water and heated to boiling. The hot solution was filtered, and when cooled, the filtrate yielded yellow crystals. Recrystallization from hot alcohol gave 1.9 g. (41%) of the yellow needles, m. p. 180-181°.

Anal. Calcd. for $C_{19}H_{25}BrN_2O$: N, 7.42. Found: N, 7.49.

The acetyl derivative of the N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide described above was made by mixing a small amount of the compound with a few drops of α-picoline and adding excess acetyl chloride. The mixture was allowed to sit for a few minutes and then 20 ml. of water was added. Yellow needles precipitated and were dried in a vacuum desiccator. The product was found to melt with decomposition at 230-240°. The N-(4-acetylaminophenacyl)-4-(1-hexyl)pyridinium bromide obtained by the condensation of 4-acetylaminophenacyl bromide and 4-(1-hexyl)pyridine melted with decomposition at 230-235°.

N-(4-Acetylaminophenacyl)-4-(1-hexyl)pyridinium Bromide



Ten grams (0.0390 mole) of 4-acetylaminophenacyl bromide[4] were dissolved in a mixture of 100 ml. of toluene and 100 ml. of n-amyl alcohol and 6.5 g. (0.04 mole) of 4-(1-hexyl)pyridine were added. The mixture was refluxed for a period of one hour and then allowed to cool. The product separated as a yellow powder and recrystallization from absolute alcohol gave 9.8 g. (60%) of the yellow crystals, m. p. 230-234° (dec.).

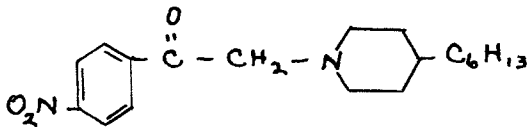
Anal. Calcd. for $C_{21}H_{27}BrN_2O_2$: N, 6.66. Found: N, 6.79.

Partial Hydrogenation of N-(4-Nitrophenacyl)-4-(1-hexyl)-pyridinium Bromide Using PtO_2 Catalyst

Ten grams (0.0246 mole) of 4-nitrophenacyl bromide were dissolved in 100 ml. of 95°/. ethanol and 200 mg. of platinum oxide catalyst were added. Hydrogenation was then carried out until only half the theoretical amount (0.0738 mole) of hydrogen required for the reduction of both the nitro group and the pyridinium group had been absorbed. The time required for this absorption was only eighteen minutes. A light yellow precipitate which was formed was dissolved in boiling ethanol and filtered in order to remove the catalyst. The hot filtrate was cooled and 5.5 g. (55°/.) of the product precipitated, m. p. 196-199°. The exact structure of the compound has not yet been determined.

Anal. Found: N, 7.25.

N-(4-Nitrophenacyl)-4-(1-hexyl)piperidine



Ten grams (0.0246 mole) of 4-nitrophenacyl bromide were dissolved in 100 ml. of acetone and a large crystal of KI was added. The solution was cooled to -5° in an acetone ice-bath and 10 g. (0.0585 mole) of 4-(1-hexyl)piperidine were added dropwise with stirring 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. Filtration of the black reaction mixture followed by three washings with ether 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, 8.28. Found: N, 8.07.

CHAPTER III

DISCUSSION

The sequence of reduction (exclusive of the carbonyl group) in both catalytic reduction with Raney Nickel and platinum oxide was determined with a fair degree of accuracy in this investigation, although the mechanism and some of the partially reduced products in the case of platinum oxide reduction were not determined.

In the case of Raney Nickel reduction the nitro group is apparently reduced first and this is followed by reduction of the pyridine group. Evidence for this statement lies in the fact that two products were isolated from the Raney Nickel reduction, and that one of these was proven to be N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide. This fact was proven by synthesizing N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide by two other methods and comparing these products to the corresponding product from the Raney Nickel hydrogenation. The other product isolated from the Raney Nickel hydrogenation has properties similar to those of the compound made by the platinum oxide reduction of N-(4-aminophenacyl)-4-(1-hexyl)-pyridinium bromide. This indicates that the pyridine group may be reduced by extensive hydrogenation using Raney Nickel as a catalyst.

Reduction using platinum oxide as a catalyst presents a more complicated problem. In this case it is obvious that the reduction is a stepwise one as evidenced by the fact that about half of the theoretical amount of hydrogen for reduction of both the nitro group and the pyridine group is absorbed much slower. Evidence for the fact that the pyridine ring is the first reduced is gained from the fact that platinum oxide reduction of N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide gives the completely hydrogenated material, N-(4-aminophenacyl)-4-(1-hexyl)piperidinium hydrobromide in about five minutes while N-(4-nitrophenacyl)-4-(1-hexyl)piperidine gives the fully hydrogenated product in the form of the free base only after several hours.

The partially reduced material from platinum oxide hydrogenation has proven to be interesting from a physiological point of view, but as yet has not been duplicated by another means of synthesis, nor has its structure been proven. There is a possibility that it may be N-(4-nitrophenacyl)-4-(1-hexyl)-piperidinium hydrobromide which has not been isolated, a nitroso compound, an azo compound or a hydrazo compound. Absorption curves from ultraviolet light tend to support the possibility of a hydrazo compound. At this time the problem is still under investigation.

All compounds are reported in this paper as having the carbonyl group intact. Since no reliable derivatives have

been made from the fully hydrogenated products, the only true evidence that the carbonyl remains intact lies in the fact that the fully hydrogenated product may be made by hydrogenating N-(4-aminophenacyl)-4-(1-hexyl)pyridinium bromide in the presence of platinum oxide for only five minutes. It seem unlikely that reduction of the carbonyl group would proceed this rapidly.

The insolubility of all compounds proven to have the pyridine group reduced is somewhat surprising. These compounds are almost insoluble in most common organic solvents as well as water and dilute acids and bases.

Compounds prepared in this investigation are being tested for physiological activity by Parke, Davis and Company.

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