1-(4,4'-DINITRODIPHENYLMETHYL)-PIPERIDINES;

1-(4-NITROBENZYL)-AND 1-(4-NITROBENZOYL)-PIPERIDINES

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THESIS

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By

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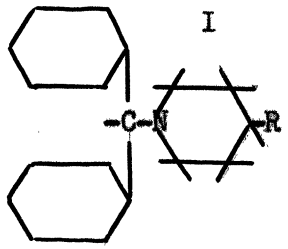
PART I

1-(4,4'-DINITRODIPHENYLMETHYL)-PIPERIDINES

INTRODUCTION

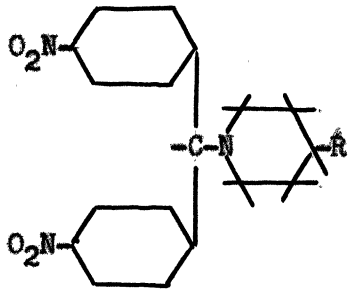
In continuance of the work done by Truitt and Middleton on 1-(diphenylmethyl)-4-(1-alkyl)-piperidines (I), a series of 1-(4,4'-dinitrodiphenylmethyl)-4-(1-alkyl)-pyridines and piperidines (II) have been prepared.[1]

I



R = alkyl group

II



Capraro showed that N-diphenylmethyl-N,N-diethyl amine (III) has antihistamic activity.[2] Denton, Schedl, Neier and Lawson have shown that substitution of N-piperidyl group for other substituted amino groups in certain antispasmotic compounds greatly increased their activity.[3]

It has been shown by Burger, Graef and Bailey that 4,4'-diamino-diphenylmethyl-sulfone (IV) has tuberculostatic activity.[4]

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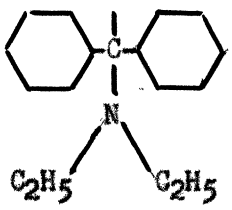
[1]Price Truitt and W. J. Middleton, J. Am. Chem. Soc., 73, 5669 (1951).

[2]V. Capraro, Farm. Sci. e tec., 2, 98-102 (1947). C.A., 41, 6989h (1947).

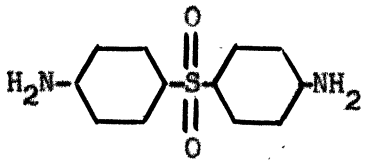
[3]J. J. Denton, H. P. Schedl, W. B. Neier and Virginia Lawson, J. Am. Chem. Soc., 71, 2054 (1949).

[4]A. Burger, E. Graef, and M. Bailey, J. Am. Chem. Soc., 68, 1725 (1946).

III



IV



Burger et al advanced the theory that a more lipid solubilizing group in place of the sulfone linkage in (IV) might increase its activity. This theory has been borne out by the work of Kirkwood and Phillips[5] and by that of Markees and Burger.[6]

The present work was undertaken with 1-(4,4'-diaminodiphenylmethyl)-4-(1-alkyl)-piperidines as the eventual goal. When the attempted methods of reduction of the corresponding nitro compounds yielded no results, the condensations of 4,4'-(N,N'-diacetylamino)-diphenylmethyl bromide and 4,4'-diaminodiphenylmethyl bromide with pyridines and piperidines were attempted in these laboratories; but these efforts also failed. Thus it was decided to use 4,4'-dinitrodiphenylmethyl bromide. Condensations of this substance with 4-(1-alkyl)-pyridines, 4-(1-alkyl)-piperidines, quinoline and isoquinoline were successful.

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[5]S. Kirkwood and P. H. Phillips, J. Am. Med. Assoc., 117, 2405 (1941).

[6]S. Markees and A. Burger, J. Am. Chem. Soc., 70, 3329 (1948).

CHAPTER II

EXPERIMENTAL PROCEDURE

4,4'-Dinitrodiphenylmethyl Bromide

Twenty grams of 4,4'-dinitrodiphenylmethane and 350 ml. of carbon tetrachloride were placed in a one-liter, three-neck flask fitted with condenser, mechanical stirrer and dropping funnel. The dropping funnel was charged with 4.26 ml. of bromine in 100 ml. of carbon tetrachloride.

The mixture was stirred and refluxed while illuminated by two 15 watt fluorescent lights. The bromine was added as rapidly as it reacted. A light straw yellow solution was obtained at the end of about five hours.

The solvent was evaporated on a steam bath and the solid charcoaled and recrystallized from ethyl alcohol (95%). The yield of crude material was quantitative. Careful recrystallization will make the final yield better than 95%.

For ease in recrystallization and to insure quantitative yield, care must be taken to use the proper amount of bromine. A small excess of bromine will cause some dibromination and a small deficiency will allow some of the starting material to be returned. Both starting material and the dibromo compound are much less soluble in ethyl alcohol than the mono bromo derivative.

mono bromo	m.p.	85°C
dibromo	m.p.	164.5 - 165°C

1-(4,4'-Dinitrodiphenylmethyl)-piperidine

Five grams of 4,4'-dinitrodiphenylmethyl bromide were mixed with five ml. of piperidine in a 50 ml. flask. This mixture was stirred and warmed on a hotplate for five minutes and then mixed with water to dissolve the excess piperidine. The resulting gum was dissolved in alcohol and charcoaled. The yield was 4.1g of a tan powder, m.p. 116-7°C. This represents 80% of the theoretical yield.

Anal. Calc. for $C_{18}H_{19}N_3O_4$; N, 12.30. Found; N, 12.54.

1-(4,4'-Dinitrodiphenylmethyl)-pyridinium Bromide

Thirty ml. of acetone and 1 ml. (0.02 moles) of pyridine were placed in a 200-ml., three-neck flask equipped with a condenser closed with a drying tube, mechanical stirrer and dropping funnel. Several crystals of potassium iodide were added as a catalyst.

Five grams (0.015 moles) of 4,4'-dinitrodiphenylmethyl bromide were dissolved in least amount of acetone (about 60 ml.) and charged to the dropping funnel. The solution was added to the flask over a period of one hour while the mixture was refluxed.

The acetone was evaporated at reduced pressure and water was added to dissolve the potassium iodide. The water was then decanted and the residue was recrystallized from alcohol. The yield was 4 g. (80%) of a light yellow powder, m.p. 340°; decomposes 370°.

Anal. Calc. for $C_{18}H_{14}N_3O_4Br$; N, 10.09. Found; N, 10.25.

The following preparations in this series of compounds were made by the above procedure except for the variations noted.

1-(4,4'-Dinitrodiphenylmethyl)-4-methylpyridinium Bromide

The reaction mixture was refluxed for one hour after addition of the 4-methylpyridine. The yield was 50% of a gray powder which decomposed at 284°C.

Anal. Calc. for $C_{19}H_{16}N_3O_4Br$; N, 9.75. Found; N, 9.67.

1-(4,4'-Dinitrodiphenylmethyl)-4-(1-nonyl)-piperidine

Six and 0.24 grams (0.03 moles) of 4-n-nonylpiperidine were used. Reaction time was 30 minutes. After washing with water, a gum resulted which was washed with ether to give a 50% yield of white powder, m.p. 195-6°C.

Anal. Calc. for $C_{27}H_{32}N_3O_4Br$; N, 8.99. Found; N, 8.87.

1-(4,4'-Dinitrodiphenylmethyl)-4-(1-amyl)-pyridinium Bromide

One and 0.54 grams (0.015 moles) of 4-n-amylpyridine were used and the mixture was refluxed one hour after the addition. Recrystallization was effected from diethyl ether; m.p. 314-315°C.

Anal. Calc. for $C_{23}H_{19}N_3O_4Br$; N, 8.62. Found; N, 8.49.

1-(4,4'-Dinitrodiphenylmethyl)-quinolinium Bromide

The yield was 50% of tan powder which decomposed at approximately 310°C.

Anal. Calc. for $C_{22}H_{16}N_3O_4Br$; N, 9.00. Found; N, 9.20.

1-(4,4'-Dinitrodiphenylmethyl)-isoquinolinium Bromide

The yield was 50% of tan powder which decomposed at approximately 310°C.

Anal. Calc. for $C_{22}H_{16}N_3O_4Br$; N, 9.00. Found; N, 9.16.

CHAPTER III

DISCUSSION

The usual methods of preparing quaternary salts or free bases from pyridines, such as standing at room temperature in diethyl ether or refluxing in benzene or toluene, failed with these compounds. Only the piperidine free base was obtained in good yield by warming in excess piperidine. The pyridinium salt was prepared by this method but in very low yield. It was found the more drastic method of refluxing in acetone with a potassium iodide catalyst was necessary for appreciable yields of the rest of the compounds.

Some 2-alkylpyridines were tried but the yields were extremely low and although the quinolinium bromide was obtained in 50% yield, the 1,2,3,4-tetrahydroquinoline failed to react to any appreciable extent.

Solubilities of these compounds made them difficult to recrystallize, as they were extremely insoluble in most common solvents. It was necessary to purify some of the higher alkylpyridines and piperidines derivatives entirely by washing with water and ether.

As was mentioned in the introduction, the initial intent was to reduce the nitro groups to form the corresponding amino compounds. Reductions were attempted in a low-temperature, low-pressure Parr hydrogenator. Rainey nickel and Adam's catalysts were tried. Dioxane, ethyl alcohol, benzene, diethyl ether were tried for solvents. Also an iron acetic acid reduction was attempted. None of these was successful. I believe that a high pressure

and possibly high temperature hydrogenation would be successful. The main difficulty with the Parr apparatus was the low solubilities of the compounds, usually a gram or less in the 125 ml. capacity of the bomb.

PART II

1-(4-NITROBENZYL)-AND 1-(4-NITROBENZOYL)-PIPERIDINES

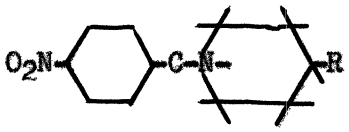
CHAPTER I V

INTRODUCTION

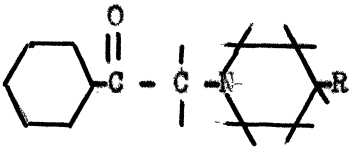
To further study the possibilities of the 1-(4,4'-dinitrodiphenylmethyl)-4-(1-alkyl)-piperidines, it was thought that perhaps the 1-(4-nitrobenzyl)-4-(1-alkyl)-piperidines (I) might show some activity. Thus a series of four of these compounds have been prepared. It was also found possible to reduce these to the corresponding amino compounds.

In the search for possible compounds of similar structure to those already prepared in these laboratories, it was noted that Blicke and Blake reported anesthetic properties for 1-phenacylpiperidine.[1] Therefore, Truitt, Bryant, Goode and Arnwine prepared a series of 1-phenacyl-4-alkylpyridinium halides (II) and their reduction products. These compounds showed a slight pressor activity.[2]

I



II



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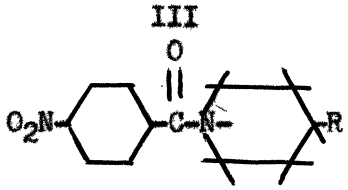

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[1] F. F. Blicke and E. S. Blake, J. Am. Chem. Soc., 52, 235 (1930).

[2] Price Truitt, B. Bryant, W. E. Goode and B. C. Arnwine, J. Am. Chem. Soc., 74, 2179-81 (1952).

A series of 1-(4-nitrophenacyl)-4-(1-alkyl)-piperidines have also been prepared in these laboratories and submitted for testing.[3]

As a result of the aforementioned work it was thought that perhaps the 1-(4-nitrobenzoyl)-4-(1-alkyl)-piperidines (III) and their reduction products would yield interesting results upon testing. Thus a series of six of these compounds were prepared, five of which were reduced to the corresponding 4-amino compounds.

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[3]Price Truitt, R. E. Hall, and B. C. Arnwine, J. Am. Chem. Soc., 74, 4552 (1952).

CHAPTER VII

MATERIALS

The 4-nitrobenzoyl chloride used in these preparations was Eastman Kodak practical grade which was used without further purification.

The 4-(1-alkyl)-pyridines were obtained from Reilley Coal Tar Company and were distilled before using.

The 4-(1-alkyl)-piperidines were made by the method of Adkins by hydrogenating at 170°C with an initial room temperature pressure of 1800 psi; Rainey nickel was used as a catalyst.[4]

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[4]Homer Adkins, Leo F. Kuick, Mark Farlow and Bruno Wojcik, J. Am. Chem. Soc., 56, 2425, (1934).

CHAPTER VI

EXPERIMENTAL PROCEDURE

4-Nitrobenzyl Bromide

Forty grams (0.29 moles) of p-nitrotoluene and 350 ml. of carbon tetrachloride were placed in a 500 ml., three-neck flask equipped with a reflux condenser, mechanical stirrer and dropping funnel.

The mixture was brought to a gentle reflux and two 15-watt fluorescent tubes were placed along side of the flask. The dropping funnel was charged with 46.7 grams (0.29 moles) of bromine in 100 ml. of carbon tetrachloride.

The bromine was added as the color disappeared and reflux was continued until the mixture was a straw yellow. The carbon tetrachloride was evaporated in an air blast and the residue was charcoaled and recrystallized from ethanol.

Fifty-five grams of a product melting at 99°C, 88% yield, was obtained.

1-(4-Nitrobenzyl)-pyridinium Bromide

Five grams (0.023 moles) of 4-nitrobenzyl bromide, 100 ml. of toluene and 1.83 grams (0.023 moles) of pyridine were refluxed for three hours.

The mixture was cooled, filtered, and washed with ether. White crystals melting at 234°C (80% yield) were obtained.

Anal. Calc. for $C_{12}H_{11}N_2O_2Br$; N, 9.85. Found; N, 9.65

1-(4-Nitrobenzyl)-piperidine Hydrobromide

Five grams (0.023 moles) of 4-nitrobenzyl were refluxed with 100 ml. of toluene and 1.96 grams (0.023 moles) of piperidine for two hours.

The mixture was cooled, filtered, and washed with ether. White crystals melting at 230°C, representing approximately an 80% yield, were obtained.

Anal. Calc. for $C_{12}H_{17}N_2O_2Br$; N, 6.30. Found; N, 6.43.

1-(4-Nitrobenzyl)-4-(1-octyl)-pyridinium Bromide

Five grams of (0.023 moles) of 4-nitrobenzyl bromide were refluxed with 100 ml. of toluene and 4.4 grams (0.023 moles) of 4-(1-octyl)-pyridine for two hours.

The mixture was cooled, filtered, and washed with ether. The product was immediately placed in a dessicator as it was very deliquescent. No melting point was obtained.

Anal. Calc. for $C_{20}H_{27}N_2O_2Br$; N, 6.88. Found; N, 6.74.

1-(4-Nitrobenzyl)-4-(1-octyl)-piperidine Hydrobromide

Five grams (0.023 moles) of 4-nitrobenzyl bromide was refluxed in 100 ml. of toluene with 4.6 grams (0.023 moles) of 4-(1-octyl)piperidine for two hours.

The mixture was cooled, filtered, and washed with ether. The product was immediately placed in a dessicator as it was very deliquescent.

Anal. Calc. for $C_{20}H_{33}N_2O_2Br$; N, 6.78. Found; N, 6.68.

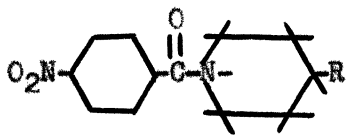
Reduction of 1-(4-Nitrobenzyl)-4-(1-octyl)-pyridinium Bromide

Six grams (0.015 moles) of the above quaternary salt was dissolved in 125 ml. of ethanol and placed in a Parr low-pressure hydrogenator. Two-tenths of a gram of Adams' catalyst was added. The initial pressure was 70 psi and at the end of five hours, 0.09 moles of hydrogen had been absorbed.

The solvent was evaporated and the residue recrystallized from alcohol. A yellow powder was obtained, m.p. 139°C.

Anal. Calc. for $C_{12}H_{20}N_2Br$; N, 7.38. Found; N, 7.30.

1-(4-Nitrobenzoyl)-4-(1-alkyl)-piperidines



Nine and 0.4 grams (0.05 moles) of 4-nitrobenzoyl chloride were dissolved in 200 ml. of absolute ether and 0.1 mole of the corresponding 4-(1-alkyl)-piperidine was added slowly with shaking.

After standing an hour, the mixture was filtered to remove the 4-(1-alkyl)-piperidine hydrochloride.

The ether filtrate was evaporated to dryness. The residue was charcoaled and recrystallized from ethanol. All yields were about 75%.

1-(4-Nitrobenzoyl)-4-methylpiperidine

White crystals which melted at 97°C were obtained.

Anal. Calc. for $C_{13}H_{16}N_2O_3$; N, 11.30. Found; N, 11.42.

1-(4-Nitrobenzoyl)-4-(1-amyl)-piperidine

White crystals were obtained, mp. 45-45°C.

Anal. Calc. for $C_{17}H_{24}N_2O_3$; N, 9.22. Found; N, 9.23.

1-(4-Nitrobenzoyl)-4-(1-hexyl)-piperidine

White crystals, m.p. 91°C, were obtained.

Anal. Calc. for $C_{18}H_{26}N_2O_3$; N, 8.85. Found; N, 9.04.

1-(4-Nitrobenzoyl)-4-(1-octyl)-piperidine

White crystals, m.p. 59-60°C, were obtained.

Anal. Calc. for $C_{20}H_{30}N_2O_3$; N, 8.08. Found; N, 8.05.

1-(4-Nitrobenzoyl)-4-(1-nonyl)-piperidine

White crystals, m.p. 59.5-60°C, were obtained.

Anal. Calc. for $C_{21}H_{32}N_2O_3$; N, 7.78. Found; N, 7.95.

1-(4-Nitrobenzoyl)-morpholine

Cream colored crystals melting at 91°C were obtained.

Anal. Calc. for $C_{11}H_{12}N_2O_4$; N, 11.86. Found; N, 11.90.

1-(4-Aminobenzoyl)-4-(1-alkyl)-piperidines

Approximately 0.014 mole of the corresponding 4-nitro free base was dissolved in 150 ml. of methanol and 50 ml. of water. This solution was placed in a 250-ml., two-neck flask along with 15 grams of iron powder and 1.5 ml. of glacial acetic acid. The mixture was refluxed for eight hours.

After the addition of 100 ml. of methanol, the solution was neutralized with ammonium hydroxide and filtered. The filtrate was then eluted with water to cloudiness and cooled.

The products after recrystallization from methanol represented about a 60% yield.

1-(4-Aminobenzoyl)-4-methylpiperidine

Tan crystals melting at 89°C were obtained.

Anal. Calc. for $C_{13}H_{18}N_2O$; N, 12.83. Found; N, 12.93.

1-(4-Aminobenzoyl)-4-(1-amyl)-piperidine

Tan crystals melting at 129°C were obtained.

Anal. Calc. for $C_{17}H_{26}N_2O$; N, 10.22. Found; N, 10.39.

1-(4-Aminobenzoyl)-4-(1-hexyl)-piperidine

Tan crystals melting at 100°C were obtained.

Anal. Calc. for $C_{18}H_{28}N_2O$; N, 9.77. Found; N, 9.97.

1-(4-Aminobenzoyl)-4-(1-octyl)-piperidine

Tan crystals melting at 75-75.5°C were obtained.

Anal. Calc. for $C_{20}H_{32}N_2O$; N, 8.86. Found; N, 8.93.

1-(4-Aminobenzoyl)-4-(1-nonyl)-piperidine

Tan crystals melting at 60-61°C were obtained.

Anal. Calc. for $C_{21}H_{34}N_2O$; N, 8.49. Found; N, 8.47.

CHAPTER VII

DISCUSSION

The bromination of the 4-nitrotoluene has been reported.[1] Because of the experience in these laboratories in brominations of this type, a new method was used which gave, as expected, a much higher yield: 88% as compared to 59%.

The 1-(4-nitrobenzyl)-piperidine was reported in Beilstein, prepared by another method. No difficulty was encountered in obtaining the compound by the method given here.[2]

The iron and acetic acid reductions of the 1-(4-nitrobenzoyl)-4-(1-alkyl)-piperidines were used only after difficulty was encountered by other methods of producing the amino compounds. Difficulty was had in these laboratories with the reduction products of 1-phenacyl-4-(1-alkyl)-pyridines.[3] Also the catalytic reduction of an adduct of unknown composition between 4-nitrobenzoyl chloride and 4-(1-alkyl)-pyridines would not proceed at low pressures. High pressures were not looked into because Byron "et al" have shown that higher pressures reduce the carbonyl in compounds of similar structure.[4]

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[1] A. H. Blatt, Organic Synthesis, Collective Vol. II, New York, John Wiley and Sons, 1943.

[2] Franchimont Van Rijn, Beil, 20, 24.

[3] Op. cit.

[4] Riegel Byron and Harold Wittcoff, J. Am. Chem. Soc., 68, 1805 (1946).

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