Demethylation of 2 g. of this butene derivative followed by recrystallizations from benzene–alcohol as above yielded 1.5 g. of phenolic substance in colorless plates, m. p. 197–198°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.64; H, 7.76.

The acetate* formed colorless plates, m. p. 129–130°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.86; H, 6.72.

This stilbenediol and the acetate showed no depression of the melting points on admixture with the specimens prepared from the condensation product between biacetyl and *o*-cresol.

2,3-di-*p*-Anisyl-1,3-butadiene.*—To a mixture of 8 g. of 2,3-di-*p*-anisyl-2,3-butanediol[6] and 0.5 g. of phenyl-β-naphthylamine, 23 cc. of acetyl bromide[15] was added dropwise with stirring and cooling with an ice-bath. After the excess of acetyl bromide was distilled off under reduced pressure, the residue was poured into 10% sodium carbonate solution and extracted with benzene. The benzene solution was washed with water, dried and distilled. There was obtained 5 g. of a fraction, b. p. 225–235° under 11 mm., which was dissolved in a hot mixture of benzene and methanol and allowed to cool. Recrystallizations of the solids thus obtained from the same solvent yielded 2.5 g. of colorless prisms, m. p. 108–109°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.84; H, 6.99.

2,3-bis-(*p*-Methoxy-*o*-tolyl)-1,3-butadiene.*—Ten grams of 2,3-bis-(*p*-methoxy-*o*-tolyl)-2,3-butanediol was dehydrated with 25 cc. of acetyl bromide in the same manner as above, yielding 4 g. of a fraction, b. p. 200–210° at 5 mm., from which 2.6 g. of colorless prisms melting at 108–108.5° were obtained after recrystallizations from a mixture of alcohol and benzene.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.67; H, 7.28.

2,3-Di-*p*-anisylbutane.—Reduction of 2.5 g. of the di-*p*-anisylbutadiene with 4.5 g. of metallic sodium, 60 cc. of anhydrous alcohol and 25 cc. of xylene was carried out in the same way as in the preparation of 2,2-bis-(*p*-methoxy-*o*-tolyl)-3-butanol. Recrystallizations of the product from ligroin gave 1 g. of colorless prisms, m. p. and mixed m. p. with the *meso*-form of 2,3-di-*p*-anisylbutane[17] 133–133.5°.

2,3-bis-(*p*-Methoxy-*o*-tolyl)-2-butene.—To a solution of 1.2 g. of the above ditolylbutadiene derivative in 24 cc. of absolute alcohol was added, under refluxing, 2.5 g. of metallic sodium in small portions. The product was treated in the usual way and recrystallized from alcohol. There were obtained 0.7 g. of colorless prisms, m. p. and mixed m. p. with the above-mentioned 2,3-bis-(*p*-methoxy-*o*-tolyl)-2-butene 100–101°.

Summary

Condensation of biacetyl with phenol or with *o*-cresol resulted in the formation of a diphenolic ketone, 2,2-bis-(*p*-hydroxyphenyl)-3-butanone or 2,2-bis-(*p*-hydroxy-*m*-tolyl)-3-butanone, respectively.

Condensation of biacetyl with *m*- or *p* cre ol took a different course, yielding 2,3,6,6′-tetramethyl- or 2,3,5,5′-tetramethylcoumarano-3′,2′,-2,3-coumarane, respectively.

These coumarano-coumaranes were synthesized by a different route, starting from 6-acetyl-*m*-cresol and from *o*-acetyl-*p*-cresol, respectively.

Two isomers of diethylstilbestrol, *i. e.*, α,α′,2,2′-tetramethyl-4,4′-stilbenediol and α,α′,3,3′-tetramethyl-4,4′-stilbenediol were prepared.

KYÔTO, JAPAN RECEIVED OCTOBER 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

A Novel Rearrangement of a Piperidine Ring

BY ROBERT H. REITSEMA[1]

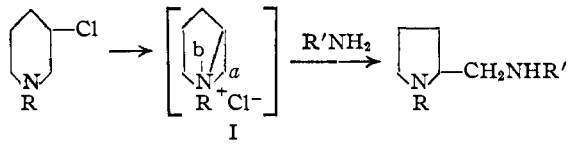
A ring contraction in the piperidine series has been observed during a study of the methods of synthesis of 3-aminopiperidines.[2] 3-Chloropiperidines are readily available as a result of Paul's synthesis of 3-hydroxypiperidines from tetrahydrofurfuralamines.[3] Treatment of 1-ethyl-3-chloropiperidine with benzylamine did not give the expected 3-benzylaminopiperidine, however. Instead, a compound which is apparently 1-ethyl-2-benzylaminomethylpyrrolidine was obtained. A similar anomalous result was found when the product from the reaction of 1-methyl-3-chloropiperidine and benzylamine was compared with authentic 1-methyl-3-benzylaminopiperidine.

The nature of the product of the reaction was elucidated by various techniques. The material was recovered unchanged after it had been boiled six hours in concentrated hydrochloric acid. Its titration curve was very similar to that of a 4-benzylaminopiperidine. These observations eliminated the possibility that a 2-benzylaminopiperidine had formed by attack of the benzyl group at the 2-position after removal of the chlorine ion or after dehydrohalogenation. A 2-aminopiperidine is an aminoacetal and would not be stable to acids or have a normal titration curve. Mixed melting points of the picrates with the corresponding 4-benzylaminopiperidine picrates showed that a rearrangement to the 4-position had not taken place. A monomeric structure for the compound was shown by a molecular weight determination and by consideration of boiling points. Only one active hydrogen could be detected and no absorption of hydrogen occurred either in the presence of platinum oxide at room temperature and atmospheric pressure or in the presence of Raney nickel at elevated temperature and pressure. Thus a linear structure was not possible since that would require a double bond and two active hydrogens.

The only likely explanation of the reaction is that the new compounds are 2-aminomethylpyrrolidine derivatives. It has been well established

(1) Present address: A. M. Todd Co., Kalamazoo, Mich.
(2) Reitsema and Hunter, THIS JOURNAL, **71**, 1680 (1949).
(3) Paul, *Compt. rend.*, **221**, No. 15, 412 (1945).

that 1,2-chloroamines react as though an intermediate cyclic imonium salt formed. This then opens in either of two ways depending on the nature of the reactants. Formation of a similar intermediate (I) from 3-chloropiperidine would explain the formation of 2-aminomethylpyrrolidines as resulting from cleavage at *a*.

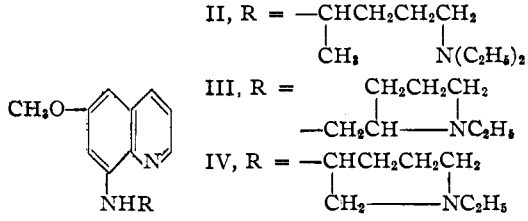


I

Fuson and Zirkle[4] have reported the reverse reaction, a ring expansion of 2-chloromethylpyrrolidine to a 3-chloropiperidine, and postulated the formation of the same intermediate. In this case cleavage occurred at *b* to form the piperidine ring. The direction of imonium ring opening is dependent upon the nature of the attacking nucleophylic agent and a strongly basic group evidently favors the formation of the pyrrolidine structure.

Ammonia in place of benzylamine also failed to give the expected 3-aminopiperidine. Condensation of 1-ethyl-3-chloropiperidine with ammonia gave low yields of impure 1-ethyl-2-aminomethylpyrrolidine. The same compound was obtained by catalytic hydrogenolysis of the benzyl group of 1-ethyl-2-benzylaminomethylpyrrolidine.

Treatment of 6-methoxy-8-aminoquinoline with 1-ethyl-3-chloropiperidine by analogy with the above reactions gave 6-methoxy-8-(1-ethyl-2-pyrrolidylmethylamino)-quinoline (III). This compound is not as similar to Plasmochin (II) as IV, the expected product of the reaction, would be. However, III also may retain the curative



properties of Plasmochin while reducing the toxicity as is often the case with cyclic analogs. Tests have shown that III is less effective for *clinical* use than many of the new antimalarials.

When the anomalous results were first observed the structure of the 1-alkyl-3-hydroxypiperidines was verified to make certain that the rearrangement of alkylaminomethyltetrahydrofurans actually gave 3-hydroxypiperidines. This was accomplished readily by catalytic reduction of 1-ethyl-3-piperidone and comparison of the two hydroxypiperidines. Another substantiation of the structure has now been published.[5]

Completion of work in progress toward the synthesis of authentic 2-aminomethylpyrrolidine derivatives has had to be postponed. As a result of the use of the same intermediate by Fuson and Zirkle[4] for their reaction it no longer seemed necessary to delay the publication of these results.

Experimental[6,7]

1-Ethyl-2-benzylaminomethylpyrrolidine.—A solution of 18.4 g. (0.1 mole) of 1-ethyl-3-chloropiperidine hydrochloride and 21.4 g. (0.2 mole) of benzylamine in 20 cc. of water was heated in an oil-bath for forty-eight hours at 65–75°. The semi-solid mixture was added to 35 cc. of water, a layer of ether was added, and solid potassium carbonate was added until the solution was basic. The ether was decanted, the moist residue was washed thoroughly with ether, and the combined organic extracts were dried over magnesium sulfate. After removal of the ether the residue was distilled to give 16.0 g. (73.4%) of amine, b. p. 134° (1 mm.); 126° (0.5 mm.).

The dipicrate melted at 190–191° after one recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{28}N_8O_{14}$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.08; H, 4.16; N, 16.17.

A mixed melting point of this picrate with an authentic sample of 1-ethyl-3-benzylaminopiperidine picrate,[2] m. p. 200–202°, melted at 176–178°.

A molecular weight determination on the free base gave 221 (theory, 218). A titration curve showed breaks at *p*H of 4.1 and 7.5. This was compared with the curves of 4.6 and 8.1 for 1-ethyl-4-benzylaminopiperidine.

1-Methyl-2-benzylaminomethylpyrrolidine.—1-Methyl-3-chloropiperidine, from 67.0 g. (0.39 mole) of the crude hydrochloride, was treated with 83.5 g. (0.78 mole) of benzylamine and 60 cc. of water as described for 1-ethyl-3-chloropiperidine. From the reaction was obtained by distillation 37.7 g. (42.5%) which boiled sharply at 110–112° (0.2–0.3 mm.). The dipicrate, prepared in ethanol, melted at 173–174°.

Anal. Calcd. for $C_{25}H_{26}N_8O_{14}$: C, 45.32; H, 3.96; N, 16.91. Found: C, 45.61; H, 4.22; N, 17.05.

1-Ethyl-2-aminomethylpyrrolidine.—(a) A solution of 2.18 g. (0.01 mole) of 1-ethyl-2-benzylaminomethylpyrrolidine in 50 cc. of absolute ethanol was shaken under hydrogen in the presence of 2.0 of palladium-carbon catalyst. Uptake of hydrogen was negligible in the cold. The bottle containing the solution was warmed at about 50° and allowed to shake overnight. The absorption had ceased after one equivalent of hydrogen was taken up. The catalyst was removed by filtration and washed with ethanol (toluene odor in the solution). A portion of the solution was treated with saturated picric acid solution to give a picrate which after recrystallization from ethanol melted at 177–178.5° and was shown by analysis to be the debenzylated compound, 1-ethyl-2-aminomethylpyrrolidine dipicrate.

Anal. Calcd. for $C_{19}H_{22}N_8O_{14}$: C, 38.91; H, 3.78; N, 19.11. Found; C, 39.03; H, 3.92; N, 18.08.

No absorption of hydrogen was observed when the material was shaken with hydrogen and platinum oxide catalyst.

(b) To a solution of 20 g. of dry ammonia in 150 cc. of 95% ethanol was added 15.1 g. (0.1 mole) of 1-ethyl-3-chloropiperidine. After twenty days of standing at room temperature the inorganic crystals which had formed were removed by filtration of the cold solution. The filtrate was evaporated to a thick oil which gave a picrate, m. p. 158–177° (dec.). After several recrystallizations from ethanol 1-ethyl-2-aminomethylpyrrolidine dipicrate melted at 178–180°. Authentic 1-ethyl-3-amino-piperidine dipicrate melts at 231–232° (dec.).[2]

6-Methoxy-8-(1-ethyl-2-pyrrolidylmethylamino)-quinoline.—A mixture of 30.2 g. (0.174 mole) of 8-

(4) Fuson and Zirkle, THIS JOURNAL, **70**, 2760 (1948).

(5) Paul and Tchelitcheff, *Bull. soc. chim. France*, 341 (1947).

(6) Microanalyses by Mr. Harold Emerson and Staff of these laboratories.

(7) Melting points uncorrected.

amino-6-methoxyquinoline, 16.0 g. (0.087 mole) of 1-ethyl-3-chloropiperidine hydrochloride and 25 cc. of water was heated with stirring at 60–70° for twenty hours. The temperature of the solution was raised to 110° for two hours. The warm solution was added to 75 cc. of warm water, made acidic to congo red with concentrated hydrochloric acid, cooled, filtered and the gold crystals were washed with water. The filtrate was brought to *p*H 4.5 with solid sodium acetate and extracted four times with 100-cc. portions of ether. Then the solution was made strongly basic (*p*H 12) and a black tar separated. This was taken up in about 300 cc. of ether. After drying the ethereal extracts over magnesium sulfate the ether was removed and the residue was distilled at reduced pressure. The main portion, 9.1 g., boiled at 186–190° (0.2 mm.). After recrystallization from absolute ethanol–ether, light yellow hygroscopic needles of 6-methoxy-8-(1-ethyl-2-pyrrolidylmethylamino)-quinoline dihydrochloride melted at 214–216° with some sintering at 212°.

Anal. Calcd. for $C_{17}H_{23}N_3O\cdot 2HCl$: C, 56.98; H, 7.03; Cl, 19.79. Found: C, 56.55, 56.93; H, 6.84, 6.51; Cl, 18.76.

The dipicrate melted at 202.5–203.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{29}H_{29}N_9O_{15}$: C, 46.84; H, 3.93; N, 16.95. Found: C, 46.76; H, 4.13; N, 16.13.

1-Ethyl-3-hydroxypiperidine.—A solution of 26.4 g. (0.206 mole) of 1-ethyl-3-piperidone was reduced in methanol with hydrogen in the presence of Raney nickel at 125° and an initial hydrogen pressure of 2270 pounds. After forty minutes 75% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the methanol distilled at atmospheric pressure. The residue was distilled at water pump pressure using a short helice-packed column to give 1-ethyl-3-hydroxypiperidine which boiled at 99–100° (19 mm.); $n^{19.5}D$ 1.4774. The benzoate hydrochloride was prepared from 1 g. of the distillate in 15 cc. of methylene chloride by adding 1.1 cc. of benzoyl chloride and heating for ten minutes. After removal of the solvent a sample of the residue was recrystallized from methanol–ether to give white needles, m. p. 197–198°.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.36; H, 11.62; N, 10.66.

The benzoate hydrochloride prepared from a sample of 1-ethyl-3-hydroxypiperidine obtained from ethyl tetrahydrofurfuralamine melted at 195–198°. Mixed melting point of the two benzoates was 196–198°.

Summary

1. Treatment of 1-alkyl-3-chloropiperidines with amines has been shown to give products distinct from the expected 3-aminopiperidines. On the basis of various studies these products have been given the structure of 2-aminomethylpyrrolidines.

2. A new analog of Plasmochin is described.

3. Additional proof of the structure of 3-hydroxypiperidines formed from tetrahydrofurfuralamines has been obtained.

KALAMAZOO, MICHIGAN RECEIVED OCTOBER 7, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Syntheses in the Pyrazine Series: The Proof of the Structure and the Reactions of 2,6-Dibromopyrazine

BY KURT H. SCHAAF[1] AND PAUL E. SPOERRI

In their investigations of the preparations and properties of the pyrazyl halides, Erickson and Spoerri[2] prepared a dibromopyrazine (III) by the reaction of hydroxypyrazine (I) with a mixture of phosphorus pentabromide and phosphorus oxybromide. Bromopyrazine (II) was obtained as a second product of the reaction. As the identity of the dibromo derivative was not established, it seemed desirable to determine its structure and to study its chemical behavior.

Since the physical properties of III differ from those reported for 2,5-dibromopyrazine by Ellingson and Henry,[3] it was concluded that III might be either 2,3- or 2,6-dibromopyrazine.

By heating the unknown dibromopyrazine (III) with cuprous cyanide and cupric sulfate, it was converted into the hitherto unknown 2,6-dicyanopyrazine (IV) and 2-bromo-6-cyanopyrazine (V). The dinitrile was then hydrolyzed by means of concentrated sulfuric acid and yielded pyrazine-2,6-diamide (VI).

The hydrolysis of 2,6-dicyanopyrazine (IV) by means of aqueous sodium hydroxide yielded the known pyrazine-2,6-dicarboxylic acid (VII). The identity of this compound was established by a mixed melting point determination with pyrazine-2,6-dicarboxylic acid which was prepared in the following manner.

2-Methylquinoxaline (VIII) was oxidized to pyrazine-2,5,6-tricarboxylic acid (IX) by means of potassium permanganate in alkaline medium. This acid, which had been previously prepared by Stoehr,[4] was decarboxylated and yielded pyrazine-2,5- and 2,6-dicarboxylic acids. The latter derivative showed no depression in the melting point when mixed with the dicarboxylic acid (VII) obtained by the hydrolysis of the new dinitrile (IV).

In order to gain some understanding of the reaction which takes place when hydroxypyrazine (I) is brominated, bromopyrazine (II) was treated with phosphorus pentabromide and phosphorus

(1) In partial fulfillment for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn. The author wishes to express his thanks to his employer, Nopco Chemical Company, Inc., Harrison, N. J., for permission to use their laboratory facilities for the experimental part of this investigation.

(2) A. E. Erickson, Ph.D. Dissertation, Polytechnic Institute of Brooklyn, 1945; A. E. Erickson and P. E. Spoerri, THIS JOURNAL, **68**, 400 (1946).

(3) R. C. Ellingson and R. L. Henry, paper presented at the 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April, 1946 and private communication with Dr. R. C. Ellingson.

(4) C. Stoehr, *J. prakt. Chem.*, **55**, 248 (1897).