groups are apparently attacked in anhydrous solution by nitrogen tetroxide, the avidity of the methylene carbon atom for nitrogen tetroxide is apparently increased and no satisfactory method of decomposing the intermediate to yield mesoxalate has thus far been discovered.

Summary

1. An improved method for preparing diethyl mesoxalate has been described. It involves the action of nitrogen tetroxide on diethyl malonate.

2. Two new mesoxalates prepared by application of this nitrogen tetroxide reaction are: di-β-chloro-ethyl mesoxalate and di-β-bromo-ethyl mesoxalate.

3. Di-β-diethylamino-ethyl malonate has been prepared for the first time.

4. The pharmacology of these new ester combinations is being investigated.

NEW HAVEN, CONNECTICUT

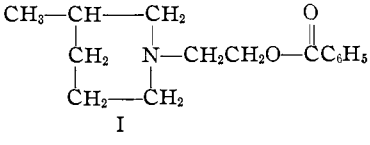
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

PIPERIDINE DERIVATIVES. VI. 3-METHYLPIPERIDINO-ALKYL BENZOATES[1]

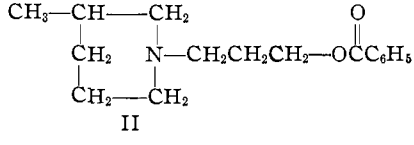
BY J. R. THAYER AND S. M. McELVAIN

RECEIVED AUGUST 3, 1928 PUBLISHED DECEMBER 10, 1928

In a previous communication[2] a number of substituted and unsubstituted piperidino-alkyl benzoates were described together with a brief report on their pharmacological behavior. Of these compounds it was noted that those containing an alkyl group substituted in the piperidine nucleus possessed the greatest local anesthetic efficiency. It seemed, therefore, advisable to ascertain the effect of variations in the alkylene group on the pharmacological properties of the type of compound represented by 3-methylpiperidino-ethyl and propyl benzoates (I and II).



I



II

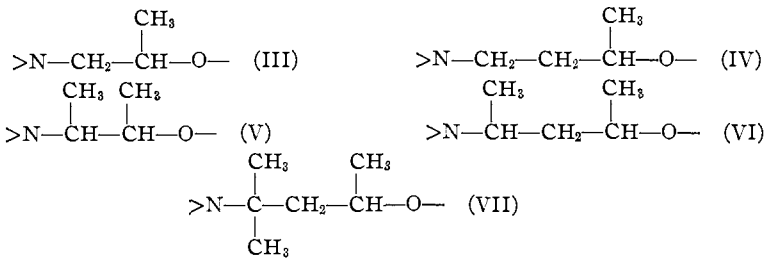
In the previous work it was found that the number of carbon atoms in the alkylene group that joins the nitrogen to the oxygen was quite important. In I where there are two carbon atoms in this alkylene group,

[1] This paper is an abstract of a portion of the thesis submitted by J. R. Thayer to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

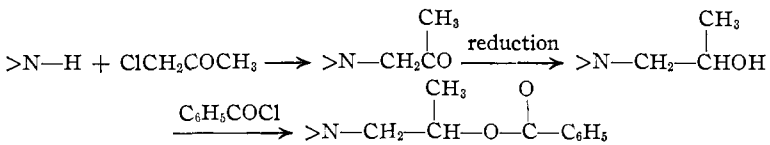
[2] McElvain, THIS JOURNAL, **49**, 2835 (1927).

the compound was found to have no local anesthetic action on mucous membranes, while in II the presence of the third carbon atom caused the compound to show appreciable anesthetic action on mucous membranes.[3] The work reported in this paper is concerned with the preparation and attempted preparation of a number of 3-methylpiperidino-alkyl benzoates in which the alkylene group between the nitrogen and the oxygen (Types I and II) contains one or more substituent methyl groups.

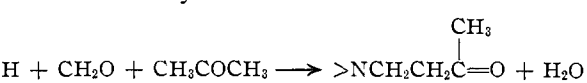
The structures which were considered and whose syntheses were attempted may be represented as follows



Of the above types only III and IV were successfully synthesized. The former (III) was prepared by a series of reactions which may be indicated thus (>NH in all succeeding formulas = 3-methylpiperidine)



The desired structure (IV) was prepared by a method which has been developed by Mannich and his coworkers[4] for the synthesis of 1,3-keto bases. This synthesis involves a reaction between a secondary amine, paraformaldehyde and acetone. Using 3-methylpiperidine as the secondary amine, this reaction may be indicated as follows



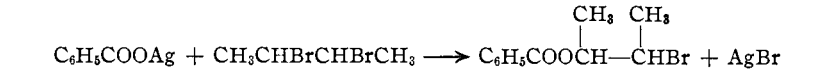
The catalytic reduction of this keto amine yielded the corresponding alcohol, which was converted into Structure IV by benzoylation with benzoyl chloride.

The preparation of V and VI was attempted by condensing α,β-dimethyl-β-bromo-ethyl benzoate and α,γ-dimethyl-γ-chloropropyl benzoate with 3-methylpiperidine just as I and II were prepared by the condensation of chloro-ethyl and chloropropyl benzoates with the secondary amine. The α,β-dimethyl-β-bromo-ethyl benzoate was prepared by the action

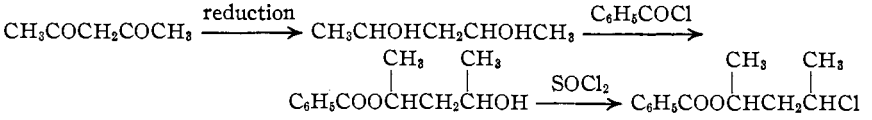
[3] Ref. 2, p. 2839.

[4] Mannich and others, *Arch. Pharm.*, **255**, 261 (1917); **265**, 589 (1927).

of 2,3-dibromobutane on silver benzoate, thus

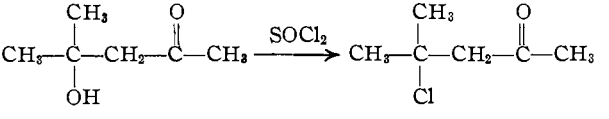


α,γ-dimethyl-γ-chloropropyl benzoate was prepared from acetylacetone by the following reactions



In the preparation of I and II it was found that one mole of β-chloroethyl benzoate or γ-chloropropyl benzoate reacted smoothly in twenty to thirty minutes at 100° with 2 moles of 3-methylpiperidine to give one mole of the tertiary amine (3-methylpiperidino-ethyl (or propyl) benzoate) and one mole of 3-methylpiperidine hydrochloride. In the case of α,β-dimethyl-β-bromo-ethyl benzoate and α,γ-dimethyl-γ-chloropropyl benzoate, no such reaction was found to take place. Under the conditions (thirty minutes at 100°) which caused complete reaction when the halogen was attached to a primary carbon atom, practically no reaction was obtained with the compounds having the halogen attached to a secondary carbon atom. The extent of reaction was judged in all cases by the amount of 3-methylpiperidine hydrochloride that was precipitated when the reaction mixture was diluted with ether. It was found in the cases of the secondary halogen compounds that if the reaction mixture was heated for twelve to fifteen hours at 100° or three to four hours at 130° and then cooled and diluted with ether, a fairly complete recovery of one mole of 3-methylpiperidine hydrochloride (or hydrobromide) could be made. But the ether solution contained no tertiary amine, for when it was treated with dry hydrogen chloride only 3-methylpiperidine hydrochloride precipitated. The total recovery of the secondary amine salt practically corresponded to the secondary amine that was originally a part of the reaction mixture. From these results it is apparent that the tendency of secondary halogen esters of this type is to lose a molecule of halogen acid when they are treated with a secondary amine rather than to form a tertiary amine.

The attempted synthesis of the compound containing Structure VII started with diacetone alcohol, which on treatment with thionyl chloride was converted into 2-methyl-2-chloropentanone-4.



Should this chloro ketone react with 3-methylpiperidine to give a tertiary amine, then reduction of the ketone and benzoylation of the resulting

alcohol would give the desired structure (VII). After the experience with the secondary halogen esters it was not expected that the 2-methyl-2-chloropentanone-4 would react with the secondary amine to give the tertiary amine, but the reaction was tried in order to ascertain what the behavior of such a tertiary halogen compound would be. It was found that this chloro ketone reacted with the secondary amine at room temperature and after about twelve hours approximately one-half of the secondary amine was precipitated as the hydrochloride when the reaction mixture was diluted with ether. The ether solution when treated with dry hydrogen chloride yielded only 3-methylpiperidine hydrochloride. These results indicate that halogen attached to secondary and tertiary carbon atoms in compounds of the type studied here do not react with secondary amines to give tertiary amines, but rather lose a molecule of halogen acid to form, presumably, an unsaturated compound.

Experimental

1-(3-Methylpiperidino)-propanone-2 Hydrochloride.—Ten g. (1 mole) of freshly distilled chloro-acetone, dissolved in 200 cc. of ether, was treated with 20 g. (2 moles) of 3-methylpiperidine, dissolved in 200 cc. of ether. A precipitate of 3-methylpiperidine hydrochloride appeared immediately. The mixture was allowed to stand with occasional shaking for about one hour and then the precipitated amine hydrochloride was filtered off. Dry hydrogen chloride was then passed into the filtrate until the precipitation of the keto base was complete. The hydrochloride of the keto base could not be obtained crystalline at this point so the free base was liberated with 40% sodium hydroxide and extracted with ether. After removal of the ether the product was distilled under diminished pressure. Thirteen g. of a product boiling at 101–102° (18 mm.) was obtained. This free base was then dissolved in ether and reprecipitated as the hydrochloride. On recrystallization it melted at 162–163°.

Anal. Subs., 0.2031, 0.1889: AgCl, 0.1511, 0.1406. Calcd. for $C_9H_{15}ONCl$: Cl, 18.51. Found: 18.40, 18.42.

1-(3-Methylpiperidino)-propanol-2 Hydrochloride.—A solution of 15.5 g. of 1-(3-methylpiperidino)-propanone hydrochloride in 75 cc. of alcohol was reduced catalytically using 0.3 g. of Adams' platinum–oxide platinum black catalyst. The reduction was complete in three and one-half to four hours. The catalyst was removed from the reduced solution and the alcohol evaporated off under diminished pressure. The residue was treated with 40% sodium hydroxide and extracted with three 100-cc. portions of ether. The ether solution was dried over anhydrous sodium sulfate, after which the solvent was removed and the amine distilled under diminished pressure. The amino alcohol boiled at 98–100° (18 mm.); yield, 9 g. It was converted into the hydrochloride by precipitation from ethereal solution with hydrogen chloride and analyzed in this form. The hydrochloride melted at 184–185°.

Anal. Subs., 0.1633, 0.2710; AgCl, 0.1220, 0.2020. Calcd. for $C_9H_{20}ONCl$: Cl, 18.32. Found: 18.47, 18.43.

α-Methyl-β-(3-methylpiperidino)-ethyl Benzoate Hydrochloride (III).—The residue obtained after the evaporation of the solvent from the reduction of 1-(3-methylpiperidino)-propanone hydrochloride was benzoylated by heating with benzoyl chloride at 150–160° for twenty to thirty minutes. The acylation proceeded normally and the amino ester hydrochloride was isolated by diluting the reaction mixture with ether.

After several recrystallizations from an alcohol–ether mixture the product melted at 165–166°; yield, 5 g.

Anal. Subs., 0.2370, 0.1982: AgCl, 0.1165, 0.0980. Calcd. for $C_{16}H_{24}O_2NCl$: Cl, 11.92. Found: 12.16, 12.23.

1-(3-Methylpiperidino)-butanone-3 Hydrochloride.—A mixture of 13.5 g. of 3-methylpiperidine hydrochloride, 3.6 g. of paraformaldehyde, 30 cc. of acetone and 5 cc. of absolute alcohol was heated on a water-bath until the paraformaldehyde went into solution. This required three to four hours. The reaction mixture was then diluted with 100 cc. of dry ether and allowed to stand in an ice box until crystallized. This precipitated keto amine hydrochloride after recrystallization from an alcohol–ether mixture melted at 151–152°; yield, 12 g.

Anal. Subs., 0.1980, 0.2061: AgCl, 0.1378, 0.1431. Calcd. for $C_{10}H_{20}ONCl$: Cl, 17.25. Found: 17.22, 17.18.

α-Methyl-γ-(3-methylpiperidino)-propyl Benzoate Hydrochloride (IV).—A solution of 7 g. of 1-(3-methylpiperidino)-butanone-3 hydrochloride in 50 cc. of alcohol was reduced catalytically with Adams' platinum–oxide platinum black catalyst. The reduction was complete in one to two hours with the absorption of the theoretical amount of hydrogen. The catalyst was filtered off from the reduced solution and the alcohol removed from the filtrate under diminished pressure. The residue was benzoylated with benzoyl chloride as described above for α-methyl-β-(3-methylpiperidino)-ethyl benzoate hydrochloride. The amino ester hydrochloride after recrystallization melted at 178–180°; the yield was 3.5 g.

Anal. Subs., 0.1441, 0.1659: AgCl, 0.0666, 0.0781. Calcd. for $C_{17}H_{26}O_2NCl$: Cl, 11.38. Found: 11.42, 11.64.

α,β-Dimethyl-β-bromo-ethyl Benzoate.—To 216 g. (1 mole) of β-butylene bromide (Eastman) dissolved in 200 cc. of toluene, was added 114 g. (0.5 mole) of silver benzoate. The mixture was stirred and refluxed for six hours. After this period of heating another 114 g. of silver benzoate was added and the mixture refluxed for an additional six hours. The reaction mixture was then filtered to remove the insoluble silver salts and the precipitate washed with 100 cc. of toluene. The filtrate was shaken with 10% sodium hydroxide to remove any benzoic acid that was present and then distilled under diminished pressure. Eighty g. (31%) of a product that boiled at 139–141° (4 mm.) was obtained. In spite of the apparent purity of the compound it failed to show the correct halogen content upon analysis by the Carius method. The analysis showed 20.5–21.0% of bromine, whereas the theoretical amount for the bromo ester is 31.10%. On redistillation of the product through a 15-cm. fractionating column, it boiled at 140–141 (4 mm.), but the analysis of the product so obtained gave practically the same results as indicated above. The only explanation of these low analyses that seems possible is that a small amount of the dibenzoate was present in the bromo ester and that the two could not be completely separated by fractional distillation.

α,γ-Dimethyl-γ-chloropropyl Benzoate.—Acetylacetone was reduced catalytically with Adams' platinum–oxide platinum black catalyst to pentane-diol-2,4, which was isolated in 60% yield. This diol has previously been prepared by the action of methyl magnesium iodide on aldol[5] and by the reduction of pentane-ol-4-one-2 with sodium amalgam.[6] Twenty-six g. (0.25 mole) of this glycol was heated at 110–120° and to this was added slowly from a dropping funnel 35 g. (0.25 mole) of benzoyl chloride. The mixture was kept at this temperature for about half an hour after all the benzoyl chloride had been added. The reaction mixture was then cooled, 60 g. of thionyl

[5] Franke and Kohn, *Ber.*, **37**, 4730 (1904).

[6] Poray-Coschitz, *Chem. Centr.*, [I] 1327 (1904).

chloride added, and the resulting solution heated for about half an hour under a reflux on a water-bath. Water was then added to decompose the excess of thionyl chloride and the chlorobenzoate was extracted with ether and dried over calcium chloride. After the removal of the solvent the chloro ester was distilled under diminished pressure. There was obtained 18–20 g. of product, b. p. 134–135° (2 mm.); n_D^{20}, =1.5074; d_{20}^{20}, 1.1008.

Anal. Subs., 0.4813, 0.4749: AgCl, 0.3031, 0.2981. Calcd. for $C_{12}H_{15}O_2Cl$: Cl, 15.65. Found: 15.58, 15.53.

Reaction of α,β-Dimethyl-β-bromo-ethyl Benzoate and α,γ-Dimethyl-γ-chloropropyl Benzoate with 3-Methylpiperidine.—A mixture of 0.1 mole of 3-methylpiperidine and 0.05 mole of the halogen ester was heated on a steam cone for thirty minutes. At the end of this time the mixture was cooled and diluted with ether in order to precipitate any of the 3-methylpiperidine hydrohalide that would have been formed had any reaction taken place. There was no indication of reaction during this period of heating. The time of heating was extended to four hours and dilution with ether showed that some reaction had taken place, but it was not nearly complete. After twelve hours of heating at 100°, however, approximately half of the 3-methylpiperidine originally used was precipitated by ether as the hydrobromide, showing that the reaction had been completed. The ether solution after the removal of the secondary amine hydrobromide was treated with dry hydrogen chloride. A precipitate was obtained which proved to be 3-methylpiperidine hydrochloride. The combined hydrobromide and hydrochloride obtained was practically equivalent to the total amount of 3-methylpiperidine started with. There was no qualitative difference in the behavior of α,β-dimethyl-β-bromo-ethyl benzoate and α,γ-dimethyl-γ-chloropropyl benzoate toward the secondary amine.

2-Chloro-2-methylpentanone-4.—To a solution of 58 g. of diacetone alcohol in 100 cc. of ether was added 60 g. of thionyl chloride and the mixture was refluxed for thirty minutes. Water was then added to decompose the unreacted thionyl chloride and the ether solution of the chloro-ketone dried over anhydrous sodium sulfate. The ether was distilled off and the chloro-ketone distilled under diminished pressure. The product boiled at 50–52° (14 mm.) and the yield was 50 g. (74%). When first distilled it was a colorless oil, but it began to darken almost immediately on standing. After standing for three to four hours, there was sufficient hydrogen chloride evolved to cause noticeable fumes when the bottle containing the product was unstoppered. The chloro-ketone was washed with dilute sodium carbonate solution, dried with calcium chloride, redistilled and immediately weighed out for analyses. A chlorine content of 23.05% was found, whereas the theoretical is 26.39%. On account of its instability no other physical constants of the chloro-ketone were determined.

Reaction of 2-Chloro-2-methylpentanone-4 with 3-Methylpiperidine.—To a solution of 6.8 g. (0.05 mole) of the chloro-ketone in 100 cc. of ether was added 10 g. (0.1 mole) of 3-methylpiperidine and the mixture allowed to stand at room temperature. Precipitation of 3-methylpiperidine hydrochloride began at once and after twelve hours' standing the reaction mixture was filtered. Approximately one-half of the secondary amine was recovered as the hydrochloride. The filtrate was treated with dry hydrogen chloride and the precipitate was 3-methylpiperidine hydrochloride, which together with that obtained by the first filtration of the reaction mixture corresponded to practically all of the 3-methylpiperidine that was originally put into the reaction.

Pharmacological Report

α-Methyl-β-(3-methylpiperidino)-ethyl benzoate hydrochloride (III) and α-methyl-γ-(3-methylpiperidino)-propyl benzoate hydrochloride (IV)

are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A brief report of a portion of this work is given in the table below. For comparison the corresponding values for β-(3-methylpiperidino)-ethyl benzoate hydrochloride (I), γ-(3-methylpiperidino)-propyl benzoate hydrochloride (II), cocaine and procaine are included. The anesthetic efficiencies were determined in the usual way by the application of a 2% solution of the anesthetic to the rabbits cornea and noting the duration of anesthesia. The toxicities were determined by subcutaneous injection into white mice and also by intravenous injection into white rats.

TABLE I

PHARMACOLOGICAL DATA

	Av. duration of compound anes., min.	Subcutaneous toxicity to white mice (mg./kg.) M. T. D.	M. L. D.	No. of mice used	Intravenous toxicity to white rats (mg./kg.) M. T. D.	M. L. D.	No. of rats used
I	0	3000	3500	29	25	30	11
II	11	450	500	7	20	25	9
III	2.5	2000	2500	30	20	25	14
IV	28	250	300	40	12.5	15	10
Cocaine	29.0	200	250	18	15	17.5	12
Procaine	0	900	1000	17	45	50	10

Discussion of the Pharmacological Data

A comparison of compounds I and II with III and IV shows that the introduction of a methyl group in the alkylene group that separates the oxygen and nitrogen in these substances causes a considerable change in their pharmacological behavior. The compounds (III and IV) containing the methyl substituted alkylene group have distinctly higher anesthetic effect and higher toxicities than the corresponding compounds (I and II) in which the alkylene group is unsubstituted. Compound IV has practically the same pharmacological properties as cocaine. It may be of interest to note that in compounds II and III where there are the same number of carbon atoms in the alkylene groups, the straight chain compound (II) appears to be the most efficient anesthetic.

Summary

1. α-Methyl-β-(3-methylpiperidino)-ethyl benzoate and α-methyl-γ-(3-methylpiperidino)-propyl benzoate have been prepared as the hydrochlorides. They have been found to have higher anesthetic efficiencies and higher toxicities than the corresponding compounds in which the alkylene group between the oxygen and nitrogen is unsubstituted.

2. It has been found that certain halogen compounds in which the halogen is attached to a secondary or tertiary carbon atom do not react

with a secondary amine to give a tertiary amine, but undergo an internal loss of halogen acid to form, presumably, an unsaturated compound.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE UNIVERSITY CHEMICAL LABORATORIES, CAMBRIDGE, ENGLAND]

A PRELIMINARY EXAMINATION OF ROTENONE AND SOME OF ITS DEGRADATION PRODUCTS

BY GORDON MITCHELL WRIGHT

RECEIVED AUGUST 11, 1928 PUBLISHED DECEMBER 10, 1928

For many years considerable interest has been taken in a number of tropical plants, extracts of which have been used as fish and arrow poisons. More recently there has been a commercial development of these plants as sources of insecticides, and in this connection the root of *Derris elliptica Benth.* or *Tuba* has been widely used. On the agricultural side considerable attention has been given to the properties of *Derris* and it seemed of interest to obtain some light on the chemical structure and properties of the toxic principle.

A toxic principle from the root was first isolated as an amorphous substance by Greshoff,[1] who assigned it the name "Derrid." This worker showed that derrid did not contain nitrogen and was not a glucoside. Wray[2] also appears to have isolated the same substance, though he assigned to it the name "Tubain."

Derrid was also obtained by van Sillevoldt[3] as an amorphous powder, m. p. 73°, with an empirical formula $C_{33}H_{30}O_{10}$. It was suggested that it contained three mexthoxyl groups and two hydroxyl groups, although benzoylation or acetylation failed. Further, "anhydroderrid," yellow needles, m. p. 210–214°, of formula $C_{33}H_{28}O_9$, was obtained. A crystalline substance, m. p. 158°, from the roots of *Derris elliptica Benth.* was obtained by Lenz,[4] who gave it the name "Derrin." Takeo Ishikawa[5] isolated a toxic substance, m. p. 163.5°, from the same source and assigned to it the name "tubotoxin" and the empirical formula $C_{18}H_{18}O_5$. The work of the previous author was extended by Kariyone and Atsumi,[6] who confirmed the above formula. This compound, which in alcoholic solution reduced Fehling's solution, formed a phenylhydrazone, $C_{18}H_{18}O_5{=}N{\cdot}NHC_6H_5$, m. p. 255°, and a monoxime, $C_{18}H_{18}O_5{=}NOH$, m. p. 245°. It was suggested that a diacetyl derivative, m. p. 125–155°, was obtained but

[1] Greshoff, *Ber.*, **23**, 3538 (1890).
[2] Wray, *Pharm. J.*, [3] **23**, (1892).
[3] van Sillevoldt, *Arch. Pharm.*, **237**, 595 (1899).
[4] Lenz, *ibid.*, **249**, 298 (1911).
[5] Takeo Ishikawa, *Japan Med. Lit.*, **1**, 7 (1916).
[6] Kariyone and Atsumi, *J. Pharm. Soc. Japan*, **491**, 6 (1923).