separates as colorless needles and at other times as colorless rhombic blocks. In one experiment a modification was obtained which melted at 71°; after resolidifying the melting point rose to 80–81°.

Anal. Calcd. for $C_8H_{11}O_2N_2Br$: N, 11.34. Found: N, 11.45, 11.38.

Summary

1. 2,6-Dialkoxypyrimidines are formed smoothly by interaction of 2,6-dichloropyrimidine with sodium alcoholates.

2. The 2,6-dialkoxypyrimidines and the 2-oxy-3-alkyl-6-alkoxypyrimidines rearrange on heating to form 1,3-dialkyluracils. This method of operating makes possible the synthesis of uracil derivatives which hitherto have not been available for the development of pyrimidine chemistry.

3. A new method for the alkylation of pyrimidines of the uracil type in position 3 has been developed.

4. This new reaction will be applied for the synthesis of hexose and pentose derivatives of pyrimidines. It is possible that some of these sugar derivatives will be found to be identical with the naturally occurring nucleosides. This same technique will also be applied in the purine series.

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

PIPERIDINE DERIVATIVES. IX. METHYLPIPERIDINO-ALKYL CINNAMATES

BY C. F. BAILEY AND S. M. MCELVAIN

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It has been pointed out in two previous communications[1] from this Laboratory, that those piperidino-alkyl benzoates containing a methyl group as a substituent in the piperidine nucleus were much more effective as local anesthetics than the corresponding compounds in which the piperidine nucleus was unsubstituted or was substituted by certain other aliphatic groups. In two very interesting papers concerned with the correlation of aromatic properties with physiological action, Gilman and co-workers[2] have shown that in the amino-alkyl ester type of anesthetic a distinct local anesthetic effect is found associated with those structures in which the carbonyl group of the ester is attached to an unsaturated carbon atom. Of all such types of compounds that have been investigated, the cinnamates are by far the most effective. Apothesine, γ-diethylaminopropyl cinnamate, is a well-known example of this type of ester.

Since the methylpiperidino-alkyl nucleus has been found to be so efficient

[1] McElvain, THIS JOURNAL, **49**, 2835 (1927); Bailey and McElvain, *ibid.*, **52**, 1633 (1930).

[2] Gilman and co-workers, *ibid.*, **47**, 245 (1925); *ibid.*, **50**, 437 (1928).

in the benzoate series, it seemed desirable to prepare and submit for pharmacological study an analogous series of cinnamates. This paper gives the preparation, properties and a brief statement of the pharmacological action of the following six compounds: 2-methyl-, 3-methyl- and 4-methylpiperidino-ethyl and propyl cinnamates.

These substances were prepared by the condensation of the methylpiperidines with β-chloro-ethyl cinnamate and γ-chloropropyl cinnamate. The tertiary amino esters so obtained were isolated and used in the form of their hydrochlorides.

Experimental

Methylpiperidines.—The 2-methyl-, 3-methyl- and 4-methylpiperidines that were used were obtained from α-, β- and γ-picolines, respectively, by methods previously described.[1]

β-Chloro-ethyl Cinnamate.—This ester has previously been prepared[3] by the action of ethylene chlorohydrin on cinnamic acid in the presence of sulfuric acid. This procedure was not tried in this work since the following method gave very satisfactory results. To 111 g. of cinnamic acid in a 1-liter flask fitted with a reflux condenser, 179 g. of thionyl chloride was slowly added from a dropping funnel. The evolution of sulfur dioxide and hydrogen chloride began almost immediately. After all of the thionyl chloride had been added the mixture was heated on a steam-bath for two hours. The excess thionyl chloride was then removed by distillation. To the remaining material 61 g. of ethylene chlorohydrin was slowly added and the resulting solution heated for two hours at 180° in an oil-bath. The reaction mixture was then allowed to cool, poured into water and the immiscible layer taken up in ether. After drying over calcium chloride the ether was removed and the remaining ester distilled under diminished pressure. There was obtained 126 g. (80% of the theoretical) of β-chloro-ethyl cinnamate which boiled at 162–163° (3 mm.). On distillation the ester crystallized in the receiver. Its melting point was found to be 35–37°. (The literature reference to this compound states that the melting point is 31°.)

Anal. (Stepanoff). Calcd. for $C_{11}H_{11}O_2Cl$: Cl, 16.86. Found: 17.03, 17.12.

γ-Chloropropyl Cinnamate.—This ester does not appear to have been described in the literature. It was prepared according to the procedure described above for β-chloro-ethyl cinnamate except that an equivalent amount of trimethylene chlorohydrin was used instead of ethylene chlorohydrin. The yield was 75% of the theoretical. The γ-chloropropyl cinnamate boiled at 174–177° (3 mm.); d_{20}^{20} 1.1512; n_D^{25} 1.5677. This ester is a liquid at ordinary temperatures.

Anal. (Stepanoff). Calcd. for $C_{12}H_{13}O_2Cl$: Cl, 15.81. Found: Cl, 15.83, 15.82.

Methylpiperidino-alkyl Cinnamates.—These compounds were prepared by the general procedure that was used[1] for the corresponding benzoates. There was, however, a distinct difference between the chloro-alkyl cinnamates and the chloro-alkyl benzoates in the ease with which they condensed with 2-methylpiperidine. It had been noted that the benzoates did not condense with 2-methylpiperidine to any appreciable extent under the conditions (100° for one hour) which caused quite complete condensation with 3- and 4-methylpiperidine. In the case of the chloro-alkyl cinnamates a temperature of 100° for one hour caused quite complete condensation with each of the methylpiperidines. These cinnamates were isolated as the hydrochlorides and recrys-

[3] German Patent 239,650; *Chem. Centr.*, II, 1497 (1911).

tallized to a constant melting point from an alcohol–ether mixture. They are summarized in Table I.

TABLE I

METHYLPIPERIDINO-ALKYL CINNAMATE HYDROCHLORIDES

	Piperidino-alkyl group	M. p., °C.	Analyses, Cl, % Calcd.	Found
1	β-2-Methylpiperidino-ethyl	178–180	11.47	11.45
2	γ-2-Methylpiperidinopropyl	179–181[a]	10.97	10.90
3	β-3-Methylpiperidino-ethyl	161–163	11.47	11.29
4	γ-3-Methylpiperidinopropyl	193–196	10.97	10.90
5	β-4-Methylpiperidino-ethyl	142–145	11.47	11.39
6	γ-4-Methylpiperidinopropyl	178–181[a]	10.97	10.98

[a] The melting point of a mixture of No. 2 and No. 6 was 168–172°.

Pharmacological Report

These compounds are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A preliminary report of their pharmacological properties is given in Table II. The anesthetic effect was determined by an application of a 2% solution of the anesthetic to the rabbit's cornea and noting the duration of anesthesia. Toxicities were determined by subcutaneous injection into white mice and intravenous injection into white rats. The various compounds are designated in Table II by the numbers associated with them in Table I. The analogous values for the corresponding benzoates are given in parentheses along with the cinnamate values.

TABLE II

PHARMACOLOGICAL DATA

Compound	Av. duration of anesthesia, 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
1	11 (0)	1100 (1500)	1200 (2000)	14	25 (25)	30 (30)	9
2	14 (15)	200 (800)	250 (900)	10	4 (15)	5 (17.5)	15
3	10 (0)	1700 (3000)	1800 (3500)	30	35 (25)	40 (30)	11
4	11 (11)	500 (450)	600 (500)	13	35 (20)	40 (25)	8
5	13 (11)	..[a] (1300)	..[a] (1400)	..	20 (40)	25 (42.5)	8
6	21 (14)	500 (....)[a]	600 (....)[a]	..	12.5 (20)	15 (22.5)	8

[a] Not determined because of scarcity of material.

Discussion of the Pharmacological Data

It is seen from the above data that, in general, the methylpiperidino-alkyl cinnamates are more active physiologically than the corresponding

benzoates. This greater activity is particularly noticeable in the case of the ethyl esters, for 1 and 3 show quite marked anesthetic effect on the rabbit's cornea while the corresponding benzoates are without any such effect. The 4-methylpiperidino derivatives seem appreciably more active than the isomeric 3-methyl- and 2-methylpiperidino derivatives. With the exception of γ-3-methylpiperidinopropyl cinnamate, the toxicities of the members of the cinnamate series are, in general, greater than those of the benzoates.

Summary

1. The methylpiperidino-ethyl and propyl cinnamates have been prepared and described.

2. A comparison of their pharmacological properties with those of the corresponding benzoates is given.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

ATTEMPTED CORRELATIONS OF CONSTITUTION WITH SWEET TASTE IN THE FURAN SERIES. THE VERY HIGH SWEETENING POWER OF 5-BENZYL-2-FURFURALDOXIME

BY HENRY GILMAN AND J. B. DICKEY

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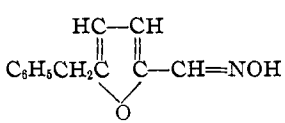
Introduction

In extension of studies[1] concerned with some correlations of constitution with sweet taste in the furan series we have come upon a compound which is sweeter than saccharin. The compound is *syn*-5-benzyl-2-furfuraldoxime



and it was found to be 690 times sweeter than sugar. The *anti*-form of this oxime is about 100 times sweeter than sugar.

These two isomers were prepared earlier by Fenton and Robinson,[2] but apparently they overlooked the sweet taste of the compounds.

It is interesting to note that both the *syn*- and the *anti*-oximes of 5-hydroxymethyl-2-furfural

[1] (a) Gilman and Hewlett, *Iowa State Coll. J. of Sci.*, **3**, 27 (1929). This article contains leading references to pertinent papers and standard texts. We omitted in that paper reference to (b) Asahina and Fujita, *J. Pharm. Soc. Japan*, **490**, 1084 (1922); [*C. A.*, **17**, 2578 (1923)].

[2] Fenton and Robinson, *J. Chem. Soc.*, **95**, 1334 (1909).