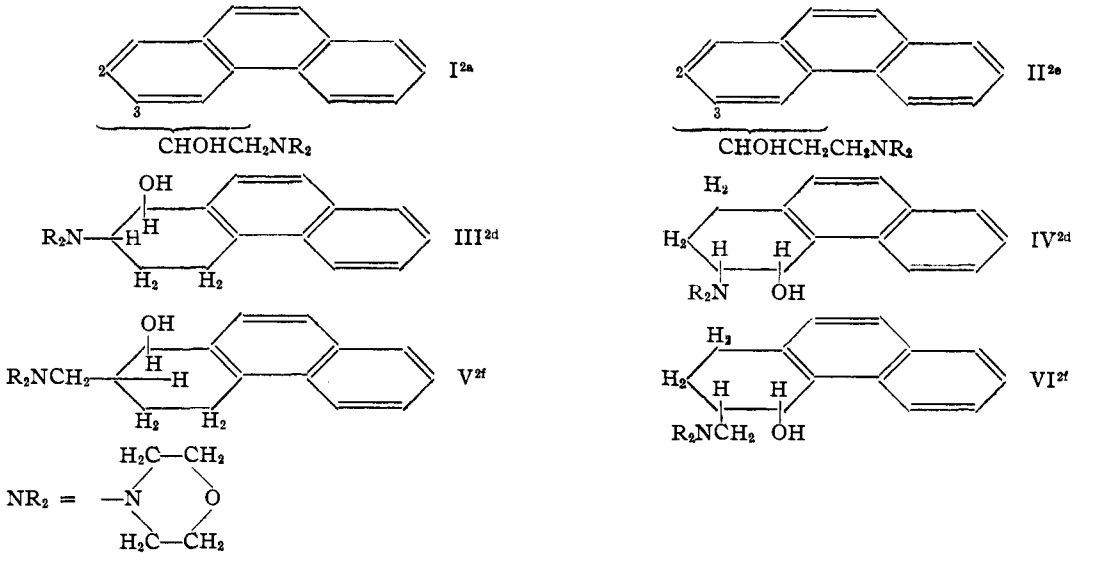

All of the amino alcohols that have been tested so far (Nos. 4, 8, 20, 24, 27, 33, 37, 40 of the accompanying table)[7] show only low analgesic action or none at all. In the instances where a comparison with analogous diethylamino and piperidino compounds was possible, it became apparent that replacement of the diethyl or piperidino group by the morpholino group resulted in a decrease of analgesia in the ratio from 2:1 to about 8:1.

(7) Eddy, unpublished results.

Summary

The synthesis of a series of morpholino alcohols from 2-acetylphenanthrene, 3-acetylphenanthrene, 3-methoxy-9-acetylphenanthrene, 1-keto-tetrahydrophenanthrene and 4-keto-tetrahydrophenanthrene is described.

UNIVERSITY, VIRGINIA RECEIVED JULY 9, 1938

[CONTRIBUTION FROM THE DEPT. OF CHEMICAL ENGINEERING, UNIVERSITY OF CINCINNATI, AND THE RESEARCH LABORATORIES OF THE WM. S. MERRELL COMPANY]

An Investigation of the Effect of Chemical Structure on Local Anesthetic Action of Diothane Analogs[1]

BY ELSIE M. WALTER[2]

Most local anesthetics in general use contain a benzene ring somewhere in their structure. In fact, many early experimenters claimed that a compound must contain a benzoyl group to exhibit anesthetic action. In 1925, Gilman and Pickens[3] studied the effect of various aromatic rings on the anesthetic action of procaine. They prepared the furan, thiophene, and pyrrole analogs of procaine. Their results indicate that the order of decreasing activity is benzene > pyrrole > thiophene > furan > methyl. More recently, however, Phatak and Emerson[4] prepared various alkyl esters of 2-furoic acid where the alkyl varied from methyl to amyl. They found that all of the compounds possess local anesthetic action which increases with the size of the alkyl from methyl to amyl. The amyl furoate has approximately the same activity as cocaine. It was pointed out by the authors that the corresponding benzoates show either incomplete or no anesthetic action.

Since very little work has been done on the effect of substituting various aromatic rings for the benzene ring in the structure of local anesthetics, it was decided to prepare some furan analogs of Diothane (piperidinopropanediol diphenylurethan hydrochloride[5]) and compare their

(1) From a thesis in partial fulfilment of the requirements for the degree of Chemical Engineer, University of Cincinnati, June, 1938.

(2) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(3) H. Gilman and R. M. Pickens, THIS JOURNAL, **47**, 245 (1925).

(4) N. M. Phatak and G. A. Emerson, *J. Pharmacol.*, **58**, 174 (1936).

(5) T. H. Rider, THIS JOURNAL, **52**, 2115 (1930); T. H. Rider and E. S. Cook, *J. Pharmacol.*, in press.

physiological action with that of the corresponding benzoyl compounds. The difuroate, dibenzoate, diacetate, dicinnamate, and difuranacrylate of piperidinopropanediol were prepared and tested pharmacologically. The dibenzoate was previously reported by Pyman.[6] The remaining compounds have not been reported before.

Experimental

1-Piperidinopropane-2,3-diol dibenzoate was prepared from 1-piperidinopropane-2,3-diol and benzoyl chloride by the Schotten–Baumann reaction according to the method of Pyman,[6] but it was recrystallized from petroleum ether instead of alcohol. The piperidinopropanediol used in all the reactions was made from the previously described specially purified piperidine.[7] The dibenzoate formed needle-like white crystals, m. p. 64–65°, uncorr., as reported by Pyman.[6] The hydrochloride was prepared by dissolving the free base in ether and introducing gaseous hydrogen chloride. The gummy, white hydrochloride on washing with anhydrous ether became solid and was ground to a fine white powder; m. p. 126–130°, uncorr.

Anal. Calcd. for $C_{22}H_{26}O_4NCl$: Cl, 8.78. Found: Cl, 8.84.

1-Piperidinopropane-2,3-diol difuroate was prepared from piperidinopropanediol and furoyl chloride in the same manner as the dibenzoate. The ester was decolorized with charcoal in ether solution. It was precipitated as a fluffy white solid by evaporating the ether solution to a small volume and adding petroleum ether. It can also be crystallized from ether in white needle-like crystals; m. p. 73–74°, uncorr. The hydrochloride was prepared in the same manner as the dibenzoate hydrochloride; m. p. 163–164.5°, uncorr.

Anal. Calcd. for $C_{18}H_{22}O_6NCl$: Cl, 9.19. Found: Cl, 9.28.

1-Piperidinopropane-2,3-diol diacetate was prepared by slowly adding with stirring 32 g. (0.2 mole) of piperidinopropanediol to 45 g. (0.44 mole) of acetic anhydride kept in an ice-bath. After the addition was completed, the mixture was heated to 75° and then allowed to stand at room temperature for about five hours. After neutralizing with sodium carbonate in an ice-bath, the ester was extracted with ether and the solution was dried over sodium sulfate. After removing the ether, the diacetate remained as a colorless oil which becomes orange upon exposure to light and air. The hydrochloride was prepared in the usual manner and stored in a desiccator, since the ester hydrolyzes readily on exposure to moisture; m. p. 128–133°, uncorr.

Anal. Calcd. for $C_{12}H_{22}O_4NCl$: Cl, 12.68. Found: Cl, 12.80.

1-Piperidinopropane-2,3-diol dicinnamate could not be prepared by the Schotten–Baumann reaction because of the hydrolysis of cinnamoyl chloride. An attempt to produce it from the diacetate by the Perkin reaction failed also. Condensation of the alcohol and acid chloride was successful in benzene but the resulting ester did not crystallize and could not be completely freed of benzene. Condensing the acid chloride and the alcohol without a solvent was the most satisfactory method.

Seven grams (0.044 mole) of cinnamoyl chloride was melted and 3.2 g. (0.02 mole) of piperidinopropanediol were added slowly with stirring. The material formed a clear yellow viscous mass. After cooling and washing with numerous portions of dry ether and standing for several days under ether the crude hydrochloride crystallized. This was purified by neutralizing with the theoretical quantity of 5% sodium hydroxide, extracting with ether, precipitating with 2 *N* hydrochloric acid, and regenerating the free base with sodium hydroxide. The hydrochloride was prepared by treating the free base, in absolute ether, with hydrogen chloride gas, freeing from excess hydrochloric acid by washing with ether, and crystallizing from water; m. p. 159–161°, uncorr.

Anal. Calcd. for $C_{26}H_{30}O_4NCl$: Cl, 7.78. Found: Cl, 8.10.

1-Piperidinopropane-2,3-diol difuranacrylate was prepared similarly to the dicinnamate. Furanacrylic acid was prepared according to the method of Gibson and Kahnweiler[8] and was converted into the acid chloride according to the method of T. Sasaki.[9] Three and two-tenths grams (0.02 mole) of piperidinopropanediol was added slowly with stirring to 6 g. (0.044 mole) of melted furanacryloyl chloride. The crude hydrochloride was a very viscous light brown oil. The free base, obtained by neutralizing the hydrochloride with the theoretical amount of sodium hydroxide, extracting with ether, and decolorizing with charcoal, was also a heavy viscous oil. The purified hydrochloride was obtained similarly to that of the dicinnamate and was a colorless oil when first prepared but became colored in a few hours. It has resisted attempts to crystallize it.

Anal. Calcd. for $C_{22}H_{26}O_6NCl$: Cl, 8.14. Found: Cl, 8.19.

Pharmacological.—The following table roughly evaluates the strength of the compounds as local anesthetics. The tests were made with a solution of the hydrochlorides in distilled water. The time in minutes required for the production of sensory anesthesia in the exposed sciatic nerve of the frog, and the duration of anesthesia after one-minute application of the solution to the cornea of the rabbit are given.

Ester	Concn., %	Frog sciatic onset, min.	Rabbit cornea Onset, min.	Rabbit cornea Duration, min.
Dibenzoate	1	2	2	7
Difuroate	1	4	2.5	4
Diacetate	1	..	..	No action
Dicinnamate	<1	2	2.5	6–7
Difuranacrylate	1		1.5	8–8.5
Difuranacrylate	2	..	1.5	13
Procaine	1			Incomplete

(6) F. L. Pyman, *J. Chem. Soc.*, **93**, 1793 (1908).

(7) E. S. Cook and T. H. Rider, THIS JOURNAL, **59**, 1739 (1937); T. H. Rider and E. S. Cook, *ibid.*, **59**, 1741 (1937); E. S. Cook, *ibid.*, **59**, 2661 (1937).

(8) H. B. Gibson and C. F. Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).

(9) T. Sasaki, *Biochem. Z.*, **25**, 272 (1910).

The dibenzoate caused irritation of the eye. The dicinnamate caused a milky film to appear over the cornea, sloughing of the tissue, and about twelve hours later, marked conjunctival irritation and swelling of the eyelids. The difuroate and the difuranacrylate seemed to have a lachrymatory effect, but caused very little, if any, irritation of the eyes. There was considerable difficulty in obtaining a solution of the dicinnamate. A few drops of hydrochloric acid were used to produce the 1% suspension for testing on the cornea, and a 25% solution of propylene glycol was required to produce the 1% solution for testing on the sciatic nerve of the frog.

It will be seen that the dibenzoate was more active than the difuroate, which agrees with the findings of Gilman and Pickens.[3] However, introduction of a double bond appears to reverse this order, the difuranacrylate being more active than the dicinnamate. In the furan series, the introduction of the double bond gave an expected increase in activity, the furanacrylate being twice as active as the furoate. A similar increase in activity is not found on comparing the dicinnamate with the dibenzoate, but this may have been due to the low solubility of the dicinnamate and the precipitation on application to the eye. The dicinnamate showed rapid penetration when applied to the nerve. As was expected, the diacetate was inactive. The furan compounds have the advantage over the benzene analogs of being more soluble and less irritating.

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Summary

The diacetate, dibenzoate, difuroate, dicinnamate, and difuranacrylate of piperidinopropanediol were prepared. The results of the pharmacological tests indicate that the furan ring has a favorable effect on anesthetic action. It apparently increases the solubility and decreases the irritation in this series of compounds.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

Addition Reactions of Unsaturated Alpha-Ketonic Acids. V

BY MARIE REIMER AND ELIZABETH CHASE

Earlier papers in this series[1] have shown that the behavior of the unsaturated side-chain of benzalpyruvic acid is influenced strongly by methoxyl groups in different positions in the benzene ring: the stability of the dibromo addition products, the tendency to formation and the stability of hydrates, the color of the compounds alone and in solution in concentrated sulfuric acid show decided variation in the different compounds. Most striking is the fact that a methoxyl group in the para position entirely inhibits the photochemical reaction so conspicuous a characteristic of benzalpyruvic acid and its esters[2] and noticeable to a less degree with the *o*- and the *m*-methoxy-substituted acids. Because of the prevalence of methoxyl groups in natural products and because of differences in activity noticed when methoxyl replaces hydrogen in several different classes of compounds,[3] it becomes of interest to determine whether the blocking of the sunlight reaction is a function of the *p*-methoxyl group, as such, or whether and to what extent other groups in the para position in the benzene ring have the same effect. Such studies are now under way in this Laboratory.

The present paper deals with benzalpyruvic acid in which there is a methyl group in the para position. The methyl group was chosen because of certain well-known similarities in the influence of methyl and methoxyl: the effect on orientation in the benzene ring, on ease of substitution and on the coupling reaction,[4] for example. These, however, are influences of these groups on hydrogen of the ring. In reactions involving a side-chain wide differences have been described, not-

(1) No. IV, Reimer, Tobin and Schaffner, THIS JOURNAL, **57**, 211 (1935).

(2) Reimer, *ibid.*, **46**, 783 (1924).

(3) *Cf.* Reimer, *ibid.*, **48**, 2454 (1926).

(4) V. Auwers and Borsche, *Ber.*, **48**, 1716 (1915).