fied in any way. The barrier of the film balance was advanced to maintain any desired pressure on the monomolecular film during the dipping of the slide. This mechanical technique replaces the conventional "piston oil" and flexible barrier technique.

The effects of the nature of the backing material, the compression of the monomolecular film, the rate of dipping and the temperature upon the ability of the films to be picked up were studied. Certain generalizations may be made in regard to preparing built-up films. (1) The monomolecular films on the water surface must be in the "solid condensed" state to be capable of transferring many layers to a solid backing. (2) The formation of the "solid condensed" state is favored by increase in lateral pressure and decrease in temperature. (3) The condition of the backing surface is most important. A hydrophobic surface favors film deposition. (4) The highest speed of dipping that will not excessively agitate the surface is the most desirable. For this reason thin slides are preferred to thick ones.

Of the compounds in the series, only methyl stearate and ethylene glycol distearate formed built-up films more than two to five molecular layers thick. Even at a temperature of 10°, the other compounds formed "liquid" films from which only 2 to 5 monolayers could be picked up. Electron diffraction studies of these films will be reported in a later paper.

The X-ray examination of the methyl stearate and ethylene glycol distearate confirmed the spacings found by others.[11]

Summary

With an improved film balance under carefully controlled conditions measurements are made of area per molecule, and collapse pressure on water surfaces for monolayers of certain esters which have possible use as addition agents in lubricating oils, namely, methyl stearate, α-chlorostearate, dichlorostearate, oleate, ricinoleate and chlororicinoleate, ethylene glycol distearate and ricinoleate, and tricresyl phosphate.

The addition of hypochlorous acid to the double bonds of methyl oleate and ricinoleate was studied by spreading monolayers on an aqueous solution of chlorine in the film balance trough.

Films are built up by the Blodgett–Langmuir technique. Only methyl stearate and ethylene glycol distearate formed solid condensed films which could be picked up in any number of monolayers and subjected to X-ray diffraction analysis. The remaining esters formed "liquid" films from which only 2 to 5 monolayers could be picked up for electron diffraction analysis.

(11) E. Stenhagen, *Trans. Faraday Soc.*, **34**, 1328–1337 (1938).

URBANA, ILLINOIS RECEIVED JUNE 3, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE INSTITUTUM DIVI THOMAE]

Some Dialkylaminoalkyl Furoates and Benzoates as Topical Anesthetics[1]

BY ELTON S. COOK AND CORNELIUS W. KREKE

Experience has shown that the acid portion of the aminoester local anesthetic molecule is, in general, preferably aromatic.[2] Interest therefore attaches to a comparison of the ability of various aromatic groups to confer local anesthetic activity. The early paper of Gilman,[3] dealing with the β-diethylaminoethyl esters of acids containing aminobenzene, benzene, pyrrole, thiophene and furan rings, showed all of the esters to possess low topical activity. The intracutaneous activity decreased in the order given, the furan compound barely showing activity even by this method of testing. Phatak[4] confirmed this fact but found that the substitution of alkyl groups in the 5-position of the furan ring brought about topical activity. Phatak and Emerson[5] earlier found that simple alkyl esters of 2-furoic acid possessed activity whereas the corresponding benzoates were inactive; ethyl esters of 5-alkyl-2-furoic acids, however, were inactive.[4] Walter[6] reported that, while the difuroate of 1-piperidinopropane-2,3-diol was less active than the corresponding diben-

(1) Presented before the Division of Medicinal Chemistry Cincinnati meeting of the American Chemical Society, April 11, 1940.

(2) For discussion see E. S. Cook, *Studies Inst. Divi Thomae*, **2**, 63 (1938).

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

(4) N. M. Phatak, *Univ. Calif. Pub. Pharmacol.*, **1**, 55 (1938).

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

(6) E. M. Walter, THIS JOURNAL, **60**, 2467 (1938).

TABLE I

SALTS OF AMINO ALCOHOL FUROATES AND BENZOATES AND THEIR ANESTHETIC PROPERTIES (0.05 *M* SOLN.)

Compd. R = Diethylamino-	Formula	Halogen, % Calcd.	Found		M. p., ° C. (cor.)	*p*H	γ_{20}	Duration of anesthesia, min., cornea
β-R-ethyl-2-furoate·HCl	$C_{11}H_{18}O_3NCl$				130.4–131.9[a]	5.72	55.4	0
γ-R-propyl-2-furoate·HCl	$C_{12}H_{20}O_3NCl$	13.57	13.70	13.69	132–134	5.41	56.4	8
β-R-ethylbenzoate·HCl	$C_{13}H_{20}O_2NCl$				125.2–126.2[b]	5.70	53.6	Incomplete
β-R-ethylbenzoate·HBr	$C_{13}H_{20}O_2NBr$	26.44	26.96	26.78	119.2–120.2	5.50	63.9	0
γ-R-propylbenzoate·HCl[c]	$C_{14}H_{22}O_2NCl$	13.04	13.10	13.01	110.9–114.9	5.72	53.1	0
γ-R-propylbenzoate·HBr	$C_{14}H_{22}O_2NBr$	25.24	25.57	25.67	120–122	6.20	57.9	1
R = Dibutylamino-								
β-R-ethyl-2-furoate·HBr	$C_{15}H_{26}O_3NBr$	22.95	23.19	23.26	90.9–91.9	5.15	58.6	5
γ-R-propyl-2-furoate·HBr	$C_{16}H_{28}O_3NBr$	22.07	22.06	22.21	93.6–95.6	3.81	57.9	4
β-R-ethylbenzoate·HCl	$C_{17}H_{28}O_2NCl$	11.29	11.39	11.36	100.7–104.2	5.50	47.7	Incomplete
β-R-ethylbenzoate·HBr	$C_{17}H_{28}O_2NBr$	22.30	22.63	22.56	113.8–115.8	5.20	47.8	2
γ-R-propylbenzoate·HCl	$C_{18}H_{30}O_2NCl$	10.81	10.93	10.93	98.6–102.6	5.45	51.8	2
γ-R-propylbenzoate·HBr	$C_{18}H_{30}O_2NBr$	21.46	21.59	21.69	121.1–124.6	5.26	48.7	1
β-Ethylphenylaminoethyl-2-furoate·HBr	$C_{15}H_{18}O_3NBr$	23.49	23.62	23.56	119.5–122.5	2.20	50.3	2
Cocaine·HCl						4.87	51.9	20

[a] Prepared by Gilman and Pickens[3]; m. p. reported as 127°. [b] Prepared by E. V. Lynn and F. V. Lofgren, *J. Am. Pharm. Assoc.*, **14**, 970 (1925); m. p. reported as 124°. [c] The free base was prepared by Gault, *Bull. soc. chim.* (4) **3**, 376 (1908).

zoate, the furan compound appeared to be more soluble and less irritating.

Although the furoic esters appear to be inferior to the benzoic esters of the two amino alcohols on which comparative data exist, it seemed worth while to investigate the furoates and benzoates of a number of additional amino alcohols as a step preliminary to other studies. The results are reported in the present paper.

Experimental Part

Amino Alcohols.—β-Ethylphenylaminoethanol was the gift of Carbide and Carbon Chemicals Corporation. The other amino alcohols were purchased from the Eastman Kodak Co. All alcohols were redistilled before use.

Esters.—β-Diethylaminoethyl furoate hydrochloride, previously reported by Gilman and Pickens,[3] was prepared by their procedure of heating the alcohol and 2-furoyl chloride together in dry benzene for one hour. γ-Diethylaminopropyl furoate hydrochloride was prepared in the same manner. This method did not prove to be generally satisfactory and the other esters, both furoates and benzoates, were made by a Schotten–Baumann procedure similar to that employed by Pyman.[7] Usually 0.11 mole of the amino alcohol was placed in a glass stoppered bottle with 140 cc. of 10% sodium hydroxide. To this was added slowly 15 g. of the acid chloride with constant shaking and cooling in an ice-bath. The ester was immediately extracted with ether and the solution was dried over anhydrous sodium sulfate. The free base was not isolated but the hydrochloride or hydrobromide was prepared by passing dry hydrogen chloride or hydrogen bromide into the solution of the free base in dry ether. The salts were crystallized from absolute alcohol by the addition of ether. Yields were generally fair but they are not reported since no attempt was made to obtain optimum conditions. The hydrochlorides of β-dibutylaminoethyl furoate, γ-dibutylaminopropyl furoate and β-ethylphenylaminoethyl furoate could not be crystallized. Neither the hydrochloride nor the hydrobromide of β-ethylphenylaminoethyl benzoate crystallized satisfactorily. The analyses and melting points of the salts are given in Table I.

Pharmacological.—Preliminary tests for topical anesthetic activity were carried out on the rabbit cornea. For these tests 0.05 *M* solutions were used. The results are given in Table I. In this table are also included the *p*H (glass electrode) of the solution used and the surface tension (γ). The surface tension was obtained by the ring method at a temperature of 20°. Check determinations on water gave an average value for γ_{20} as 72.1. The accepted value is 72.75.[8]

It will be seen that none of the compounds is very active as a surface anesthetic. This bears out the previous experience with the furoates and with many benzoates. All of the compounds gave rather acid solutions, although not generally as acid as cocaine hydrochloride, and most gave evidence of slight irritation. The extreme acidity and severe irritation shown by β-ethylphenylaminoethyl furoate hydrobromide was caused by the fact that the compound was hydrolyzed in water solution to precipitate the free base. Hence, more acid was added to bring about solution. The surface tensions were of the same order as that of the cocaine. With the exception of the esters of β-diethylaminoethanol, the furoates are generally somewhat more active than the benzoates, although the latter seem to have definite activity on the tongue. No significant difference appears to be found between the

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

(8) "International Critical Tables," Vol. IV, McGraw-Hill Book Co., New York, N. Y., 1928, p. 477.

and hydrobromides. The pharmacological extended.

Summary

and furoates of a number of amino alcohols have been prepared. Both types of esters have a low order of topical anesthetic activity but the furoates are frequently somewhat superior.

CINCINNATI, OHIO RECEIVED APRIL 25, 1940

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FURMAN UNIVERSITY]

sym-Tritolylbenzene

BY JOHN R. SAMPEY

ızenes have been made by the con- methyl phenyl ketones in various Hydrogen chloride and sulfuric acid ısed most often as the condensing ıdensations with the former, how- l slowly; Claus[1,d] allowed six to eight ıs condensations, and in a trial run *p*-tolyl ketone saturated with dry loride we obtained only a 30% yield ylbenzene in five weeks. Condensa- d by sulfuric acid have been accom- low yields; Bernhauer[1,g] reported a *sym*-tritolylbenzene from the action cid and potassium pyrosulfate on *p*- ɔhenone.

y to the preparation of a series of ıes, a systematic investigation was effect of changes in time, temperature, ration on the yield of *sym*-tritolyl- the action of sulfuric acid and po- ɔsulfate or potassium acid sulfate on yl ketone. Condensations were made ıres ranging from room temperature he acid concentrations were varied of concentrated sulfuric acid per 10.0 of ketone to 5.0 cc. of acid. The he two potassium salts ranged from

At the lower concentrations of acid and the lower temperatures much unchanged ketone was recovered, while at the higher concentrations the yield of triarylbenzene was reduced by the formation of a dark resinous mass. After more than fifty experiments the following conditions were found to give optimum yields in a reasonable time.

Exactly 10.0-g. samples of methyl *p*-tolyl ketone were placed in large Pyrex test-tubes (29 × 200 mm.) attached to reflux condensers and protected by calcium chloride tubes. Concentrated sulfuric acid, 0.2 cc. to 0.3 cc., and potassium pyrosulfate, 2.0 g., or potassium acid sulfate, anhydrous, 2.0 g., were added. The test-tubes were suspended in an oil-bath heated to 190° for six hours. The tubes were then removed, chilled, and 25 cc. of water added; the mixture was warmed and stirred with a heavy glass rod until the potassium salt dissolved. The tritolylbenzene was separated and crystallized from hot acetic acid; yield 67–70% *sym*-tritolylbenzene, m. p. 170–171°.

Recognition is made of the assistance of Dr. E. Emmet Reid on this investigation.

Summary

sym-Tritolylbenzene has been prepared in 67–70% yields by the condensation of methyl *p*-tolyl ketone with sulfuric acid and potassium pyrosulfate or potassium acid sulfate, anhydrous.

GREENVILLE, SOUTH CAROLINA RECEIVED MAY 11, 1940

Ber., **7**, 1123 (1874); **26**, 1444 (1893); (b) Vor- 2836–2844 (1929); (c) LeFèvre, *J. Chem. Soc.*, Claus, *J. prakt. Chem.*, [2] **41**, 405 (1890); (e) *ntr.*, **102**, II, 3101 (1931); (f) Odell, THIS JOURNAL,) Bernhauer, *J. prakt. Chem.*, **145**, 301–308 (1936).