137°)[5] was reacted on with diazomethane in the presence of 0.8 g. (2 mols) of piperidine; yield, 0.5 g.; m. p. 109°, which is in agreement with the melting point given by Liebermann and Lindenbaum.[6]

Anal. Subs., 3.314 mg.: AgI, 8.533 mg. Calcd. for $C_9H_{10}O_4$: OCH_3, 34.07. Found: OCH_3, 33.99.

(4) **Monomethyl-β-resorcylic Acid.**—When using one molecule of piperidine a mixture of the two monomethyl-β-resorcylic acids was obtained. This mixture melted gradually between 169 and 174°, and gave with ferric chloride a violet coloration which had a distinctly greenish tint. The two isomers in question show the following properties: 2-hydroxy-4-methoxybenzoic acid melts at 160–161°, and gives a violet coloration with ferric chloride, whereas 2-methoxy-4-hydroxybenzoic acid melts at 187–189°, and gives a red-brown coloration with ferric chloride. The former substance therefore predominated in the mixture.

Anal. Subs., 7.310 mg.: AgI, 10.571 mg. Calcd. for $C_8H_8O_4$: OCH_3, 18.45. Found: OCH_3, 19.08.

(5) **Trimethylgallic Acid.**—One gram of triacetylgallic acid (m. p. 175°)[7] was methylated in the presence of an excess of piperidine; yield, 0.8 g.; m. p. 169°, with slight evolution of carbon dioxide.

Anal. Subs., 4.017 mg.: AgI, 13.303 mg. Calcd. for $C_{10}H_{12}O_5$: OCH_3, 43.86. Found: OCH_3, 43.72.

Summary

A method is described for the replacement of acetyl groups by methyl groups, using diazomethane and piperidine.

BRISTOL, ENGLAND

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

LOCAL ANESTHETICS DERIVED FROM QUINOLINE AND ISOQUINOLINE

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

RECEIVED JUNE 23, 1930 PUBLISHED OCTOBER 6, 1930

Several previous communications[1] from this Laboratory have described the preparation of substituted piperidino-alkyl benzoates and substituted piperidino-alkyl cinnamates. Since these compounds possessed local anesthetic action, some of them to a marked degree, it seemed desirable to prepare for pharmacological study a series of hydroquinolino-alkyl benzoates in which the nitrogen, instead of being a member of a piperidine ring, is incorporated in a bicyclic structure such as that present in certain of the reduced forms of quinoline and isoquinoline. It seemed of par-

[5] Bergmann and Dongschat, *Ber.*, **52**, 179 (1919).

[6] Liebermann and Lindenbaum, *ibid.*, 41, 1613 (1908).

[7] Fischer, Bergmann and Lipschitz, *ibid.*, 51, 53 (1918), give m. p. 171–172° (corr.) for triacetylgallic acid.

[1] McElvain, THIS JOURNAL, **49**, 2835 (1927); Thayer and McElvain, *ibid.*, **50**, 3348 (1928); Bailey and McElvain, *ibid.*, **52**, 1633 (1930); Bailey and McElvain, *ibid.*, **52**, 2007 (1930).

ticular interest to ascertain whether or not there would be any marked pharmacological difference in the anesthetics derived from the stereoisomeric decahydroquinolines. Also an anesthetic derived from tetrahydroisoquinoline would possess a phenylene-dialkylamino structure and would be an interesting type to compare with those anesthetics containing phenyl alkyl groups which have been previously reported[2] as being unusually potent pharmacologically.

This paper describes the preparation, properties and pharmacological action of the hydrochlorides of the following amino esters: (1) β-tetrahydroquinolino-ethyl benzoate, (2) γ-tetrahydroquinolinopropyl benzoate, (3) *trans*-β-decahydroquinolino-ethyl benzoate, (4) *trans*-γ-decahydroquinolinopropyl benzoate, (5) *cis*-β-decahydroquinolino-ethyl benzoate, (6) *cis*-γ-decahydroquinolinopropyl benzoate, (7) γ-tetrahydroisoquinolinopropyl benzoate. These compounds were prepared by the condensation of the corresponding secondary amines with β-chloro-ethyl benzoate and γ-chloropropyl benzoate.

Tetrahydroquinoline was prepared by the catalytic reduction of quinoline. The *cis* and *trans* isomers of decahydroquinoline were prepared by the complete catalytic reduction of quinoline; the reduced material obtained in this manner was separated into the pure isomeric forms by a modification of the method of Hückel and Stepf.[3] The literature contains numerous references to the *trans* isomer (m. p. 48°)[4] but the existence of the *cis* isomer, which is a liquid at ordinary temperatures, had not been demonstrated previous to the work of Hückel and Stepf.

Tetrahydroisoquinoline was prepared by the method of Pictet and Spengler,[5] which involves the condensation of methylal and β-phenylethylamine in concentrated hydrochloric acid solution. The tetrahydroisoquinoline so obtained was not entirely pure, and it was observed that the strength of the hydrochloric acid used in the condensation plays an important part in determining the course of the reaction. In dilute acid solution methyl-β-phenylethylamine, instead of tetrahydroisoquinoline, is formed.

Experimental

Tetrahydroquinoline.—This compound was prepared by the catalytic reduction of quinoline, using a nickel catalyst at a temperature of 150° and at pressures of 150–170 atmospheres of hydrogen.[6] The boiling point of the product was 122–124° (10 mm.)

[2] Thayer and McElvain, THIS JOURNAL, **49**, 2862 (1927); Bolyard and McElvain, *ibid.*, **51**, 922 (1929); Bailey and McElvain, *ibid.*, **52**, 1633 (1930).

[3] Hückel and Stepf, *Ann.*, **453**, 163 (1927).

[4] Bamberger and Lengfeld, *Ber.*, **23**, 1145 (1890); Ipatieff, *ibid.*, **41**, 992 (1908); Skita and Meyer, *ibid.*, **45**, 3593 (1912).

[5] Pictet and Spengler, *ibid.*, **44**, 2030 (1911).

[6] The reduction of quinoline was carried out by Mr. Howard Cramer under the direction of Professor Homer Adkins and will be described in detail by them in a forthcoming paper.

Trans- **and** *Cis-***decahydroquinoline.**—Quinoline was completely reduced catalytically, using a nickel catalyst at a temperature of 200° and at pressures of 150–200 atmospheres of hydrogen. The relative proportions of *cis* and *trans* isomers varied in different runs. By chilling with ice–salt mixture the *trans* isomer crystallized and, after filtering with suction and pressing on a clay plate to remove adhering liquid, it melted at 48°.[4] The hydrochloride melted at 278–279°; Hückel and Stepf report 275° as the melting point of this compound.

The crude *cis*-decahydroquinoline remaining after removal of the *trans* isomer was converted to the benzoyl derivative by treatment with benzoyl chloride and dilute alkali. Hückel and Stepf[3] recommended partial purification of the hydrochloride before preparation of the benzoyl derivative, but it was found that better yields were obtained by making the benzoyl derivative directly from the crude base. After two recrystallizations from ligroin (b. p. 90–150°) the material was pure, melting at 96°. From 97 g. of crude base there was obtained 45.3 g. of the pure benzoyl-*cis*-decahydroquinoline.

Continued refluxing with 15% sodium hydroxide solution did not hydrolyze benzoyl-*cis*-decahydroquinoline, but it was found that by refluxing with 20% hydrochloric acid, hydrolysis was complete after sixty to seventy hours. At the end of this time the solution was cooled, after which benzoic acid was filtered off and the filtrate was evaporated on a steam-bath. The free base was liberated with 10% sodium hydroxide and extracted with ether. After drying the ethereal solution with sodium sulfate, the ether was evaporated and the amine was distilled under diminished pressure. By such treatment of 45 g. of benzoyl-*cis*-decahydroquinoline there was obtained 21.9 g. (85% of the theoretical) of *cis*-decahydroquinoline which boiled at 83–83.5° (16 mm.). The hydrochloride was prepared and found to melt at 222–224°; Hückel and Stepf reported 226° as the melting point of this compound.

Tetrahydroisoquinoline.—This compound was prepared by a modification of the method of Pictet and Spengler.[5] To a solution of 20 g. of β-phenylethylamine (b. p. 85–88° at 14 mm.) in 120 cc. of concentrated hydrochloric acid, 20 g. of methylal (b. p 41–45°) was slowly added through a separatory funnel. During the addition the reaction mixture was warmed on a steam-bath. Heating was continued for five hours, after which the solution was evaporated to dryness. The residue was dissolved in 90 cc. of water; to this solution, cooled to 7°, was added a solution of 23 g. of sodium nitrite in 40 cc. of water. The mixture was warmed and extracted with ether. After evaporation of the ether, the nitrosamine was reduced with 33 g. of zinc and 90 cc. of concentrated hydrochloric acid. The mixture was made alkaline with 60 g. of sodium hydroxide and steam distilled until all of the oily layer had passed over. The distillate was acidified and evaporated to dryness; the residue was made alkaline, and the free base was extracted with ether. After drying with sodium sulfate and evaporating the ether, the amine was distilled. The yields were 2.2–3 g. (10–14% of the theoretical) of material boiling at 220–233°. The picrate after two recrystallizations from alcohol melted at 199–200°; Helfer[7] reported 197–198° as the melting point of tetrahydroisoquinoline picrate. The hydrochloride after five recrystallizations from alcohol–ether melted at 194–195°; Helfer[7] reported 195–196°.

In an attempt to improve the yield of tetrahydroisoquinoline a run was made using 120 cc. of dilute hydrochloric acid containing only slightly more hydrogen chloride than the amount required to dissolve the β-phenylethylamine. The time of heating was seventeen hours; the rest of the procedure was that described above; 3 g. (14%) of material boiling at 88–95° (16 mm.) was obtained. This was shown to be methyl-β-

[7] Helfer, *Helv. Chim. Acta*, **6**, 794 (1923).

phenylethylamine.[8] The picrate was prepared and found to melt at 140–141°;[9] a mixed melting point with an authentic specimen of methyl-β-phenylethylamine picrate showed no depression.

Hydroquinolino-alkyl Benzoates.—These compounds were prepared by the general procedure of heating two moles of the secondary amine with one mole of β-chloro-ethyl benzoate or γ-chloropropyl benzoate. In the case of the decahydroquinolines a temperature of 140–150° for two to three hours was sufficient to cause a satisfactory reaction; in the case of tetrahydroquinoline and tetrahydroisoquinoline a somewhat higher temperature (190–200°) for the same period of time was required. The tertiary amino esters were isolated as the hydrochlorides by the procedure commonly employed for compounds of this type.[1] These hydrochlorides are summarized in Table I.

In the case of *trans*-β-decahydroquinolino-ethyl benzoate hydrochloride two apparently isomeric substances appeared to be formed. One of them was obtained pure, while the other could not be caused to attain a constant melting point. Theoretical chlorine analyses for samples melting over a wide temperature range was the evidence upon which the formation of isomers was based.

TABLE I

HYDROQUINOLINO-ALKYL BENZOATE HYDROCHLORIDES

	Hydroquinolino-alkyl group	M. p., °C.	Analyses, Cl, % Calcd.	Found
1	β-Tetrahydroquinolino-ethyl[a]	129–131	11.18	11.18
2	γ-Tetrahydroquinolinopropyl[a]	122–124	10.71	11.04
3	*Trans*-β-decahydroquinolino-ethyl[b]	155–157	10.97	10.87
4	*Trans*-γ-decahydroquinolinopropyl	171–173	10.52	10.51
5	*Cis*-β-decahydroquinolino-ethyl[b]	159–160	10.97	10.82
6	*Cis*-γ-decahydroquinolinopropyl	155–156.5	10.52	10.38
7	γ-Tetrahydroisoquinolinopropyl[c]	188–189	10.71	10.64

[a] These hydrochlorides are sufficiently hydrolyzed in aqueous solution to cause oily globules of free base to appear. [b] A mixed melting point on Nos. 3 and 5 was 135–141°. [c] The corresponding propyl benzoate derived from methyl-β-phenylethylamine melts at 128°; this compound has been prepared by Mr. A. C. Cope in this Laboratory and will be described in a future communication.

Pharmacological Report.—These compounds are being studied pharmacologically by Mr. Charles L. Rose of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. Table II contains a brief summary of this work. Each compound is designated by the number which is associated with it in Table I. Anesthetic efficiencies were determined by application of a 2% solution of the hydrochloride to the rabbit's cornea and noting the duration of anesthesia and also by the method of infiltration anesthesia, which involves the intracutaneous injection of a 1% solution of the hydrochloride into the guinea pig. Subcutaneous toxicity to white mice and intravenous toxicity to white rats were determined; these values are reported in terms of the median lethal dose (M. L. D.), which is that amount of material necessary to cause the death

[8] *Cf.* Decker and Becker, *Ber.*, **45**, 2404 (1912); Decker and Becker, *Ann.*, **395**, 342 (1913).

[9] Johnson and Guest, *Am. Chem. J.*, **42**, 340 (1909).

of 50% of a large number of animals.[10] The values for cocaine and procaine are included in Table II for comparison.

β-Tetrahydroquinolino-ethyl benzoate (1) and γ-tetrahydroquinolinopropyl benzoate (2) were hydrolyzed to such an extent that a solution could not be prepared for pharmacological tests. Hence there are no data for these compounds in Table II.

TABLE II

PHARMACOLOGICAL DATA

Compound	Av. duration of anesthesia, min. Rabbit's cornea	Infiltration	Subcutaneous toxicity to white mice mg./kg. M. L. D.	No. of mice used	Intravenous toxicity to white rats mg./kg. M. L. D.	No. of rats used
3	5	36	1000	25	25	7
4	27	81	500	40	20	24
5	21	55	700	36	30	14
6	30	60	500	25	20	15
7	7	187	1600	31	40	10
Cocaine	29	..	150	..	17.5	..
Procaine	0	..	800	..	53	..

Discussion of the Pharmacological Data.—The decahydroquinolino-alkyl benzoates are in general more satisfactory anesthetics than cocaine, since the anesthetic efficiencies of three of them are equal, or nearly equal, to that of cocaine, while the toxicities are considerably less than that of cocaine. Compounds 4 and 6, which are geometric isomers, have quite similar properties. However, 3 and 5, which are also geometric isomers, differ from each other considerably—5, the *cis* compound, being more active than 3, its *trans* isomer, both as regards anesthetic action and toxicity.

γ-Tetrahydroisoquinolinopropyl benzoate[7] has quite a low toxicity combined with high anesthetic efficiency when measured by the infiltration method. However, when measured by the corneal method, the anesthetic efficiency is quite low. The compound contains a phenylene-dialkylamino structure, and would therefore be expected to be a rather powerful anesthetic on account of its structural relationship to those anesthetics containing phenyl alkyl groups.[2] It is reported as being highly irritating to the rabbit's cornea, and it is quite probable that it is this property rather than its structure, which causes the low corneal anesthesia value.

Summary

1. A series of hydroquinolino-alkyl benzoates has been prepared and described.

2. A discussion of the pharmacological properties of these compounds is given.

MADISON, WISCONSIN

[10] Rose, Coles and Thompson, *J. Lab. Clin. Med.*, **15**, 731 (1930).