salt was extracted with benzene, dried and distilled. Its specific rotation, however, was only +32.5° instead of the accepted value +38 to +39°. It appeared probable that some *dl*B*d*A salt had been formed and incompletely resolved by digestion with acetone. The amine was accordingly recombined with *d*-acid in acetone and the crystalline deposit was digested four more times with boiling acetone. The amine recovered from this salt was then about 80% of the amount calculated from the total *dl*-amine taken and the rotation was +38.3°. The amine recovered from the acetone extracts had a rotation of −32.6°.

In a further experiment impure *l*-α-phenylethylamine (3 g.) containing about 85% of the *l*-form was combined with *dl*-acid (8.1 g.) in acetone. By repeated digestion of the precipitate and concentration of the extracts there were obtained, in order, 3.6 g. $[\alpha]_D$ −148°, 1.6 g. $[\alpha]_D$ +12°, and a mother liquor having a high dextro rotation. The fractionation was not continued, but it is evident that the fractions are principally the *l*B*l*A, *dl*B*dl*A and *l*B*d*A salts, respectively, as would be predicted from the solubilities previously recorded.

***d*-α-*p*-Tolylethylamine-*dl*-6,6′-dinitrodiphenate.**—Equimolecular amounts of the *d*-amine and *dl*-acid were combined in water and the resulting salt fractionated from water and also from ethanol and acetone. No resolution occurred. The salt forms large diamond-shaped crystals from acetone, m. p. 211.5–213° (corr.).

***dl*-α-*p*-Tolylethylamine-*d*-6,6′-dinitrodiphenate.**—The salt was formed in acetone but was not resolved by repeated crystallization from this solvent. It melts at 197.5–198° (corr.) and is more soluble in acetone than the corresponding *d*B*dl*A salt.

***dl*-α-*p*-Methoxyphenylethylamine-*d*-6,6′-dinitrodiphenate.**—The salt was formed in water, from which it separated partly as an oil, partly as powdery crystals. The salt is extremely soluble in ethanol and acetone, from which it could not be crystallized.

Partial Resolution of *dl*-Fenchylamine.—Equimolecular amounts of the *dl*-amine and *d*-acid were combined in acetone. A large amount of a powdery solid separated. When this was heated with a large volume of fresh acetone it dissolved very slowly, but only about 25% of the total salt crystallized even when the solvent was evaporated to small volume. A satisfactory method of fractionation could not be devised. The acetone mother liquor was evaporated, the sirupy residue hydrolyzed with hydrochloric acid and the amine recovered as previously described for α-phenylethylamine. The rotation of this part of the amine was +4.2° instead of +24.9° reported for the pure *d*-amine.[8]

Summary

1. *dl*-6,6′-Dinitrodiphenic acid was prepared and resolved into both active forms by means of *d*- and *l*-α-phenylethylamine in acetone solution.

2. *dl*-α-Phenylethylamine was similarly resolved with *d*-6,6′-dinitrodiphenic acid, the *d*-amine being obtained pure. All five types of the isomeric salts are described.

3. Unsuccessful attempts were made to resolve *dl*-6,6′-dinitrodiphenic acid with *d*-α-*p*-tolylethylamine and to resolve *dl*-α-*p*-tolylethylamine and *dl*-α-*p*-methoxyphenylethylamine with the corresponding *d*-acid. *dl*-Fenchylamine was partially resolved.

(8) Wallach and Binz, *Ann.*, **276**, 317 (1893).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF HAWAII]

The Preparation of Chaulmoogra Derivatives. I. Substituted Amines and Amides

BY JOHN H. PAYNE, RICHARD WRENSHALL AND KATHARINE VAN H. DUKER[1]

Derivatives of chaulmoogric acid and hydnocarpic acid have been used for some years in the treatment of leprosy, the sodium salts and the ethyl esters having found most extensive application.[2] The irritating action of these compounds when injected has been recorded frequently as an objection to their use. Sodium salts are subject to marked hydrolysis with deposition of the insoluble acids and liberation of sodium hydroxide. Both the fatty acids and the ethyl esters are relatively slowly absorbed. It would appear reasonable to expect that compounds soluble in water and not readily undergoing hydrolysis would prove more satisfactory. In order to develop such properties several derivatives have been prepared by various investigators.[3]

From a theoretical standpoint the introduction of amino, substituted amino, hydroxyl, carboxyl, sulfonic or phosphoric acid groups into compounds of chaulmoogric acid should render them more soluble in most instances. Furthermore, the incorporation of structures of known and

(1) University of Hawaii Research Fellow.

(2) These papers, too numerous to cite here, have been recorded at various times in the literature, *e. g.*, see Hasseltine, U. S. Pub. Health Bull. No. 141, 1924; Report of Leonard Wood Memorial Conference on Leprosy, *Philippine J. Sci.*, **44**, 449–80 (1931); Tomb, *J. Trop. Med. Hyg.*, **36**, 170–178, 186–189, 201–207 (1933).

(3) These papers are again too numerous to cite here, *e. g.*, see Perkins, *Philippine J. Sci.*, **21**, 1 (1922); Dean, Wrenshall and Fujimoto, THIS JOURNAL, **47**, 403 (1925); Santiago and West, *Philippine J. Sci.*, **33**, 265 (1927); DeSantos and West, *ibid.*, **38**, 293, 445 (1929).

valuable physiological action should lead to compounds of decided pharmacological interest and possibilities. The preparation of some such compounds containing substituted amino and amido groups is herein described.

Experimental

Chaulmoogric and dihydrochaulmoogric acids were prepared from the freshly extracted oil of the seeds of *Taraktogenos Kurzii* by the methods of Dean and Wrenshall.[4] These were converted into the acid chlorides by treatment with phosphorus trichloride according to the method of Naegeli and Vogt-Markus.[5] The freshly prepared acid chlorides were used in the following preparations.

Chaulmoogrylcholine Iodide.—The method of Fourneau and Page[6] was modified, giving optimum results as follows: 210 g. of chaulmoogryl chloride was added slowly with constant stirring to 170 g. of anhydrous iodine-free ethylene iodohydrin cooled in an ice-bath. The mixture was allowed to stand for one and one-half hours and then poured into ice and water. β-Iodoethylchaulmoograte separated out as a creamy white solid. This was filtered off, washed several times with cold methyl alcohol, and dried *in vacuo*. The compound becomes a cream colored semi-solid at room temperature.

Twelve grams of the β-iodoethylchaulmoograte and 15 cc. of a 20% solution of anhydrous trimethylamine in anhydrous benzene were heated in a sealed tube in a water-bath at 100° for fifteen hours. The reaction mixture was washed twice with ether, the insoluble chaulmoogrylcholine iodide separated and dried *in vacuo*. A 70% yield of the crude compound was obtained. On crystallization twice from acetone containing a minimum of methyl alcohol, chaulmoogrylcholine iodide was obtained as an almost white powder. The compound decomposes before melting at a temperature of about 150°. It is very soluble in methyl and ethyl alcohols, and insoluble in ether and acetone. It is very slightly soluble in water giving a solution having a *p*H of 4.6.

Anal. Calcd. for $C_{23}H_{44}NO_2I$: N, 2.83; I, 25.78; iodine value, 51.38. Found: N, 2.80; I, 25.70; iodine value, 51.65.

Chaulmoogrylcholine Chloride.—Chaulmoogrylcholine chloride was obtained by shaking a methyl alcohol solution of the iodide with excess silver chloride. The resulting silver iodide was filtered off and the methyl alcohol removed *in vacuo*. Upon recrystallization from hot acetone, the chaulmoogrylcholine chloride was obtained as a white fine crystalline compound. It begins to soften and decomposes at about 65°. The compound is insoluble in ether, soluble in hot acetone, ethyl and methyl alcohols. It is very soluble in water, forming a soapy solution having a *p*H of 6.4 at a concentration of 5%. The water solution is not appreciably hydrolyzed upon standing.

Anal. Calcd. for $C_{23}H_{44}NO_2Cl$: N, 3.46; Cl, 8.79; iodine value, 62.2. Found: N, 3.48; Cl, 9.05; iodine value, 62.1.

Diiodochaulmoogrylcholine Iodide and Diiodochaulmoogrylcholine Chloride.—By using ethylene iodohydrin containing dissolved iodine, the procedure for the preparation of chaulmoogrylcholine iodide results in the formation of diiodochaulmoogrylcholine iodide. The compound crystallized from acetone containing a few drops of methyl alcohol as a light yellow powder which darkened on standing. It decomposes before melting at a temperature of about 210°. The compound is insoluble in water.

Anal. Calcd. for $C_{23}H_{44}NO_2I_2$: N, 1.87; iodine value, 0.0. Found: N, 2.05; iodine value, 0.0.

Diiodochaulmoogrylcholine chloride was obtained by shaking a methyl alcohol solution of the iodide with silver chloride. The chloride was crystallized from acetone and obtained as a white powder which turned yellow rapidly in the light. It becomes semi-solid at 54° and decomposes above 185°. It is slightly soluble in water, giving a *p*H of 6.8 in saturated solution.

Anal. Calcd. for $C_{23}H_{44}NO_2ClI_2$: N, 2.13; iodine value, 0.0. Found: N, 2.26; iodine value, 0.0.

TABLE I

Compound	Appearance	Yield, average, %	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
Chaulmoogryl *p*-phenetide	Lavender tinged plates	84	115	$C_{26}H_{41}NO_2$	3.50	3.37
Chaulmoogryl ethyl-*p*-aminobenzoate (chaulmoogryl benzocaine)	Colorless tabular prisms	32	94–95	$C_{27}H_{41}NO_3$	3.27	3.43
Dihydrochaulmoogranilide	Colorless needles	45	94	$C_{24}H_{39}NO$	3.83	4.01
Dihydrochaulmoogryl *p*-phenetide	Colorless needles	70	117	$C_{26}H_{43}NO_2$	4.49	4.41
Dihydrochaulmoogryl ethyl-*p*-phenetide	Pink tinged plates	40	120–121	$C_{25}H_{47}NO_2$	3.26	3.23

In the table are summarized the physical properties and analyses of five chaulmoogryl compounds prepared by the following general method. The chaulmoogryl chloride or the dihydrochaulmoogryl chloride was added slowly with constant stirring to the ice-cooled solution of the amino derivatives in anhydrous diethyl ether. The precipitate which formed immediately, or upon partial evaporation of the ether, was filtered off and treated with hot water to remove the hydrochloride. The air-dried residue was dissolved in 95% ethyl alcohol containing a small quantity of potassium hydroxide. The alcohol solution was then diluted with water, the precipitate filtered off and recrystallized several times from 95% ethyl alcohol until a constant melting point was obtained.

The pharmacological properties of these compounds are under study at the Pharmacological Laboratories of the University of California School of Medicine.

(4) Dean and Wrenshall, *U. S. Pub. Health Report*, **756**, 1395–1399 (1922).

(5) Naegeli and Vogt-Markus, *Helv. Chim. Acta*, **15**, 65 (1932).

(6) Fourneau and Page, *Bull. soc. chim.*, [4] **15**, 550 (1914).

Summary

The following derivatives of chaulmoogric acid have been prepared: chaulmoogrylcholine iodide, chaulmoogrylcholine chloride, diiodochaulmoogrylcholine iodide, diiodochaulmoogrylcholine chloride, chaulmoogryl *p*-phenetide, chaulmoogryl ethyl-*p*-aminobenzoate, dihydrochaulmoogranilide, dihydrochaulmoogryl *p*-phenetide, and dihydrochaulmoogryl ethyl-*p*-phenetide.

These compounds are of interest as possible antileprotic agents and are under clinical investigation.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF OKLAHOMA]

Derivatives of the Hydroxydiphenyls. II. Nitrogen and Halogen Derivatives of 4-Hydroxydiphenyl[1]

BY J. C. COLBERT, WYMAN MEIGS AND ARNOLD H. STUERKE

The Orientation of Chlorine Atoms in Mono- and Dichloro-4-hydroxydiphenyl.—The preparation of mono-, di- and trichloro-4-hydroxydiphenyl was reported in a recent paper[2] from this Laboratory. By analogy with similar work[3] involving bromine derivatives it was held that chlorine probably entered first the *ortho* position to hydroxyl, second the other *ortho* position and lastly the *p'* position. It has now been found possible to obtain partial confirmation of the orientation of the derivatives previously reported by preparing two isomeric dichloromononitro-4-hydroxydiphenyls. Since 5-nitro-4-hydroxydiphenyl upon reduction, acetylation and benzoylation undergoes the rearrangement described by Raiford[4] as being peculiar to *o*-aminophenols, the structure of the mononitro derivative of 4-hydroxydiphenyl may be considered as fixed. 5-Nitro-4-hydroxydiphenyl when completely chlorinated yields a dichloro derivative whose structure, assuming the normal directive influence of the groups already present, must be 5-nitro-3,-4'-dichloro-4-hydroxydiphenyl. The only isomer of this compound obtainable starting with 4-hydroxydiphenyl must be 3,5-dichloro-4'-nitro-4-hydroxydiphenyl. Since this latter compound was prepared by the nitration of dichloro-4-hydroxydiphenyl the chlorine atoms in the dichloro derivative must occupy the two *ortho* positions. Since the same dichloro derivative results either from long chlorination of 4-hydroxydiphenyl or by chlorination of monochloro-4-hydroxydiphenyl, the monochloro-4-hydroxydiphenyl must have chlorine in the 3 position. Upon nitration 3-chloro-4-hydroxydiphenyl yields both mono and dinitro derivatives. The mononitro derivative yields the same dichloro derivative as 5-nitro-4-hydroxydiphenyl when chlorinated and is therefore to be considered 3-chloro-5-nitro-4-hydroxydiphenyl and the dinitro derivative 5,4'-dinitro-3-chloro-4-hydroxydiphenyl. 3-Chloro-5-nitro-4-hydroxydiphenyl may be readily reduced and brominates easily with the formation of 3-chloro-4'-bromo-5-nitro-4-hydroxydiphenyl. This evidence is summarized in Fig. 1.

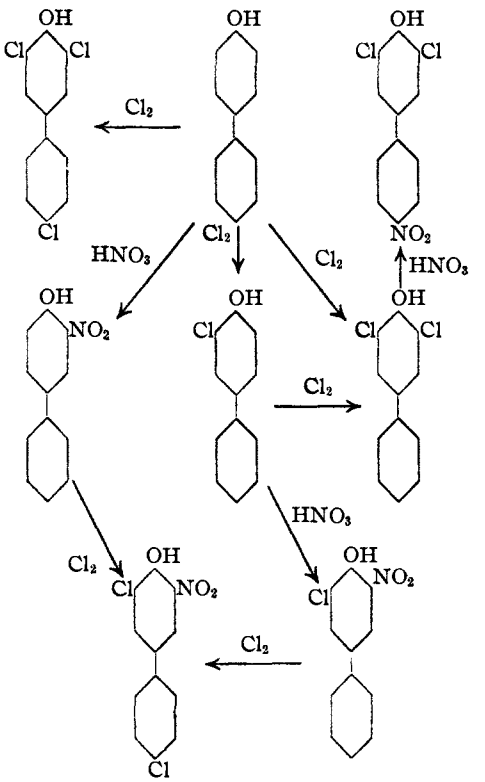

Fig. 1.—Experimental evidence for the orientation of chlorine in mono- and dichloro-4-hydroxydiphenyl.

(1) The work of Arnold H. Stuerke was financed by means of a C. W. A. grant made to the University for research purposes.

(2) Colbert and others, THIS JOURNAL, **56**, 202 (1934).

(3) Bell and Robinson, *J. Chem. Soc.*, **130**, 1128 (1927).

(4) Raiford and Colbert, THIS JOURNAL, **47**, 1127 (1925).