TABLE I

ALKYLATED ARYLS OBTAINED

Alcohol used	Aromatic hydrocarbon used	Mono-alkylated aryl compound formed	Yield, based on alcohol, %	B. p., °C. (760 mm.)	$n^{20}D$	Yield of disubstituted residue based on alcohol, %
Isopropyl	Benzene	Cumene	40	150–152	1.491	18–20
t-Butyl	Benzene	*t*-Butylbenzene	25–35	169	1.492	30[a]
Isopropyl	Toluene	Cymene[b]	43	175–178	1.493	14
t-Butyl	Chlorobenzene	*p*-*t*-Butylchlorobenzene[c]	20–25	214–216	1.509	...
Benzyl	Toluene	Phenyl *p*-tolyl methane	28	276–281	1.572	18

[a] *p*-Di-*t*-butylbenzene, $C_{14}H_{22}$, m. p. 76° after recrystallization from diethyl ether. Calcd.: C, 88.35; H, 11.65. Found: C, 88.70; H, 11.00. [b] Probably a mixture of the *ortho* and *para* isomers. [c] Calcd.: Cl, 21.02. Found: Cl, 21.0.

Experimental

General Procedure.—A mixture of 1 mole of an alcohol and 3 moles of an aromatic hydrocarbon is placed in a 1-liter, 3-necked, round-bottom flask equipped with stirrer, thermometer, dropping funnel and a gas escape tube, terminating in a calcium chloride trap. The temperature of the reaction mixture is lowered to about 0° and 1.1 mole of chlorosulfonic acid is added dropwise to the reaction mixture, with stirring, at a rate such that, with moderate external cooling of the reaction vessel, the temperature does not exceed 10°. After all of the chlorosulfonic acid is added (thirty to sixty min.), the entire reaction mixture is stirred at 5–10° for three hours. The product is poured into an ice-water mixture and the organic layer washed twice with water. After drying over calcium chloride, the organic layer is fractionally distilled.

Summary

The alkylation of benzene and some of its derivatives with secondary and tertiary monohydric aliphatic alcohols in the presence of chlorosulfonic acid has been described. The presently preferred method consists of the slow addition of one mole of chlorosulfonic acid to a mixture of one mole of the alcohol and three moles of the aromatic hydrocarbon at about 10°.

Primary alcohols, with the exception of benzyl alcohol, did not undergo the condensation.

EDGEWOOD ARSENAL, MARYLAND
RECEIVED OCTOBER 22, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF RALPH L. EVANS ASSOCIATES AND THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

N-Oxides of Atabrine and Plasmoquine

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The prospects of discovering improved chemotherapeutic agents among heterocyclic N-oxides were supported by two previous findings.

One was the analogy to certain alkaloids and observations that the conversion of tertiary bases into the corresponding N-oxides brought about a considerable reduction of the toxicity of such bases. Thus morphine N-oxide was found not to be habit-forming.[1,2,3,4] The lethal dose of atropine N-oxide hydrochloride is 4.7 times that of atropine sulfate. Two-tenths g./kilo is not fatal to dogs.[5,6] The action of scopolamine N-oxide is equal to that of scopolamine but the former compound is considerably less toxic.[5,7] Strychnine N-oxide was compared with strychnine, and the minimum lethal doses for white rats are given as 0.000385 g./kg. for strychnine and 0.02 g. for strychnine N-oxide.[8]

The second incentive for this investigation was the more recent work of Clemo and McIlwain,[9] who have identified the bacterial pigment, *iodinine*, as a dihydroxyphenazine di-N-oxide. McIlwain[10] has also prepared several heterocyclic N-oxides which were found to possess antibacterial properties approaching those of iodinine.

We were primarily interested in the effect of N-oxidation on the plasmodicidal action of the two antimalarial drugs, atabrine and plasmoquine. In both instances we hoped to decrease the toxicity and thus render more favorable the chemotherapeutic index. This outcome appeared especially promising in the case of plasmoquine which, although it is one of the few gametocidal drugs known, is not so widely used as atabrine on account of its greater toxicity and the consequent increased risk.

Preliminary tests of the di-N-oxides of atabrine and plasmoquine as conducted through the Survey of Antimalarial Drugs, have shown that the new compounds are considerably less toxic than

(1) Polonovski, Nayrac and Tiprez, *Bull. acad. med.*, [3] **103**, 174 (1930).

(2) Anton, Theiss and Weissig, *Deut. med. Wochschr.*, **61**, 1195 (1935).

(3) Polonovski, *J. pharm. chim.*, [8] **11**, 429 (1930).

(4) Krueger and Eddy, "Pharmacology of Opium Alkaloids," U. S. Public Health Service, 1943, p. 988.

(5) Polonovski, *Compt. rend.*, **181**, 887 (1925); *Ber. ges. Physiol.*, **58**, 405 (1931).

(6) Houben, "Fortschritte der Heilstoffchemie," Vol. III, 184.

(7) Houben, *ibid.*, III, 208.

(8) Gurmendi, *Bol. soc. quim. Peru*, **4**, 270 (1938).

(9) Clemo and McIlwain, *J. Chem. Soc.*, 479 (1938).

(10) McIlwain, *ibid.*, 322 (1943).

the parent drugs, whereas, when tested on parasitized ducks, their antimalarial potencies were found to be one-half and one-eighth those of atabrine and plasmoquine, respectively.[11] A detailed account concerning the assays of these compounds will be found in a forthcoming monograph "A Survey of Antimalarial Drugs, 1941–1945," edited by F. Y. Wiselogle under the auspices of the National Research Council.

Commercially available atabrine dihydrochloride and plasmoquine methylene-*bis*-hydroxynaphthoate (Winthrop Chemical Co.) were used as starting materials. The free bases were isolated by the usual method and oxidized in aqueous medium at 0°, using an excess of 3% hydrogen peroxide. It was necessary to work under mild conditions in order to prevent extensive decomposition and side reactions, such as the hydrolytic scission of the atabrine molecule into 3-chloro-7-methoxyacridone and diethylaminoisopentylamine. As the two di-N-oxides are water-soluble, the reaction is completed when all base has gone into solution in the dilute hydrogen peroxide. It was found advisable to evaporate the aqueous solutions under reduced pressure and thus to eliminate the excess of peroxide before attempting to isolate the products. In the case of atabrine di-N-oxide the dihydrochloride was readily precipitated in crystalline form by an excess of hydrochloric acid. Difficulties were encountered with plasmoquine di-N-oxide as this new base forms low-melting salts which could not readily be purified. The methylene-*bis*-2-hydroxy-3-naphthoate, however, is sparingly soluble in water and could be crystallized from dilute acetone.

Experimental

Atabrine Base.—Twelve grams of commercial atabrine dihydrochloride was dissolved in 240 ml. of water with slight warming and an excess of 40% aqueous sodium hydroxide was added. The alkaline mixture was cooled to room temperature and extracted exhaustively with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The yield was 10 g. (almost quantitative); m. p. 84° (lit.[12] 86–88°).

Atabrine Di-N-oxide.—Ten grams of atabrine base was suspended in 100 ml. of 3% aqueous hydrogen peroxide solution and the suspension was kept in a refrigerator for six days with frequent shaking. As the oxidation proceeded, the base dissolved gradually to form a yellow-brown solution. This was evaporated to dryness at 15 mm. pressure and a bath temperature below 40°. The residue consisted of crystalline atabrine di-N-oxide of m. p. 120°, dec. It is soluble in water, alcohol, acetone and chloroform; insoluble in ligroin.

Atabrine Di-N-oxide Dihydrochloride.—The atabrine di-N-oxide was dissolved in 200 ml. of water and 100 cc. of 3 *N* hydrochloric acid was added. The yellow microcrystalline precipitate was isolated in almost quantitative yield. When recrystallized from dilute hydrochloric acid, it formed short yellow needles; m. p. 184–186°, dec.

Anal. Calcd. for $C_{23}H_{32}O_3N_3Cl_3$ (mol. wt., 504.5): C, 54.7; H, 6.3; Cl, 21.1; N, 8.3. Found: C, 54.3; H, 6.7; Cl, 21.0; N, 8.8.

Atabrine Di-N-oxide Dipicrate.—An excess of alcoholic picric acid solution was added to the solution of atabrine di-N-oxide base in alcohol. The picrate formed on standing at 0° and was recrystallized from methylcellosolve plus water. Orange red prisms were formed; m. p. 185°.

Anal. Calcd. for $C_{23}H_{30}O_3N_3Cl\cdot 2C_6H_3O_7N_3$ (mol. wt., 889.5): N, 14.16. Found: N, 14.10.

Plasmoquine Base.—Nine grams of commercial plasmoquine methylene-*bis*-hydroxynaphthoate was triturated with 190 ml. of 10% aqueous sodium hydroxide solution. The alkaline mixture was extracted with ether to exhaustion. The combined ether extracts were dried over anhydrous sodium sulfate and the ether evaporated on a steam-bath. The residual plasmoquine base was a viscous light brown oil, weighing 4 g. (quantitative yield). The picrate melts at 120–125° (lit. 128–137°[13]).

Plasmoquine Di-N-oxide.—Two and nine-tenths grams of plasmoquine base was suspended in 38 ml. of 3% hydrogen peroxide and the mixture was kept in the refrigerator with frequent shaking until all base had gone into solution. This solution was evaporated under reduced pressure at 35° until a viscous residue of the di-N-oxide was obtained. This is soluble in water, alcohol and dilute mineral acids; less soluble in ether and ethyl acetate.

Dipicrate.—An alcoholic solution of picric acid was added to the alcoholic solution of the base. The precipitate was recrystallized from alcohol; m. p. 70°.

Chloroplatinate.—To the solution of the base in dilute hydrochloric acid was added a 5% solution of chloroplatinic acid. The precipitate was recrystallized from ethyl alcohol; m. p. 190°.

Methylene-bis-salicylate.—A solution of the di-N-oxide in the calculated amount of 3 *N* hydrochloric acid was mixed with an equimolecular amount of disodium methylene-*bis*-salicylate in aqueous solution. The precipitated salt was filtered and washed with water; m. p. 55–57°.

Methylene-bis-2-hydroxy-3-naphthoate.—To a solution of plasmoquine di-N-oxide dihydrochloride in water (prepared as above) was added an equimolecular amount of disodium-methylene-*bis*-2-hydroxy-3-naphthoic acid in aqueous solution. The resulting precipitate was filtered and washed with water. A pure sample was obtained by triturating the crude product with acetone and reprecipitating the salt with water from its acetone solution. Small yellow prisms were formed; m. p. 278–280°, dec.

Anal. Calcd. for $C_{19}H_{29}O_3N_2\cdot C_{23}H_{16}O_6$ (mol. wt. 735.5): C, 68.49; H, 6.18. Found: C, 68.71; H, 6.33.

Acknowledgment.—The authors are indebted to the management of Ralph L. Evans Associates for permission to publish these results and to Mildred Howson for valuable assistance in the experimental work.

Summary

The di-N-oxides of atabrine and plasmoquine and some of their derivatives have been prepared. The detoxification of tertiary bases through N-oxidation is discussed.

NEW YORK 17, NEW YORK
RECEIVED SEPTEMBER 26, 1945

(11) The Antimalarial Survey then reported that they completed mouse toxicity tests on our atabrine di-N-oxide and the tests show no significant difference in toxicity from atabrine dihydrochloride dihydrate except a 10% greater voluntary food intake at the same diet concentrations.

(12) Heilbron, "Dictionary of Organic Compounds."

(13) Tchitchibabine and Hoffmann, *Compt. rend.*, **208**, 525 (1939).