74°, d^{20} 1.0141 and $n^{20}D$ 1.5127. *Anal.*[10] Calcd. for $C_9H_{11}Cl$: C, 69.90; H, 7.17; Cl, 22.93. Observed: C, 71.66; H, 8.11; Cl, 22.4. Oxidation with chromic acid in glacial acetic acid solution yielded a small quantity of acid, m. p. 230–235°. The physical constants checked fairly closely those of *p*-chlorocumene prepared by a boron fluoride alkylation method in this Laboratory,[11] but the discrepancies seemed to indicate that a mixture of isomeric chlorocumenes were present, among which the para predominated.

A higher-boiling chlorocumene fraction, b. r. 125–126 (100 mm.), was observed to have d^{20} 0.9816 and $n^{20}D$ 1.5075. The acid derivative was prepared and purified by sublimation, m. p. 239–241°, checking the literature for *p*-chlorobenzoic acid. Diisopropylbenzene impurities probably caused the depression of specific gravity and refractive index values.

(10) The microanalyses were carried out by Miss L. Baker and Miss L. May in the Laboratories of Columbia University.

(11) Vermillion and Hill, THIS JOURNAL, **67**, 2209 (1945).

To determine whether xylenes[8] were formed, a 2-g. sample of the refractionated cumene digestion products was used in an attempt to prepare a derivative by the method of Baril and Hauber.[12] No xylene picrates were obtained and 98% of the picric acid was recovered unchanged.

Summary

The method of alkylation by transfer of alkyl groups has been applied successfully to the alkylation of monochlorobenzene by transfer of isopropyl groups from cumene, in the presence of aluminum chloride. The para isomer has been shown to be present among the chlorocumenes thus prepared.

(12) Baril and Hauber, *ibid.*, **53**, 1087 (1931).

NEW BRUNSWICK, NEW JERSEY
RECEIVED AUGUST 22, 1945

[CONTRIBUTION FROM THE C. W. S. TECHNICAL COMMAND, EDGEWOOD ARSENAL]

Condensation of Aliphatic Alcohols with Aryl Hydrocarbons in the Presence of Chlorosulfonic Acid[1]

BY WALTER H. C. RUEGGEBERG,[2] MERCHANT L. CUSHING[3] AND WALTER A. COOK[4]

The alkylation of benzene and some of its derivatives with aliphatic alcohols under the catalytic influence of sulfuric acid,[5] boron trifluoride,[6] mixed catalysts containing boron trifluoride,[7] hydrogen fluoride[8] and aluminum chloride[9] has been previously reported. Although the use of halosulfonic acids has not been previously described for this type of condensation, both chlorosulfonic acid[10] and fluorosulfonic acid[11] have been employed by the petroleum industries as alkylation catalysts in reactions between a saturated and an olefinic hydrocarbon.

In connection with the insecticide program conducted by the Chemical Warfare Service during the war, it was found that chlorosulfonic acid is a good condensing agent for the synthesis of 1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane (DDT) from chloral hydrate and chlorobenzene.[12]

Furthermore, the behavior of chlorosulfonic acid in the condensation between the above named reagents is believed to throw some light on the mechanism by which this condensation takes place. The proposed over-all mechanism involves the formation of an alkyl hydrogen sulfate which undergoes condensation with the aromatic hydrocarbon. In the case of the DDT type compound, this scheme is postulated to consist of the following reactions

$$CCl_3CH(OH)_2 + ClSO_3H \longrightarrow CCl_3CH(OH)OSO_2OH + HCl$$

$$CCl_3CH(OH)OSO_2OH + RH \longrightarrow CCl_3CH(OH)R + H_2SO_4$$

$$CCl_3CH(OH)R + ClSO_3H \longrightarrow CCl_3CH(OSO_2OH)R + HCl$$

$$CCl_3CH(OSO_2OH)R + RH \longrightarrow CCl_3CHR_2 + H_2SO_4$$

R = aromatic nucleus

In view of these facts, it appeared worth while to extend this condensation to monohydric alcohols with the aim of preparing alkylated benzenes directly. It was found that secondary and tertiary aliphatic alcohols undergo the desired condensation readily, while primary alcohols, except benzyl alcohol, are extremely sluggish, producing only a trace of product under conditions identical with those used for the secondary and tertiary alcohols. The results obtained are given in Table I.

An attempt to prepare bis-(2-phenylethyl) sulfide from thiodiglycol and benzene resulted in the formation of much mustard gas, bis-(2-chloroethyl) sulfide.

Because of the urgency of more important war research and development problems, this method of alkylation has by no means been fully explored. It is our aim, however, to point out at this time the nature of the reaction and the ease with which alkylated benzenes can be prepared from alcohols and aryl hydrocarbons in the presence of chlorosulfonic acid. The method is generally applicable to other halosulfonic acids.

(1) Published with the permission of the Chief, Chemical Warfare Service.

(2) Captain, C. W. S., Army of the United States.

(3) Captain, C. W. S., Army of the United States.

(4) Present address: University of Akron, Akron, Ohio.

(5) Meyer and Bernhauer, *Monatsh.*, **53-54**, 721 (1929).

(6) McKenna and Sowa, THIS JOURNAL, **59**, 470 (1937).

(7) Toussaint and Hennion, *ibid.*, **62**, 1145 (1940); Welch and Hennion, *ibid.*, **63**, 2603 (1941).

(8) Simons and Archer, *ibid.*, **62**, 1623 (1940).

(9) Suter and Ruddy, *ibid.*, **65**, 762 (1943).

(10) Vesterdal, U. S. Patent 2,282,505; *C. A.*, **36**, 5832 (1942).

(11) Ipatieff and Linn, U. S. Patent 2,366,731; *C. A.*, **39**, 2642 (1945).

(12) Rueggeberg, Cook, Dawson, Wearn and Mitchell, report on file at Edgewood Arsenal.

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

BY FRED LINSKER AND MARSTON TAYLOR BOGERT

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).