ward direction indicates that the reaction is considerably more rapid than the rates we observed for 12.

Acknowledgment.—We express our appreciation to the Research Corporation for financial aid during most of the time this work was in progress.

EAST LANSING, MICHIGAN

[CONTRIBUTION OF THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Inhibition of Phenol Alkylations by Ethers. Kinetic Evidence for Phenol–Ether Complexes

BY HAROLD HART, FRANK A. CASSIS AND JOHN J. BORDEAUX

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The nuclear alkylation of phenol by *t*-butyl chloride is inhibited by dioxane, the decrease in reaction rate being proportional to the concentration of dioxane. The inhibition can be quantitatively accommodated by assuming that a hydrogen-bonded complex of 2:1 phenol:dioxane is formed, and that phenol so bound cannot participate in the alkylation reaction. The same explanation fits the data for tetrahydropyran if a 1:1 complex is assumed. The availability of the phenolic hydroxyl, presumably for solvating the halogen of the alkyl halide, thus appears significant in the alkylation reaction.

It has been observed[1] that the nuclear alkylation of phenol by *t*-butyl chloride (equation 1) is prevented when the phenol

$$t\text{-}C_4H_9Cl + C_6H_5OH \longrightarrow t\text{-}C_4H_9\text{—}C_6H_4\text{—}OH + HCl \quad (1)$$

contains about 21 mole per cent. of dioxane. An equivalent amount of *p*-xylene, which has about the same dielectric constant as dioxane, causes only the decrease in rate expected from dilution of the reactants. It was the purpose of the present work to examine this inhibition in more detail. Accordingly, the rate of the alkylation reaction was determined with several different concentrations of dioxane, and of tetrahydropyran in the reaction mixture.

Experimental

Materials.—Phenol and *t*-butyl chloride were purified as described previously.[1] Dioxane was purified according to the procedure of Fieser.[2] Tetrahydropyran was prepared by the catalytic hydrogenation of du Pont dihydropyran over Raney nickel at low pressure.

Apparatus.—The apparatus and rate measurement procedure already have been described.[1,3]

Results

The reaction was followed, as in earlier work, by the rate of evolution of hydrogen chloride with time, a series of time *vs.* pressure readings being obtained. Since phenol was used in excess in all of these experiments, and since the number of moles of hydrogen chloride generated was small compared with the total moles of phenol,[3] the reaction followed pseudo-first-order kinetics

$$\text{rate} = k(t\text{-butyl chloride})$$

Plots of log $(p_t - p)$ (which is equivalent to the concentration of unreacted halide) against t yielded straight lines,[4] from the slopes of which k was calculated. Some of these plots are shown in Fig. 1. A summary of the data for pertinent experiments is given in Table I.

The first two experiments were performed to furnish standard conditions for the reaction without any diluent added. The results agree closely with those previously obtained.[1] Experiments 3–7 show the effect of increasing amounts of dioxane. At a mole percentage (dioxane in phenol–dioxane mixture) of only 14%, the apparent rate constant is reduced to about 3% of the value without added dioxane, clearly showing the marked inhibition by dioxane. Experiments 7–9 show that tetrahydropyran also exhibits this effect, although to a lesser extent, a similar concentration (14 mole per cent.) causing a decrease to 13% of the value without added tetrahydropyran. For comparison, one run (no. 10) was made with *p*-xylene. The effect is even less, the rate constant only being reduced to 36% of the value for an undiluted run. These effects are discussed in more detail below.

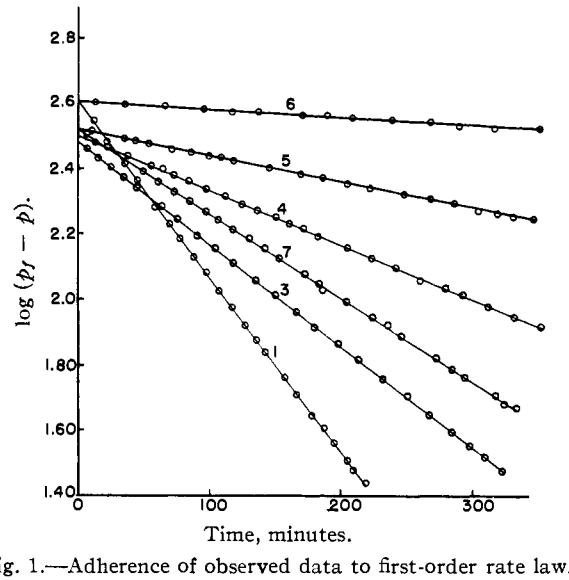


Fig. 1.—Adherence of observed data to first-order rate law.

Discussion

It is clear from the data that ethers are more effective at decreasing the alkylation rate than is *p*-xylene. We assume, therefore, that the role of *p*-xylene is principally one of a diluent, and that the observed decrease in reaction rate is due to a decrease in the concentration of reactants (particularly the phenol). It was shown previously[1] that

(1) H. Hart and J. H. Simons, THIS JOURNAL, **71**, 345 (1949).

(2) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Inc, New York, N. Y., 1941, p. 368.

(3) H. Hart and F. A. Cassis, THIS JOURNAL, **76**, 1634 (1954).

(4) The symbols have the same meaning as in previous papers (ref. 1 and 3).

TABLE I

KINETIC DATA FOR THE ALKYLATION OF PHENOL IN THE PRESENCE OF OXYGENATED COMPOUNDS

Expt.	*t*-BuCl, mole	Phenol, mole	Diluent,[b] mole	*M* of phenol[a]	p_f, mm.	P_0, mm.	$t_{1/2}$, min.[c]
1	0.01112	0.2156	.....	10.55	506.2	107.8	55.2
2	.009881	.2165	.....	10.61	499.7	104.5	53.1
3	.009150	.2120	0.006082 D	10.28	401.2	98.1	96.7
4	.01071	.2166	.01347 D	9.90	419.4	100.8	178.6
5	.01050	.2123	.02405 D	9.46	413.2	95.0	457.8
6	.01167	.2223	.03722 D	9.08	501.4	100.2	1497.3
7	.01129	.2164	.01221 P	9.86	434.3	106.1	119.0
8	.01129	.2091	.02422 P	9.38	432.0	103.6	268.8
9	.01140	.2142	.03472 P	9.06	390.0	132.0	423.7
10	.011575	.2133	.03248 X	9.00	375.1	97.8	146.1

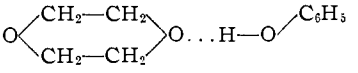
[a] These values were calculated on the basis that the added oxygenate acts only as a diluent. [b] Meaning of symbols used: D = 1,4-dioxane; P = tetrahydropyran; X = *p*-xylene. [c] These values were calculated from the first-order rate constants in the usual manner.

when phenol is the solvent, this reaction is polymolecular in phenol, the order being approximately 6. This figure also can be derived from experiment 10, using the equation[1]

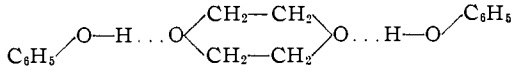
$$t_{1/2}/t_{1/2}^{\circ} = (M^{\circ}/M)^n \qquad (2)$$

in which $t_{1/2}$ refers to half-times of reaction, M is the molarity of the phenol, the superscripts refer to the reaction in pure phenol, the values without superscripts refer to the reaction with diluent present, and n is the order of the reaction with respect to phenol. Substituting data for the average of experiments 1 and 2, and for experiment 10, we get $n = 6$. For evaluating the role of the dioxane, this value need not be known more precisely, as long as the same value is used in all the calculations.

There are at least three assumptions which may be made concerning the function of the dioxane. It may serve only to dilute the reactants, or it may form complexes with the phenol, *via* hydrogen bonding, such complexes preventing phenol from participating in the alkylation reaction. In the case of dioxane, the complex may be 1:1 or 2:1 (phenol to dioxane) because there are two oxygen atoms in the molecule

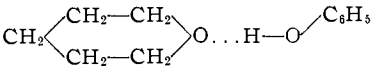


or



Using equation 2, the anticipated half-time for experiments 3–7 was calculated on the basis of each of these three assumptions. The results, together with the experimental values, are given in Table II. It is seen that the 2:1 complex fits the experimental data closely. (Compare columns 2 and 5 in Table II for experiments 3–6.)

If this interpretation is valid, then one would anticipate that tetrahydropyran, with only one oxygen, should form only a 1:1 complex



and should be a less effective inhibitor of the alkylation reaction than dioxane. The data in Table II show this to be the case. (Compare columns 2 and 4 in Table II for experiments 7–9.)

TABLE II

COMPARISON OF EXPERIMENTAL HALF-TIMES WITH THOSE CALCULATED FOR THREE ASSUMPTIONS

(1) Expt.	(2) $t_{1/2}$ (obs.), min.	(3) $t_{1/2}$,[a] min.	(4) $t_{1/2}$,[b] min.	(5) $t_{1/2}$,[c] min.	(6) Ether/phenol, mole
1	55.2	...	...	....	....
2	53.1	...	...	....	....
3	96.7	65.5	78.7	95.4	0.0287
4	178.6	84.7	118.2	174.3	.0621
5	457.8	103.1	217.6	497.7	.113
6	1497.3	134.0	461.3	1654.7	.168
7	119.0	85.9	118.4	....	.0563
8	268.8	111.3	247.6	....	.116
9	423.7	137.2	400.2	....	.162
10	146.1	144.5	...	....	.152

[a] Assuming only a diluent effect. [b] Assuming a 1:1 phenol to ether complex. [c] Assuming a 2:1 phenol to ether complex.

That phenols and ethers form hydrogen-bonded complexes is not novel. Batuev,[5] in a study of the infrared absorption spectrum of *o*-chlorophenol, found that the addition of an equivalent amount of dioxane to a solution of *o*-chlorophenol in carbon tetrachloride tended to disrupt the intramolecular chelate between the hydroxyl and the chlorine atom. This was ascribed to strong intermolecular hydrogen bonding between phenol and dioxane. Bartlett and Dauben,[6] in their work on the enhancing effect of phenols and alcohols on the acidity of solutions of hydrogen chloride in dioxane, have pointed out that the "basicity of dioxane causes phenol to be largely combined with the dioxane in which it is dissolved and not associated, as it would be in non-basic solvents of low dielectric constant." More recently, Nagakura and Baba[7] examined the profound effect of ethers on the dipole moment and near ultraviolet absorption spectrum of phenol. The results were explicable in terms of hydrogen-bonded complexes of ethers with phenol.

The stoichiometry which we observed (2:1 for the phenol–dioxane complex and 1:1 for the phenol–tetrahydropyran complex) was undoubtedly the result of a mass action effect. The phenol was

(5) M. I. Batuev, *Compt. rend. acad. sci., U.R.S.S.*, **40**, 277 (1943); *C. A.*, **38**, 6191 (1944).

(6) P. D. Bartlett and H. J. Dauben, THIS JOURNAL, **62**, 1339 (1940).

(7) S. Nagakura and H. Baba, *ibid.*, **74**, 5693 (1952).

present in such a large excess that essentially all the basic oxygens of the ethers were involved in hydrogen bonds. Nagakura and Baba[1] approached the equilibrium from the opposite direction, and found that with an inert solvent (carbon tetrachloride) it was necessary to attain a concentration 0.15 M in dioxane before all the phenol molecules (4.5×10^{-4} M) were complexed with the ether. It is probable that one has, in the case of dioxane, two equilibria, which can be shifted depending upon the relative concentrations of reactants.

$$\text{Phenol} + \text{dioxane} \rightleftarrows \text{1:1 complex}$$

$$\text{1:1 complex} + \text{phenol} \rightleftarrows \text{2:1 complex}$$

What is most significant from these results is that when phenol is bound in a complex with an ether, it is prevented from participating in the alkylation reaction. This means that the hydroxyl group plays an important role in the alkylation. This role is most likely the solvation of the halogen atom of the alkyl halide.

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EAST LANSING, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

2-Substituted Amino- and Aminomethyl-4-phenyl-1-tetralones

BY STANLEY WAWZONEK AND JOHN KOZIKOWSKI[1,2]

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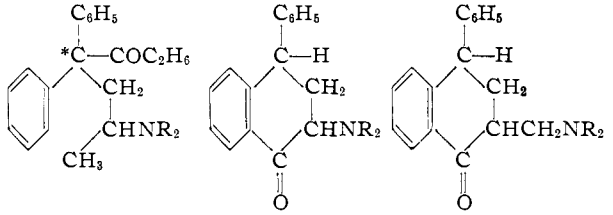
2-Dimethylamino-, 2-piperidino-, 2-morpholino-4-phenyl-1-tetralones and 2-dimethylaminomethyl-, 2-diethylaminomethyl- and 2-piperidinomethyl-4-phenyl-1-tetralone hydrochlorides have been prepared for testing as analgetics. The first group was made from 2-bromo-4-phenyl-1-tetralone while the second set was prepared by a Mannich reaction on 4-phenyl-1-tetralone with the appropriate amine hydrochloride.

Two series of compounds with the structural formulas II and III have been prepared in order to compare their pharmacological activity with that of the powerful analgetic, Methadon (I).



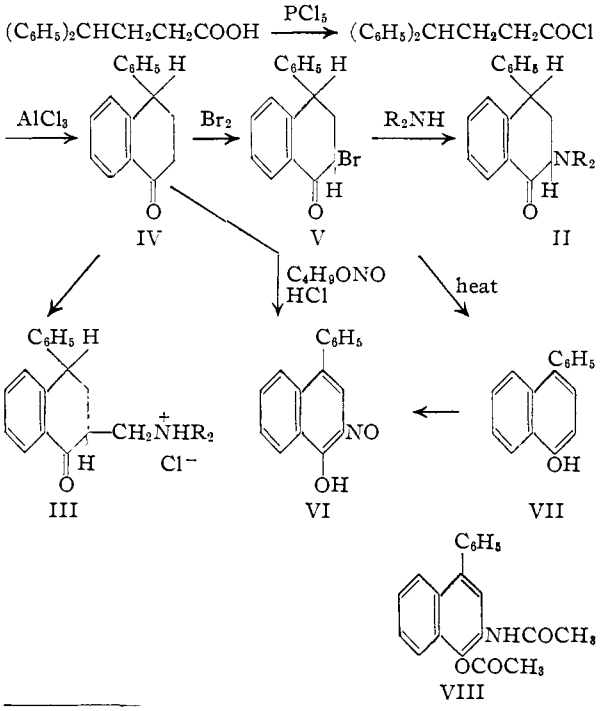
I II III

These compounds differ from Methadon in that that they do not have the quaternary carbon (C* in I) atom. One series has, however, three similar structural features; *viz.*, two phenyl groups and a dialkylaminoethyl grouping attached to carbon 4 in II. The ketonic group is not directly attached to carbon 4 but is separated by the vinyl group of the aromatic ring. The other series III has the dialkylamino group shifted from carbon 4 by an additional methylene group. These compounds were made in an effort to reduce toxic effects which the structure II might possess since it may be regarded as a substituted phenacylamine.

Both types of amines were synthesized from 4-phenyl-1-tetralone (IV) prepared from γ,γ-diphenylbutyric acid through the acid chloride.

Introduction of a substituted amino group on the ring was accomplished by bromination of the ketone and then treating the resulting 2-bromotetralone (V) with an excess of the secondary amines, dimethylamine, piperidine and morpholine.

Attempts to introduce a primary group by first forming the oximinoketone and then reducing could not be effected since butyl nitrite and hydrochloric acid gave solely 4-phenyl-2-nitroso-1-naphthol (VI). The structure of the latter compound was demonstrated by synthesis from the known 4-phenyl-1-naphthol (VII) prepared by cyclizing 4,4-diphenyl-3-butenoic acid.[3] This naphthol VII also could be obtained from the methiodide of 2-dimethylamino-4-phenyl-1-tetralone (II) and by the dehydrohalogenation of 2-bromo-4-phenyl-1-tetralone (V). Since the 4-phenyl-2-nitroso-1-naphthol (VI) melts with decomposition, the identity of the



(1) Abstracted in part from the Ph.D. thesis, August, 1953, of John Kozikowski.

(2) Ethyl Corporation Fellow, 1952–1953.

(3) W. S. Johnson and A. Goldman, THIS JOURNAL, **67**, 730 (1945).