the phenol stock solution, measured to ±0.02 ml., were added from a 10-ml. buret to the flasks containing the lactam, and carbon tetrachloride was added nearly to the mark. Carbon tetrachloride was added to the mark after the sample had come to thermal equilibrium at the temperature spectral measurements were to be run. This procedure was used to eliminate concentration corrections arising from temperature-dependent volume changes of the solution. The spectra were measured with carbon tetrachloride in the reference cell. Cells of 1-cm. path length fitted with ground-glass stoppers were used. The absorbance of the solution containing only the Lewis acid was also obtained.

The phenol–lactam complexes absorb in the same region as free phenol, but the former have larger extinction coefficients than free phenol. Spectra of phenol–lactam solutions were recorded at a constant wave length of 285 mμ. This wave length was chosen, after studying numerous spectra of lactam–phenol mixtures between the wave length of 300 and 270 mμ, because it was the wave length at which the difference between the extinction coefficient of the phenol and the complex was the greatest. Similar findings have been reported in connection with amide complexes of phenol.[9,10] Experiments on solutions which contained only lactam indicated that absorption due to free lactam was negligible at 285 mμ; thus, the following (eq. 2) applies.[21]

$$K^{-1} = \frac{C_a C_b}{A - a_a C_a}(a_c - a_a) - C_a - C_b + \frac{A - a_a C_a}{a_c - a_a} \quad (2)$$

Here, K is the equilibrium constant for 1:1 complex formation, C_a is the initial concentration of the Lewis acid, C_b is the initial concentration of the Lewis base, A is the absorbance at a specified wave length, a_a is the extinction coefficient of the Lewis acid, and a_c is the extinction coefficient of the 1:1 adduct at the specified wave length. In the derivation of eq. 2, Rose and Drago have assumed that the sole product species is a 1:1 complex, and that the Beer–Lambert law is obeyed by all absorbing species.

The graphical method described by Rose and Drago was replaced by a more rapid and precise analytical solution adaptable to computer programming. The simultaneous solution of eq. 2 for two sets of experimental data, denoted by subscripts 1 and 2, results in the quadratic expression that follows (eq. 3),

$$\left[\left(\frac{C_{a1}C_{b1}}{A_1 - B_1}\right) - \left(\frac{C_{a2}C_{b2}}{A_2 - B_2}\right)\right]D^2 + [(C_{2a} + C_{b2}) - (C_{a1} + C_{b1})]D + [(A_1 - B_1) - (A_2 - B_2)] = 0 \quad (3)$$

where $D = a_c - a_a$. The two values of D obtained from the solution of the quadratic equation are substituted into eq. 2 to solve for K^{-1}. The true values for K^{-1} and D for the system are obtained by inspection. Ideally, one true value of K^{-1} and corresponding value of D should be obtained. Practically, it is necessary to take the average of the K^{-1} values obtained from each pair of experimental values. Data for the ε-caprolactam–iodine adduct were obtained at 515 and 450 mμ, the wave lengths for the maxima of the free and the complexed iodine bands, respectively. Values of K were obtained by the use of eq. 2.

Procedure for Near-Infrared Spectral Measurements.—As a check on the ultraviolet measurements, equilibrium constants for the phenol–lactam systems were also computed from spectral data on the first overtone band of the free O–H stretching frequency at 1418 mμ.[22] Since this band is due to *free* phenol, it is possible to measure the equilibrium phenol concentration and, by assuming 1:1 complex formation, compute the concentrations of free lactam and the 1:1 complex as well. Two restrictions on the measurement of equilibrium constants by this procedure reduced the precision of the equilibrium constants to 7–10% of the mean value (in terms of standard deviation). The small extinction coefficient of 3.45 required as large a concentration of phenol as possible, as well as a path length of 10 cm. The upper limit of phenol concentration was set at 0.006 M. Above this concentration, polymeric phenol species are reported to be present in appreciable amounts.[22] The combination of these factors required spectral measurements at low absorbance, generally no greater than 0.150.

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The Replacement of Phenolic Hydroxyl Groups by Hydrogen

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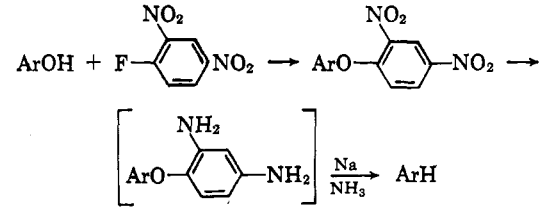
We recently required a method for the replacement of phenolic hydroxyl groups by hydrogen. There existed at the time no good general method for this simple transformation, and none of the then reported[3] procedures regularly gives high yields, although an excellent method has since been reported by Sawa[4] for removing the phenolic hydroxyl of various 3-methoxy-4-hydroxymorphinan derivatives. We have independently developed a very similar method[5] and our modification, which gives excellent yields in selected cases, notably in the morphine series[6] as does Sawa's, appears to offer some practical advantages over that of Sawa. This report deals with an attempt to define the scope and applicability of the method. We may say at the outset that, although in many cases excellent yields are obtained, the reaction is not so general as we had hoped. It appears to be most successful when methoxyl or phenyl groups are adjacent to the hydroxyl.

Our modification of the method consists of the preparation of the 2,4-dinitrophenyl ether of the phenol, its catalytic hydrogenation to the corresponding 2,4-diaminophenyl ether, and cleavage of this ether with sodium in liquid ammonia. The use of the dinitrophenyl ether offers several advantages over that of the simple phenyl ether used by Sawa.[4] Perhaps the most important is ease of preparation. Sawa's phenyl ethers were prepared by the Ullmann reaction, considerably more cumbersome than the method of Reinheimer[7] or arylation with 2,4-dinitrofluorobenzene and sodium hydride in benzene–dimethylformamide, both used in this work. The latter in particular proceeds smoothly to give excellent yields, even with highly



(1) National Science Foundation Predoctoral Fellow, 1961–1963.
(2) Union Carbide Fellow, 1963–1964.
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(5) Both methods are based on the cleavage of diphenyl ethers by sodium in liquid ammonia, a reaction which has been studied at length by F. J. Sowa and his co-workers [*J. Am. Chem. Soc.*, **59**, 603, 1488 (1937); **60**, 94 (1938)].
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TABLE I

2,4-DINITROPHENYL ETHERS OF PHENOLS[a]

Phenol	Dinitrophenyl ether, m.p., °C.	Yield, %
Guiacol	92.5–94	95
Resorcinol monomethyl ether	87–88.5	95
Hydroquinone monomethyl ether	112	94
2,6-Dimethoxyphenol[b]	167–168	95
Thymol	64.5–66.5	84
Carvacrol	Oil	93
2-Phenylphenol	114.5–115.5	85
1-Naphthol	127–128	80
2-Naphthol	94–95	94
5,6,7,8-Tetrahydro-2-naphthol[c]	116–117.2	94
p-Benzylphenol	74.5–76	96
p-Tritylphenol[d]	242–245	70

[a] With the exception of 2,6-dimethoxyphenol, 5,6,7,8-tetrahydro-2-naphthol, and *p*-tritylphenol, the 2,4-dinitrophenyl ethers of all of these phenols have been prepared by Reinheimer and his co-workers[7] and some also by earlier workers. Our melting points agree with those reported by Reinheimer. [b] Calcd. for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.78. Found: C, 52.80; H, 4.00. [c] Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49. Found: C, 61.07; H, 4.42. [d] Calcd. for $C_{31}H_{22}N_2O_5$: C, 74.09; H 4.41. Found: C, 74.27; H, 4.57.

TABLE II

HYDROGENATION AND CLEAVAGE OF 2,4-DINITROPHENYL ETHERS OF PHENOLS[a]

Phenol	Cleavage Product	Yield,[b] %
Guiacol	Anisole	60
Resorcinol monomethyl ether	Anisole	31
Hydroquinone monomethyl ether	...	0
2,6-Dimethoxyphenol	1,3-Dimethoxybenzene	100
Thymol	...	0
Carvacrol	...	0
2-Phenylphenol	Biphenyl	85
1-Naphthol	Naphthalene	50[c]
2-Naphthol	Naphthalene[d]	18
5,6,7,8-Tetrahydro-2-naphthol	Tetralin	1
p-Benzylphenol	Diphenylmethane	20
p-Tritylphenol	Tetraphenylmethane[e]	4[f]

[a] Cleavage products were analyzed by gas-liquid chromatography using appropriate internal standards, or by ultraviolet spectroscopy. Product identifications were made by comparison of retention times and infrared spectra or by melting points and mixture melting points. [b] Based on ether hydrogenated. [c] Lithium used for cleavage. [d] Longer cleavage times or more drastic conditions result in isolation of tetralin. [e] Most of the product (83%) appeared to consist of the product of Birch reduction, neutral and chromatographically homogeneous which consumed bromine without liberating hydrogen bromide. [f] Isolated yield.

hindered cryptophenols.[6,8] Table I lists the ethers prepared.

Another reason for preferring the 2,4-dinitrophenyl ether is that the sense of cleavage is clearly defined, inasmuch as catalytic hydrogenation to the corresponding diamino ether provides the structural features we deemed essential to specific cleavage.[9] Sowa's early work[5] suggested that the sense of cleavage was dependent on the electron density at the carbon atoms linked to the ether oxygen.

It now appears that this is an oversimplified view, since the influence on cleavage of an *ortho* methoxyl group is very different from that of a *para* methoxy group,[10] whereas their effect on the electron density of the *neutral* molecule should be much the same.

Other advantages are greater crystallinity and ease of purification of the dinitrophenyl ethers and the higher solubility in the cleavage solvent of the corresponding diamino compounds.[11]

The reduction by this method of a number of phenols is summarized in Table II. Those phenols with methoxyl or aryl groups in the *ortho* position appear to give acceptable to good yields of cleavage products and this generalization is in accord with our experience with the method in the 3-methoxy-4-hydroxymorphinan series.[6]

(8) A notable exception is 2,6-di-*t*-butylphenol which gives in 78% yield only C-arylated product, m.p. 168.5–169.5°, probably 2′,4′-dinitro-3,5-di-*t*-butyl-4-hydroxybiphenyl. (*Anal.* Found: C, 64.50; H, 6.53.)

(9) The specifity of cleavage observed by Sawa[4] with 4-phenyl ethers in the morphinan series would not have been predicted on the basis of Sowa's results.[5]

(10) A. J. Birch [*J. Chem. Soc.*, 102 (1947)] has found that among the dimethoxy benzenes, cleavage to monomethoxy phenols occurs as follows under comparable conditions: *ortho*, 89%; *meta*, 71%; *para*, 2.5%. These results are in sharp contrast to those obtained during the cleavage diaryl ethers, *e.g.*, 2,4,-dimethoxydiphenyl ether → 99% hydroquinone monomethyl ether and 1% guiacol [P. A. Sartoretto and F. J. Sowa, *J. Am. Chem. Soc.*, **59**, 603 (1937)], and it appears to us that Zimmerman's views [Tetrahedron, **16**, 169 (1961)] on the effect of substituents on the cleavage of ethers may require modification at least insofar as they apply to diaryl ethers.

(11) These are not isolated as such but used without purification owing to their facile autoxidation.

Experimental

Infrared spectra were taken on a Perkin-Elmer Model 421 infrared spectrophotometer, ultraviolet spectra on a Cary Model 11MS recording spectrometer. Gas–liquid chromatography was carried out on a 200-cm. column packed with 30% Apiezon L on Chromosorb.

Preparation of Ethers.—The following description is typical. A solution of 5.80 g. (34 mmoles) of 2-phenylphenol in 50 ml. of dry benzene were stirred under nitrogen with dry sodium hydride (1.50 g., 62.6 mmoles) until evolution of hydrogen ceased. 2,4-Dinitrofluorobenzene (50 mmoles) and 25 ml. of benzene were then added, followed by 20 ml. of dimethylformamide, the latter added over 10 min. The reaction mixture was stirred for 0.5 hr., refluxed for 0.5 hr., cooled, and extracted with dilute alkali and then with brine. Removal of solvent and crystallization of the residue from alcohol gave 9.70 g. (85%) of ether, m.p. 114.5–115.5°.

Hydrogenation and Cleavage of Ethers.—The following description is typical. A suspension of 3.47 g. (10 mmoles) of the 2,4-dinitrophenol ether of 2-phenylphenol in 500 ml. of methanol was hydrogenated at atmospheric pressure over 100 mg. of Adam's catalyst. Uptake ceased when 6 molar equiv. of hydrogen had been consumed. The colorless solution was filtered and concentrated to dryness under diminished pressure.

The residue was dissolved in 500 ml. of 9:1 liquid ammonia–ether and treated with small pieces of clean sodium until the solution acquired a permanent blue color. After a brief standing, enough absolute ethanol was added to destroy the blue color of the solution.

The ammonia was evaporated under an air stream and the dark residue was taken up in 250 ml. of water and extracted with three 50-ml. portions of ether. The combined ether extracts were dried with brine and anhydrous sodium sulfate and divided into two equal portions. To one portion was added 770 mg. of naphthalene to serve as an internal standard during g.l.p.c. This analysis showed the yield of biphenyl to be 85%. Processing the remaining portion of ethereal solution gave crystalline biphenyl identified by comparison with an authentic sample.

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A Search for New Drugs in the Group of Xanthine Derivatives. XXII. Chemical Properties of 1,3-Dimethyl-6H,7H-ozazolo-[2,3-*f*]xanthine System[1]

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By the action of alkali, 7-β-hydroxy-γ-chloropropyl derivatives of 8-chloro- and 8-bromotheophylline cyclized to 1,3-dimethyl-7-chloromethyl-6H,7H-oxazolo-[2,3-*f*]xanthine.[2] We have found that the 7-β-hydroxy-γ-bromo- and -γ-iodo-8-halotheophyllines (I, III and II, IV) undergo cyclization with alkali to give the 8-bromomethyl- and 8-iodomethyl-6H,7H-oxazolo[2,3-*f*]-xanthines (V and VI) in high yield; no oxazirane products were obtained. The reaction of these oxazolidine derivatives with acids was then examined.

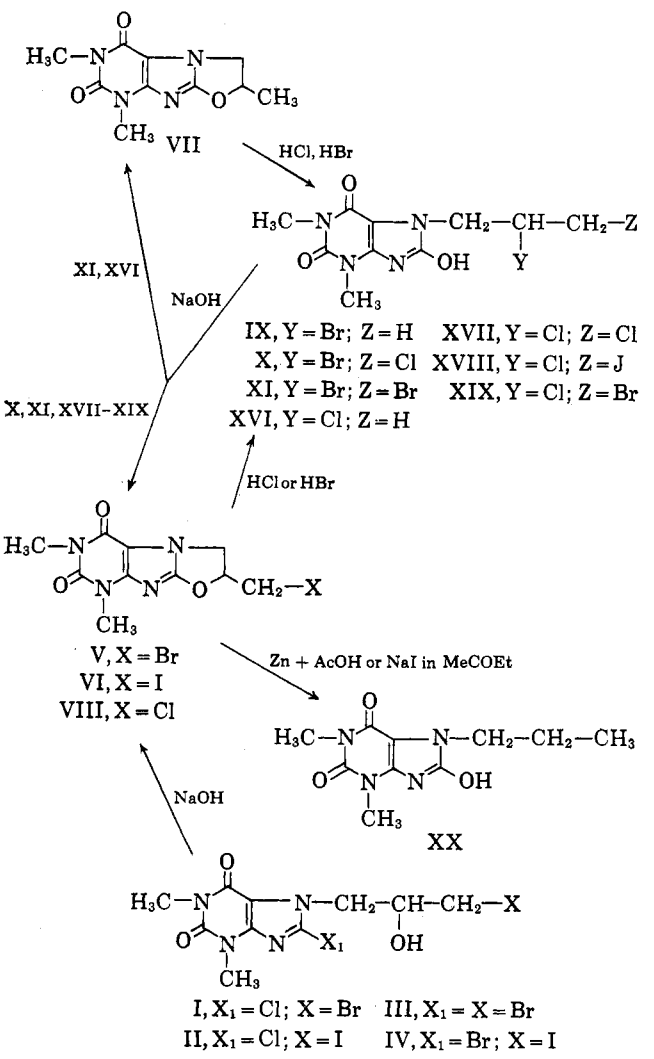
Compounds V–VIII dissolved readily in concentrated hydrobromic acid at room temperature and, after brief boiling, acidic products separated from the hot solution. The acid obtained from VII was transformed back to VII on heating with base and is assigned the uric acid structure IX. Similarly VIII gave the 7-(β-bromo-γ-chloropropyl)-1,3-dimethyluric acid (X), which was not identical with the isomeric 7-(β-hydroxy-γ-chloropropyl)-8-bromotheophylline obtained from 8-bromotheophylline and epichlorohydrin.[2] The same product XI was obtained from both the bromo compound V and iodo compound VI (Scheme I); in the latter case iodine was liberated.

Like compounds IX and X, compound XI is soluble in cold alkali and is precipitated unchanged on acidification. Recyclization by heating with sodium hydroxide solution gave 1,3-dimethyl-7-bromomethyl-6H,7H-oxazolo[2,3-*f*]xanthine (V). The dibromopropyluric acid structure XI was confirmed by an alternative synthesis shown in Scheme II.

By analogy to the work of Fischer[3] on 8-chlorocaffeine, the 7-allyl derivative XII[4] gave XIII which was readily hydrolyzed to 1,3-dimethyl-7-allyluric acid (XIV). Addition of bromine gave XI. In contrast to the uric acid derivatives IX and X, compound XI is readily methylated by dimethyl sulfate in the presence of sodium hydroxide, giving 1,3,9-trimethyl-7-(β,γ-dibromopropyl)uric acid (XV).

The cleavage of the oxazolidines V–VIII with hydrochloric acid was analogous to that observed with hydrobromic acid, giving the chloro-substituted uric acids XVI, XVII, and XIX (Scheme I). The acid XVI was converted back to VII with alkali, but much less readily than bromide IX. Halogen exchange did not occur with VI in this case, and the β-chloro-γ-iodo derivative was obtained. Attempts to reduce the halogen in position 7 of compounds V and VI by means of zinc and acetic or hydrochloric acid to obtain VII, gave only product XX, containing no halogen. The crystalline form, melting point, and analysis of compound XX (see Table I) conformed to those of VII, but the mixture melting point of the two substances was depressed. Moreover compound XX, in contrast to VII, was readily soluble in alkali and separated unchanged after acidification, indicating that it is a uric acid derivative. The structure of compound XX as 1,3-dimethyl-7-*n*-propyluric acid was confirmed by conversion with phosphorus oxychloride and dimethylaniline to 7-*n*-propyl-8-chlorotheophylline (XXI), identical with a sample prepared by alkylation of 8-chlorotheophylline with *n*-propyl bromide. On heating with sodium ethoxide solution compound XXI was converted to 1,3-dimethyl-7-*n*-propyl-8-ethyluric acid (XXII) which with hydrochloric acid gave XX. 1,3,7-Trimethyl-6H,7H-oxazolo[2,3-*f*]xanthine (VII) is not altered by heating with zinc and acetic acid, indicating that reductions of V and VI with zinc and acetic acid described above involve

SCHEME I



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