from β-(4-keto-1-cyclohexenyl) ethyl alcohol and *p*-toluenesulfonyl chloride in anhydrous pyridine at 0°. The product was obtained by adding benzene to the reaction solution after 24 hr., neutralizing the pyridine with ice cold 1 *N* hydrochloric acid, and removing the benzene from the dried organic solution. The alkylation was carried out under a nitrogen atmosphere in a dry flask which was equipped with a magnetic stirring bar, nitrogen inlet tube, and a condenser with a calcium chloride drying tube. A mixture of 15.0 g. (0.05 mole) of 4-(β-tosyloxyethyl)-3-cyclohexenone, 400 ml. of anhydrous dioxane, 1 drop of anhydrous *t*-butyl alcohol, and 1.22 g. (0.05 mole) of sodium hydride was stirred at reflux for 17 hr. Ether and 200 ml. of water with sufficient ammonium sulfate to saturate the aqueous layer were added. The water layer was separated and extracted with ether. The ether layers were combined, dried over magnesium sulfate, and filtered. The solvents were distilled through a 2-foot helix-packed column. The residue (7.78 g.) was distilled through a semimicro column[12] giving 1.81 g. (29.2%) of spiro[2.5]oct-1-en-3-one, b.p. 59° (1.5 mm.), n_D^{29} 1.5170, $\nu_{max}^{CCl_4}$ 1675 (s, conj. C=O) and 1612 cm.$^{-1}$ (m, conj. C=C $\lambda_{max}^{C_2H_5OH}$ 256 mμ (ε 10,550). Vapor phase chromatographic analysis[13] showed the presence of only one material. The NMR spectrum[9,14] exhibits peaks at 986, 1006, 1015, and 1025 c.p.s. for the vinyl protons; 1156, 1162, 1174, and 1180 c.p.s. for the methylene protons of the six-membered ring; and 1220 c.p.s. for the methylene protons of the three-membered ring.

Anal. Calcd. for $C_8H_{10}O$: C, 78.68; H, 8.19. Found: C, 78.46; H, 8.13.

Spiro[2.5]oct-1-en-3-one 2,4-dinitrophenylhydrazone was prepared in the usual way, chromatographed on acid-washed alumina using 95% hexane-5% ether as eluent, and recrystallized from absolute ethanol to give a pure sample, m.p. 172–172.5°, $\lambda_{max}^{C_2H_5OH}$ 380 mμ (ε 30,200).

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.63; N, 18.54. Found: C, 55.62; H, 4.69; N, 18.45.

4-(2,5-Dihydro-4-methoxyphenyl)-1-butanol (IIb).—The general procedure outlined by Johnson and co-workers was followed.[4] A solution of 20 g. (0.11 mole) of 4-(*p*-methoxyphenyl)-1-butanol[15] and 250 ml. of anhydrous ether was stirred while 1 l. of liquid ammonia was added. Rapid stirring was continued while 520 ml. of absolute ethanol was added followed by rapid addition of 27.6 g. (4.0 g.-atoms) of lithium wire. Then, 250 ml. of absolute ethanol was added, in conjunction with sufficient liquid ammonia to maintain a *bronze* phase throughout the reaction while at the same time keeping the bulk of the solution medium to light grey in color. After the lithium had reacted (total time about 1 hr.), the ammonia was allowed to evaporate. Water was added to dissolve the solid, and the solution was extracted with ether The ether extracts were combined, washed with water, dried over magnesium sulfate, and filtered. Distillation of the product through dry apparatus previously soaked in sodium hydroxide solution gave 16 g. (80%) of 4-(2,5-dihydro-4-methoxyphenyl)-1-butanol, b.p. 74–99° (0.1–0.2 mm.), mostly at 97–99° (0.1–0.2 mm.), $\lambda_{max}^{CCl_4}$ 3400 (m, O—H), 1693 (m) and 1665 (s C=C stretching of unconj. enol ether),[11] and 1223 cm.$^{-1}$ (s, ether C—O—C), $\lambda_{max}^{C_2H_5OH}$ 268–274 mμ (ε 25) indicating about 1% aromatic impurity.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.52; H, 9.89. Found: C, 72.23; H, 10.18.

4-(4-Keto-1-cyclohexenyl)-1-butanol (IIIb).—Using the procedure described above for the preparation of β-(4-keto-1-cyclohexenyl)ethyl alcohol, the hydrolysis of 10 g. (0.055 mole) of 4-(2,5-dihydro-4-methoxyphenyl)-1-butanol gave 7.3 g. (79%) of material, b.p. 78–115° (0.03–0.015 mm.), which was not obtained pure since polymerization hindered fractionation of the material. The *2,4-dinitrophenylhydrazone* of IIIb was obtained in the usual way—by cooling the reaction solution in Dry Ice–isopropyl alcohol to ensure complete precipitation of the derivative. The filtered crystals had to be washed immediately with water to avoid decomposition. Repeated recrystallization of the derivative from absolute ethanol gave a pure sample, m.p. 49.5–51° $\lambda_{max}^{C_2H_5OH}$ 361 mμ (ε 25,520).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 55.17; H, 5.74; N, 16.09. Found: C, 55.35; H, 5.82; N, 16.09.

Spirol[4.5]dec-1-en-3-one (Vb).—4-(4-Tosyloxybutyl)-3-cyclohexenone (IVb) was obtained as an oil in 77% yield from 4-(4-keto-1-cyclohexenyl)-1-butanol and *p*-toluenesulfonyl chloride as described above for the preparation of compound IVa. The same procedure used in the preparation of spiro[2.5]oct-1-en-3-one (Va) gave from 14.7 g. (0.045 mole) of 4-(4-tosyloxybutyl)-3-cyclohexenone and 1.08 g. (0.045 mole) of sodium hydride, 2.2 g. (32%) of a colorless oil, b.p. 82–84° (1.0 mm.), $\nu_{max}^{CCl_4}$ 1678 (s, conj. C=O) and 1612 cm.$^{-1}$ (w, conj. C=C), $\lambda_{max}^{C_2H_5OH}$ 231 mμ (ε 9,344). Vapor phase chromatographic analysis[13] showed the presence of 13.4% of an impurity. The crude spiro[4.5]dec-1-en-3-one was converted directly to its *2,4-dinitrophenylhydrazone* derivative which was recrystallized from absolute ethanol m.p. 150–151.2° (softening at 147°), $\lambda_{max}^{C_2H_5OH}$ 376 mμ (ε 30,640).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.18; H, 5.45; N, 16.96. Found: C, 58.16; H, 5.68; N, 16.90.

Spiro[4.5]decan-3-one 2,4-dinitrophenylhydrazone (VI).—A hydrogenation was carried out with 0.50 g. (0.003 mole) of spiro [4.5]dec-1-en-3-one (approximately 86% pure by vapor phase chromatographic analysis) in 10 ml. of absolute ethanol, using 75 mg. of 10% palladium-on-carbon catalyst. At the completion of the reaction 88.7% of the theoretical amount of hydrogen had been absorbed. The mixture was filtered and converted directly to its 2,4-dinitrophenylhydrazone derivative, which was recrystallized several times from absolute ethanol, m.p. 161°, $\lambda_{max}^{C_2H_5OH}$ 363 mμ (ε 24,260).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.83; H, 6.02; N, 16.86. Found: C, 57.97; H, 5.99; N, 16.90.

A mixed melting point with an authentic sample of IV, m.p. 161–161.9°, kindly supplied by Professor S. Winstein, showed no depression.

(12) Of a type similar to that described by C. W. Gould, Jr., G. Holzman, and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

(13) Gas-chromatographic columns were 9-mm. Pyrex tubes, 190 cm. long, containing 30% by weight of Dow-Corning Silicone oil No. 550 on a 50–100 mesh firebrick support. Helium was used as the carrier gas and thermistors were employed for the detection of sample peaks.

(14) Determined in carbon tetrachloride solution using tetramethylsilane as an internal standard. Positions of peaks are expressed in cycles per second relative to the proton resonance band of benzene at 1000 c.p.s. or the band of tetramethylsilane at 1255 c.p.s.

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Reactions of 2-(*p*-Toluenesulfonoxy)lepidine with Nucleophilic Reagents[1]

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We have shown[4] that 2,4-dinitrophenyl *p*-toluenesulfonate is cleaved by nucleophilic re-

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(3) R. J. Reynolds Fellow, 1956–1957. This manuscript is based on the Ph.D. thesis of J. Y. Bassett, Jr., October, 1957.

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TABLE I

REACTIONS OF 2-(*p*-TOLUENESULFONOXY)LEPIDINE WITH NUCLEOPHILIC REAGENTS[a]

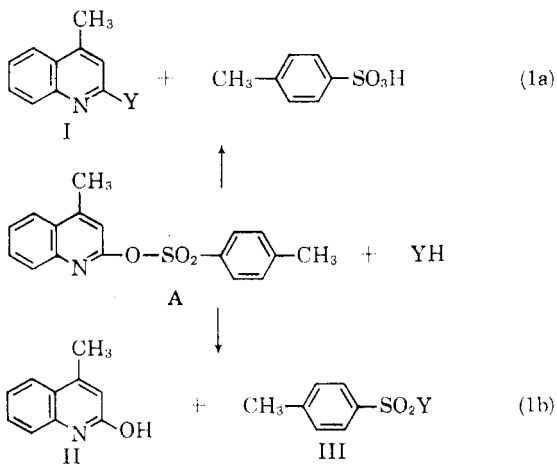
Reagent	Conditions	Yields (%) of Products of S—O Scission II	S—O Scission III	C—O Scission I
$C_6H_5S^-$	75% dioxane, reflux, 6.5 hr.	49	47	47
$CH_3COCHCO_2C_2H_5^-$	Tetrahydrofuran, 65°, 26 hr.		No reaction	
$C_6H_5NH_2$	Aniline, 100°, 10 hr.	55	50	41
$C_6H_5NH_2 + C_6H_5NH_3Cl$[b]	Aniline, 100°, 10 hr.	53	58	32
Piperidine	Piperidine, reflux, 5 hr.	39	40	58
Piperidine + $C_5H_{10}NH_2Cl$[b]	Piperidine, reflux, 5 hr.	41	39	52

[a] See Experimental for details. [b] Two moles of amine hydrochloride were used per mole of ester.

agents with either or both C—O scission and S—O scission. The principal products are, respectively, 2,4-dinitrophenyl and *p*-toluenesulfonyl derivatives of the nucleophile.

The proportions of the two modes of scission were found to vary according to the reagent. Reagents having reactive sites of high polarizability—*e.g.*, mercaptide ions and carbanions—attacked carbon preferentially. Those of lower polarizability—*e.g.*, methoxide ion—were prone to attack sulfur. It was postulated that London forces[5,6] were responsible. The region about C-1 of the 2,4-dinitrophenyl group was thought to have higher polarizability than that about the sulfur atom, with resulting extra London stabilization of the transition states for attack at carbon by reagents of high polarizability.

We now report a similar study of nucleophilic cleavage of a heterocyclic ester of *p*-toluenesulfonic acid, namely 2-(*p*-toluenesulfonoxy)lepidine (A). Since nucleophilic displacements at the 2-position of quinoline derivatives are well known,[7,8] it was to be expected that again both C—O and S—O scission would be observed (reactions 1a and 1b, respectively). It was conceivable that the



fraction of substitution in the quinoline ring (reaction 1a) would be high enough to make the reactions useful for the synthetic objective of replacing the 2-hydroxy group by other groups of nucleophilic origin.

Four nucleophiles were investigated. The results are summarized in Table I. As before,[4] yields of three products (I, II, and III) were determined for each reaction by direct isolation and weighing. And again the combined yields of products from the two modes of scission were in excess of 90%. One reagent, the acetoacetic ester anion, did not react.

In the previous study[4] it was found that the less the activation in the aryl group, the less is the extent of C—O scission. In reaction with piperidine in 60% dioxane–40% water, 2,4-dinitrophenyl *p*-toluenesulfonate gave 67% of cleavage at carbon, but the *o*- and *p*-mononitrophenyl esters gave only 36% and 39%, respectively. Since 2-bromoquinoline is somewhat more reactive than *o*- and *p*-bromonitrobenzene with piperidine[9] something more than 40% C—O scission of 2-(*p*-toluenesulfonoxy)lepidine might have been expected. The measured percentage is 58%, in piperidine as solvent.

In contrast to the earlier findings, changing the nucleophile now has little effect on the sense of cleavage. This result is compatible with the London forces explanation mentioned above, and indeed lends it support. The region about C-2 of the lepidine moiety has lower polarizability than that about C-1 in 2,4-dinitrophenyl *p*-toluenesulfonate, mainly because there is no *ortho* nitro group in the heterocyclic ester. London forces appear to be more or less equally significant in the transition states for attack at the carbon and sulfur atoms.

It is known that nucleophilic substitution in quinoline derivatives may be acid-catalyzed.[10,11] We were therefore surprised that addition of amine hydrochlorides had little or no effect on the proportions of C—O and S—O scission (Table I). Perhaps the acidity so provided was inadequate to catalyze a significant fraction of the total cleavage reaction.

The synthetic transformation of 2-hydroxyquinolines to 2-amino or 2-mercapto derivatives is

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commonly performed *via* the 2-chloro compound. Replacement of 2-OH by 2-Cl is somewhat objectionable, however, because high temperature exposure to severe reagents is required.[8,12] The *p*-toluenesulfonate ester employed in this study was made under milder conditions, was obtained in higher yield than the 2-chloro compound, and was easier to purify. Although the yields of products of substitution in the lepidine nucleus are poorer from the *p*-toluenesulfonate ester (Table I), it is conceivable that syntheses *via* the ester might be preferable when sensitive groups were present elsewhere in the system.

Experimental

Materials were purified by methods previously described,[4] except as otherwise mentioned. *2-Chlorolepidine*, m.p. 55–57°, was obtained from 2-hydroxylepidine[13] by the method of Krahler and Burger[12] in 89% yield.

2-(*p*-Toluenesulfonoxy)lepidine.—The general method of Cavalito and Haskell[14] was utilized, but with important modifications. To 25 cc. of pyridine, dried by refluxing over sodium metal for several hours and then distillation from sodium, 5.00 g. (0.031 mole) of 2-hydroxylepidine[13] and 6.80 g. (0.036 mole) of *p*-toluenesulfonyl chloride were added. A tight-fitting glass stopper was inserted, and the flask was warmed slightly on the steam bath and shaken thoroughly. As soon as all the solid material had dissolved, the solution was placed in a cold cabinet at about −20° and left there 12 hr. It was removed and its contents poured into about 250 cc. of water and ice. The mixture was stirred thoroughly. The gray crystals which formed were collected, pressed dry and dissolved in hot benzene. The benzene solution was heated with decolorizing charcoal for about 10 min. To the hot filtered solution ligroin was added until a faint turbidity appeared, and then a little hot benzene to restore clarity. The mixture was cooled in an ice bath. 2-(*p*-Toluenesulfonoxy)lepidine, m.p. 122–124°, separated as white crystals that weighed 9.3 g. (96%). Three recrystallizations from benzene–ligroin raised the m.p. to 125–126°. The ester is stable in storage.

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82. Found[15]: C, 64.75; H, 4.82.

2-Thiophenoxylepidine was prepared by reaction of 2-chlorolepidine with sodium thiophenoxide in 75% dioxane–25% water at 46° for 24 hr. The product, isolated by standard methods and crystallized from benzene–petroleum ether, consisted of white crystals of m.p. 81–82°. The yield was 68%.

Anal. Calcd. for $C_{16}H_{13}NS$: C, 76.45; H, 5.21. Found[15]: C, 76.76; H, 4.94.

2-Piperidinolepidine was prepared by reaction of 2-chlorolepidine with excess piperidine at 46° for 24 hr. The product, isolated by standard methods and crystallized from benzene–petroleum ether, consisted of white crystals of m.p. 72–73°. The yield was 76%.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02. Found[15]: C, 79.88; H, 8.10.

2-Anilinolepidine was prepared by condensation of 2-chlorolepidine with excess aniline after Knorr.[16] The yield was 69%, and the m.p. 128–130° (lit.,[16] 129–130°).

2-Chlorolepidine was recovered unchanged from exposure to ethyl sodioacetoacetate in refluxing tetrahydrofuran for 26 hr.

Reactions Summarized in Table I.—One gram of 2-(*p*-toluenesulfonoxy)lepidine was allowed to react with 5 cc. of each of the amine reagents, with or without addition of the amine hydrochloride. The reaction mixture for the sodium thiophenoxide experiment was prepared by combining 1.00 g. of the ester, in 15 cc. of dioxane, with 1.10 g. of thiophenol and 5 cc. of a 6% aqueous solution of sodium hydroxide. Products of all reactions were isolated by standard techniques, but principally by chromatography on alumina. They were the 2-lepidyl derivative of the nucleophile I, 2-hydroxylepidine II, and the *p*-toluenesulfonyl derivative of the nucleophile III. All products were identified by their melting points and by mixture melting points with authentic samples. In the case of the sodium thiophenoxide reaction, diphenyl disulfide was isolated as III rather than phenyl *p*-toluenethiolsulfonate; the disulfide is presumed to be a secondary product resulting from the action of thiophenoxide ion on the thiolsulfonate ester.[4]

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Stabilities and Some Reactions of Benzyllithium and α-Methylbenzyllithium

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An important property of an organometallic compound is its ability to effect metalation.[1] In the use of dibenzofuran (I) as a model heterocycle, the extent to which metalation takes place depends significantly upon the organometallic compound. *n*-Butylsodium[2a] and benzylsodium[2b] metalated (I) to give, after carbonation, dibenzofuran-4,6-dicarboxylic acid in yields of about 70%. However, benzylpotassium[2b] did not metalate (I) even after refluxing for forty-eight hours in toluene. *n*-Butyllithium gave monometalation in yields of 1–76% using diethyl ether as the solvent.[2b,3] Monometalation also has been accomplished using ethyl-,[2b,4a] *n*-propyl-,[3d] *n*-butyl-,[4b–d] isobutyl-,[3b] *sec*-butyl-,[3b] *tert*-butyl,[3b] 4-dibenzothienyl-,[4e] and 2,4,6-triphenylphenyllithium,[1] generally in less than 50% yield. The metalating abilities of *n*-butyl-, phenyl-, 1-naphthyl-, and *p*-anisyllithium in diethyl ether have been compared.[5] A recent

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