6-Aminocaproic Acid (III).—A 42-ml, heavy-walled glass vessel equipped with a crown cap and butyl rubber liner was charged with 190 mg of II, 100 mg of platinum oxide catalyst, and 10 ml of 95% ethanol. The vessel was capped, evacuated, filled with hydrogen (58 psig), and tumbled end over end overnight. The vessel was vented and uncapped; the catalyst was removed by filtration. After removal of the solvent by distillation, the residue was crystallized from methanol–ether to give 130 mg (84%) of III, mp 200.5–201.0°. Recrystallization gave 120 mg of pure product, mp 204.0–204.5° (lit.[11] mp 202–203°). A mixture melting point with authentic material[12] showed no depression.

Registry No.—I, 4883-67-4; 2,4-dinitrophenylhydrazone of I, 10269-95-1; II, 10269-96-2; ester of II, 10269-97-3.

(11) Reference 7, p 136.
(12) J. C. Eck in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 28.

Mono- and Diepoxy-1,4-benzoquinones

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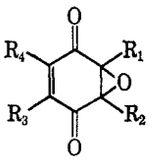
This communication describes the synthesis of a series of mono- and diepoxy-1,4-benzoquinones (I and II) by the direct, base-catalyzed peroxide oxidation of the corresponding quinones. Several monoepoxy-1,4-benzoquinones have previously been synthesized by Alder[1] in a rather complicated manner involving the epoxidation of the cyclopentadienequinone Diels–Alder adducts followed by a high-temperature-induced reverse Diels–Alder cleavage to give the epoxyquinones. No previous reports have appeared describing the unusual diepoxy-1,4-benzoquinone nucleus. These two classes of compounds may be of biological significance as antibiotics[2] as well as possible biosynthetic intermediates to the ubiquitous naturally occurring hydroxyquinones.[3]

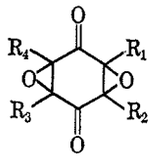
The results reported here are an integral part of an over-all program directed toward the synthesis of several recently reported natural products possessing the epoxy-1,4-benzoquinone nucleus. Sheehan[2] has described the isolation and identification of terreic acid (III), an antibiotic found in culture broths of *Aspergillus terreus*. Yamamoto, *et al.*,[3] have recently reported the characterization of IV, a possible biosynthetic intermediate in the conversion of fumigatin to spinulosin. Finally, Closse, Mauli, and Sigg[4] have identified a partially reduced epoxy-1,4-benzoquinone (V) as a natural product from the culture filtrates of Phoma species. (See Chart I.)

The lack of reports on the epoxides of 1,4-benzoquinones is somewhat surprising in view of the fact that the naphthoquinone series has been extensively studied—at least in regards to their synthesis and

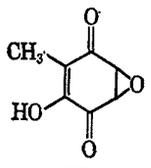
CHART I



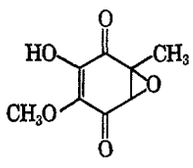
Ia, $R_1=CH_3$; $R_2=R_4=H$; $R_3=CH(CH_3)_2$
b, $R_1=R_3=C(CH_3)_3$; $R_2=R_4=H$
c, $R_1=R_2=R_3=R_4=CH_3$
d, $R_1=R_2=R_3=H$; $R_4=C(CH_3)_3$
e, $R_1=R_2=R_3=H$; $R_4=C_6H_5$



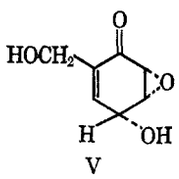
IIa, *cis*- and *trans*-$R_1=CH_3$; $R_2=R_4=H$; $R_3=CH(CH_3)_2$
b, *cis*- and *trans*-$R_1=R_3=C(CH_3)_3$; $R_2=R_4=H$
c, *cis*-$R_1=R_2=R_3=R_4=CH_3$



III



IV



V

natural occurrence.[5–17] The epoxides of several alkyl-substituted naphthoquinones are reported to be readily prepared by the direct oxidation of the quinone with 30% hydrogen peroxide in aqueous ethanol. Although we found this method to be applicable to the benzoquinone series, the yields of the resulting epoxides were generally poor owing to the facile base hydrolysis of the epoxide ring under these aqueous conditions. A modification, described below, employs nonaqueous conditions uilizing *t*-butyl hydroperoxide as the oxidizing agent, Triton B as the base, and absolute ethanol–1,4-dioxane as the solvent.

The monoepoxy-1,4-benzoquinones, Ia–e, were readily obtained in yields of 30–80% by the direct oxidation of the quinone with a stoichiometric amount of *t*-butyl hydroperoxide in 1:1 absolute ethanol–1,4-dioxane utilizing Triton B (30% methanolic benzyltrimethyl ammonium hydroxide) as the base catalyst. The epoxidations were complete within 1–3 hr as detected by gas chromatography on silicon gum rubber $^1/_8$-in. columns run isothermally between 150 and 200°. The products were isolated by pouring the reaction mixtures into water and recrystallization of the resulting precipitate from ethanol.

(1) K. Alder, F. H. Flack, and H. Beumling, *Chem. Ber.*, **93**, 1896 (1960).
(2) J. C. Sheehan, W. B. Lawson, and R. J. Gaul, *J. Am. Chem. Soc.*, **80**, 5536 (1958).
(3) M. Yamamoto, K. Nitta, K. Tango, T. Saito, and M. Tsuchimuro, *Chem. Pharm. Bull.* (Tokyo), **12**, 935 (1965).
(4) A. Closse, R. Mauli, and H. P. Sigg, *Helv. Chim. Acta.*, **49**, 204 (1966).
(5) L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3165 (1948).
(6) M. Tishler, L. F. Fieser, and N. L. Wendler, *ibid.*, **62**, 2866 (1940).
(7) L. A. Shchukina, A. S. Khokhlov, and M. M. Shemyakin, *J. Gen. Chem. USSR*, **21**, 1005 (1951).
(8) L. A. Schchukina, A. P. Kondrateva, and M. M. Shemyakin, *ibid.*, **19**, 165 (1949).
(9) L. A. Schchukina and M. M. Shemyakin, *ibid.*, **19**, 175 (1949).
(10) L. F. Fieser, W. P. Campbell, E. M. Fry, and M. D. Gates, *J. Am. Chem. Soc.*, **61**, 3216 (1939).
(11) T. Zincke, *Chem. Ber.*, **25**, 3599 (1892).
(12) T. Zincke and P. Wiegand, *Ann.*, **286**, 58 (1895).
(13) G. Reed and L. C. Vining, *Can. J. Chem.*, **37**, 1881 (1959).
(14) G. Reed, L. C. Vining, and R. H. Haskins, *ibid.*, **37**, 731 (1959).
(15) G. Reed and L. C. Vining, *Chem. Ind.* (London), 1239 (1963).
(16) L. F. Fieser, M. Tishler, and W. L. Sampson, *J. Am. Chem. Soc.*, **62**, 1628 (1940).
(17) G. A. Ellestead, H. A. Whaley, and E. L. Patterson, *ibid.*, **88**, 4109 (1966).

TABLE I[a]

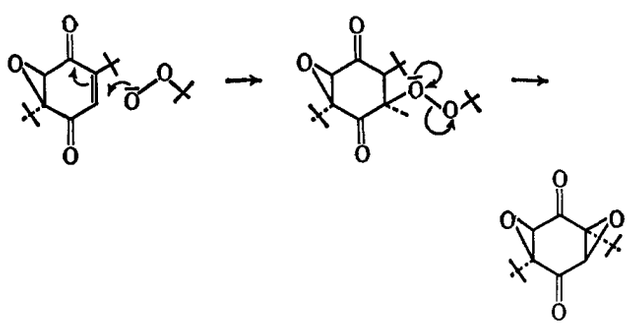
PHYSICAL PROPERTIES OF EPOXY-1,4-BENZOQUINONES

Compd	Mp, °C	Ultraviolet, mμ	Infrared, cm⁻¹	Nmr, ppm, from TMS ($CDCl_3$): ArH	=CH	=CR	O/CH	O/CR
		338 (195)	1688		6.40 (1) d	1.08 (3) d[b]	3.70 (1) s	1.61 (3) s
Ia	82–84		1680			1.12 (3) d[b]		
			1645			2.96 (1) h		
		360 (240)	1690		6.34 (1) s	1.30 (9) s	3.72 (1) s	1.21 (9) s
Ib	114–117		1679					
			1648					
	109–110	331 (230)	1690			1.66 (6) s		1.60 (6) s
Ic			1680					
		357 (240)	1685		6.42 (1) d[c]	1.92 (9) s	3.77 (2) m[c]	
Id	88–89		1675					
			1684					
		316 (7570)	1690	7.42 (5) s	6.66 (1) d[c]		3.85 (1) m[c]	
Ie	118–120		1680				3.97 (1) m[c]	
			1600					
	141–143	316 (60)	1700				3.55 (2) s	1.49 (3) s
cis IIa								0.93 (6) d
	d	319	1700				3.55 (2) s	1.49 (3) s
trans IIa								0.93 (6) d
cis IIb	*d*	321 (85)	1715				3.49 (1) s	1.19 (18) s
trans IIb	142–141	323 (81)	1700				3.57 (1) s	1.12 (18) s
cis IIc	113–114	312 (67)	1705					1.66 (12) s

[a] C and H analysis are consistent for I and II; d = doublet; h = heptet; s = singlet; m = multiplet. [b] Isopropyl methyls appear as a quartet rather than a doublet owing to the asymmetry of the ring system. [c] ABX pattern. [d] Could not be completely separated from its isomer.

The spectral data for these epoxides (Table I) are interpreted in terms of the structures shown above (Ia–e). The only example where the structural assignment is not readily obtained from the spectral data is the monoepoxide Ia of thymoquinone. The nmr spectrum of this compound does not unambiguously distinguish between the possibilities in which the epoxide ring is substituted with either a methyl group or an isopropyl group. That the former is true was established by chemical means. Base hydrolysis of this epoxyquinone gave the known hydroxyquinone (VI), 3-hydroxy-2-methyl-5-isopropyl-1,4-benzoquinone.[18] The formation of VI can be explained by the reaction sequence shown in Scheme I, p 1998.

The diepoxides IIa–c were prepared in a completely analogous way except that the molar ratio of quinone to *t*-butyl hydroperoxide was 1:2. The structures of these unusual compounds were readily assigned on the basis of the spectral data listed in Table I. The possibility of *cis* and *trans* isomers exists with the diepoxy-1,4-benzoquinones and both isomers were found for IIa and IIb. The stereochemical assignments of these isomers (Table I) are not unambiguous at this time. They have been made upon the basis of product ratios, as detected by gas chromatography and considerations of the accepted mechanism of the epoxidation.[19] When hydrogen peroxide was used as the epoxidizing agent in the oxidation of thymoquinone and 2,5-di-*t*-butyl-,4-benzoquinone the ratio of *cis* to *trans* isomers was nearly 1:1. However, with the more bulky *t*-butyl hydroperoxide one isomer (assigned the *cis* configuration) predominated. This is rationalized on the basis of the mechanism which would lead one to predict the major product to be the *cis* isomer as arising



from attack of the bulky *t*-butyl hydroperoxide anion from the least hindered side of the monoepoxide. It was shown that neither the *cis* nor *trans* isomers were interconverted under the reaction conditions, thus ruling out the possibility that the predominant isomer was a result of an equilibration process.

It is interesting to note that by all criteria thus far investigated (spectral data and gas chromatography) the diepoxide of duroquinone, IIc, appears to be a single isomer, and is assumed to have the *cis* configuration from mechanistic considerations.

Solvent effects in nmr spectroscopy have been ingeniously employed by Williams and Bhacca[20,21] to make stereochemical assignments of various ketones. Their method briefly consists of a comparison of the spectrum of a deuteriochloroform solution of the compound with that of a benzene solution. Stereochemical assignments are then made on the basis of chemical shift differences in the two solvents utilizing an empirical correlation based upon a possible benzene–carbonyl complex. One would certainly expect a difference in complex formation between the *cis* and

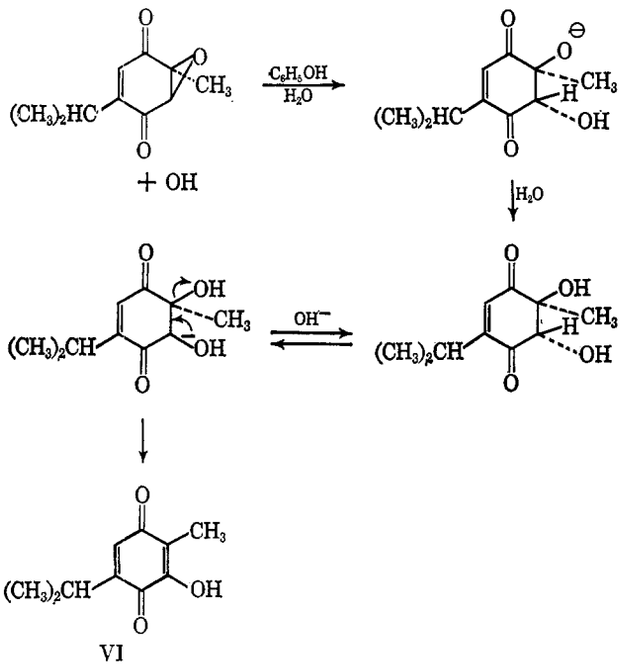
(18) E. Zanarin and A. B. Anderson, *J. Org. Chem.*, **20**, 788 (1955).

(19) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 117.

(20) N. S. Bhacca and D. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 159–181.

(21) D. H. Williams and D. A. Wilson, *J. Chem. Soc.*, 144 (1966).

SCHEME I



trans isomers of diepoxy-1,4-benzoquinones and benzene due to the difference in steric environment of the carbonyl groups. It was found that for the two examples reported here (IIa and IIb) the $\Delta^{CDCl_3}_{C_6H_6}$ values[22] for all the protons in the *cis* isomers are always more positive than the corresponding values obtained from the *trans* isomers. That this is a general trend remains to be seen, but the indications are that this technique might be used as a simple method for distinguishing between the *cis*- and *trans*-diepoxy-1,4-benzoquinones when both isomers are available.

A systematic investigation of the chemical and photochemical properties of epoxyquinones has been initiated and the results will be presented in subsequent publications.

Experimental Section

General Method for the Preparation of Monoepoxyquinones (Ia–e).—A solution of 0.1 mole of the 1,4-benzoquinone in 100 ml of a 1:1 solution of absolute ethanol–1,4-dioxane was prepared. This solution was then treated with 0.11 mole of *t*-butyl hydroperoxide. The reaction solution was cooled to 5–10° and 2 ml of Triton B was then added. Aliquots of the reaction solution were monitored by gas chromatography on 6 ft × 1/8 in. silicon gum rubber columns run isothermally between 150 to 200° until the reaction was complete (1–3 hr). The reaction solutions were then poured into 500 ml of water and the resulting precipitate was collected by filtration and purified by recrystallization from 95% ethanol.

2,3-Epoxy-2-methyl-5-isopropyl-1,4-benzoquinone (Ia).—This epoxide was prepared by the general method described above in 50% yield, mp 82–84°. The spectral date for Ia are given in Table I.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found: C, 66.69; H, 6.72.

2,3-Epoxy-2,5-di-*t*-butyl-1,4-benzoquinone (Ib).—The epoxide was prepared by the general method described above in 73% yield, mp 114–117°. The spectral data for Ib are given in Table I.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.18; H, 8.47. Found: C, 71.02; H, 8.36.

2,3-Epoxy-2,3,5,6-tetramethyl-1,4-benzoquinone (Ic).—The epoxide was prepared by the general method described above to give only 30% yield of the purified product, mp 109–110°. Gas chromatographic analysis of the reaction mixture showed that the diepoxide (IIc) was also formed in considerable amounts under these conditions. The monoepoxide was separated from the diepoxide by preparative gas chromatography. The spectral data for Ic are given in Table I.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found: C, 66.60; H, 6.92.

2,3-Epoxy-4-*t*-butyl-1,4-benzoquinone (Id).—The epoxide was prepared in 82% yield by the general method described above, mp 88–89°. The spectral data for Id are given in Table I.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found: C, 66.61; H, 6.62.

2,3-Epoxy-4-phenyl-1,4-benzoquinone (Ie).—The epoxide was prepared in 62% yield by the general method described above, mp 118–120°. The spectral data for Ie are given in Table I.

Anal. Calcd for $C_{12}H_8O_3$: C, 72.00; H, 4.00. Found: C, 72.03; H, 4.13.

General Method for the Preparation of Diepoxy-1,4-benzoquinones (IIa–c).—A solution of 0.1 mole of the 1,4-benzoquinone in 100 ml of a 1:1 solution of absolute ethanol–1,4-dioxane was prepared. This solution was treated with 0.22 mole of *t*-butyl hydroperoxide and cooled to 5–10°. Four milliliters of Triton B was slowly added, keeping the temperature below 10°. Aliquots of the reaction solution were monotered by gas chromatography on 6 ft × 1/8 in. silicon gum rubber columns run isothermally between 150–200° until the reaction was complete (1–3 hr). The gas chromatographic analysis showed the initial formation of the monoepoxide which slowly disappeared as the diepoxide formed. The reaction solutions were then poured into 500 ml of water and the resulting precipitate was purified by recrystallization from 95% ethanol.

***cis*- and *trans*-Diepoxythymoquinone (IIa).**—A mixture of the *cis* and *trans* isomers of the diepoxide of thymoquinone was prepared in 54% yield by the general method described above. Separation of the *cis* isomer was accomplished by fractional recrystallization from benzene—the *cis* isomer being less soluble than the *trans* in this solvent. This *cis* isomer showed a sharp melting point at 141–143°. The *trans* isomer was never obtained completely free of the *cis* isomer by either repeated recrystallizations or by preparative gas chromatography. The spectral data for these isomers are given in Table I.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 61.32; H, 6.09.

***cis*- and *trans*-Diepoxy-2,5-di-*t*-butyl-1,4-benzoquinone (IIb).**—A mixture of the *cis* and *trans* isomers of the diepoxide of 2,5-di-*t*-butyl-1,4-benzoquinone was prepared in 84% yield by the method described above. The *trans* isomer, mp 141–142°, was separated by repeated recrystallization from 95% ethanol. The *cis* isomer was never obtained completely free of the *trans* compound. The spectral data for these compounds are given in Table I.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.66; H, 7.93. Found: C, 66.69; H, 7.83.

***cis*-Diepoxyduroquinone (IIc).**—The diepoxide of duroquinone was prepared in 73% yield by the general method described above, mp 113–114°. Only one isomer was detected by gas chromatography. In addition the sharp melting point, as well as the spectral data presented in Table I, indicates this compound to be a single isomer. The *cis* configuration is assigned on the basis of mechanistic considerations as presented in the text of the paper.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 61.41; H, 6.02.

3-Hydroxy-2-methyl-5-isopropyl-1,4-benzoquinone (VI).—Five milliliters of 10% aqueous NaOH was added to a solution of 250 mg (0.0014 mole) of the monoepoxide of thymoquinone in 50 ml of ethanol. The solution immediately became deep purple. The reaction mixture was allowed to stand at room temperature for 25 min and then poured into 100 ml of water. This purple aqueous solution was then acidified with 10% HCl. Acidification resulted in a color change from purple to yellow and the simultaneous precipitation of the hydroxyquinone, VI. The product was collected by filtration and recrystallized from 95% ethanol yielding 209 mg of the product, 3-hydroxy-2-methyl-5-isopropyl-1,4-benzoquinone, mp 167–168°.[18] The spectral data, infrared, ultraviolet and nmr, are all consistant with structure VI.

(22) $\Delta^{CDCl_3}_{C_6H_6}$ values as defined by Williams and Bhacca[21] are the differences in chemical shifts, expressed in parts per million, measured in benzene compared with those obtained from a deuteriochloroform solution.

Registry No.—Ia, 10476-70-7; Ib, 10476-71-8; Ic, 10476-72-9; Id, 10476-73-0; Ie, 10476-74-1; *cis* IIa, 10476-75-2; *trans* IIa, 10476-76-3; *cis* IIb, 10476-77-4; *trans* IIb, 10476-78-5; *cis* IIc, 10476-79-6; VI, 10476-80-9.

Acknowledgment.—The author is indebted to the National Science Foundation for partial support of this project from Grant GP 5945.

Reissert Compound Studies. XVI. Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile with Lactones[1]

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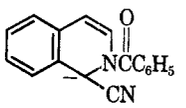
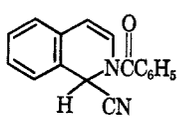
Received December 28, 1966

We have recently reported[1,3] that the Reissert anion (I) can be conveniently generated at room temperature using sodium hydride in dimethylformamide. We now wish to report use of this system in two novel reactions of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II) with β-propiolactone and β-butyrolactone.



I



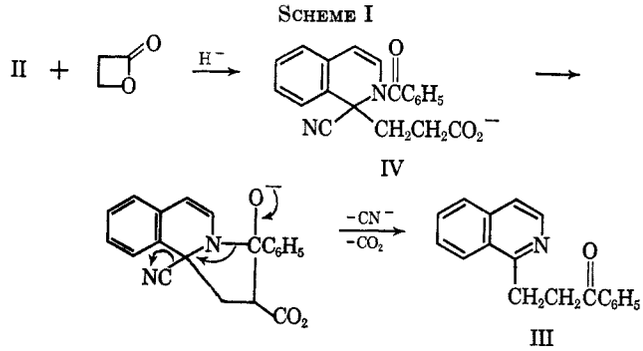
II

Reaction of II with β-propiolactone and sodium hydride in dimethylformamide led to the formation of β-(1-isoquinolyl)ethyl phenyl ketone (III). Formation of III can be rationalized according to Scheme I. Opening of the lactone by I followed by rearrangement of IV and decarboxylation gives rise to III.

The structure of III was confirmed by an alternative synthesis from the anion II and β-bromopropiophenone. This alkylation gave an intermediate corresponding in composition to the enol ester V or diketone VI; alkaline hydrolysis of this substance led to III.

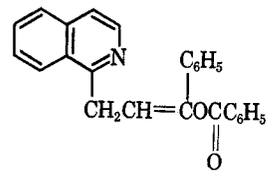
Reaction of II with β-butyrolactone did not produce a simple homolog of III but rather 1-(1-isoquinolinyl)-

SCHEME I

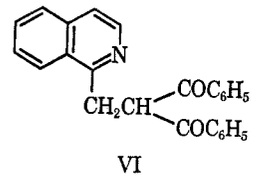


IV

III



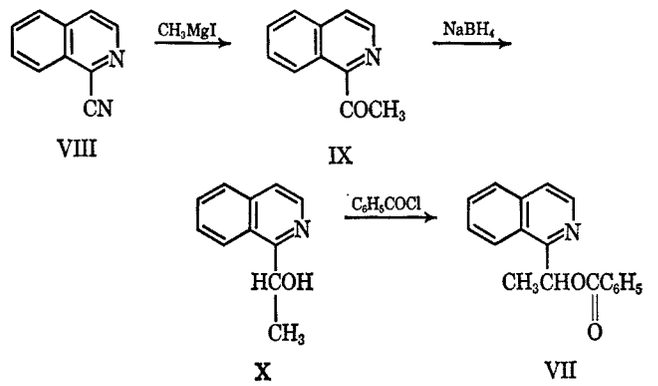
V



VI

ethyl benzoate (VII). The structure of VII was established by unequivocal synthesis according to Scheme II,

SCHEME II



VIII IX X VII

and by low temperature[4] condensation of II with acetaldehyde, which also gave VII.

Any mechanism (analogous to Scheme I) in which the anion I cleaves the lactone ring as a first step toward the formation of VII suffers from the disadvantage that the lactone must be opened in an unusual fashion (*i.e.*, cleavage of a carbon–carbon bond), and that a two-carbon fragment must be eliminated prior to or during the rearrangement step. Since VII was also formed by condensation of II with acetaldehyde and since acetaldehyde could be detected when β-butyrolactone was treated with sodium hydride in dimethylformamide (albeit in low yield), it may be that II actually reacts with acetaldehyde formed *in situ*. The greater steric hindrance to nucleophilic attack by I at the β-carbon of β-butyrolactone relative to β-propiolactone causes the reaction to follow a different pathway, initiated by nucleophilic attack by hydride at the lactone carbonyl, leading to the cleavage into what appear to be two molecules of acetaldehyde. The fact that VII is obtained in much higher yield than is acetaldehyde (in the absence of I) can be accounted for by the immediate reaction of I with acetaldehyde while in the absence of I the acetaldehyde can undergo other base-catalyzed reactions.

Treatment of II with either γ-butyro-, γ-valero-, or γ-decalactone and sodium hydride in dimethylformamide gave only 1-benzoylisoquinoline indicating that five-membered lactones are either too stable to react under these conditions or react too slowly to compete with the rearrangement to the ketone.[1,3]

For purposes of comparison the above reactions were attempted using phenyllithium in ether–dioxane at −20°.[4,5] In all cases tried (β-propio-, β-butyro-, and γ-valerolactone) starting Reissert compound (II) was recovered.

(1) Part XV: F. D. Popp and J. M. Wefer, *J. Heterocyclic Chem.*, in press.

(2) U. S. Public Health Service Predoctoral Fellow (1-F1-GM-25,896) from Institute of General Medical Sciences.

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(5) V. Boekelheide and J. Weinstock, *ibid.*, **74**, 660 (1952).