Reactions of an α-Phosphono-γ-butyrolactone Carbanion with Acid Anhydrides, Epoxides, Carbonates, and a Lactone

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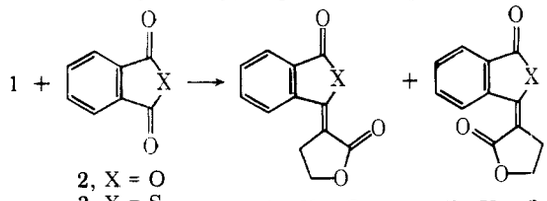
Reactions of an α-phosphono-γ-butyrolactone carbanion (**1**) with various acid anhydrides, epoxides, carbonates, and a lactone were investigated. Phthalic (**2**) and thiophthalic anhydrides (**3**) gave 3-(2-oxotetrahydrofuran-3-ylidene)phthalide (**4**) and -thiophthalide (**5**) in quantitative yields, while homophthalic (**6**) and isatoic anhydrides (**8**) produced 3-(2-oxotetrahydrofuran-3-yl)isocoumarin (**7**) and 4*H*-2-(2-oxotetrahydrofuran-3-yl)benz[*d*][1,3]oxazin-4-one (**9**) in good yields. The reaction products between **1** and *N*-methylisatoic anhydride (**11**) were solvent dependent. The reaction in benzene gave mainly 2*H*,4*H*-1-methyl-(*E*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]-oxazin-2-one (**12a**) and in DMF provided only 2*H*,3*H*,4*H*-9-methylfuro[2,3-*b*]quinolin-4-one (**13**) in high yield. Epoxides **14** led to isomeric spirolactones **15** and **16**. Epoxy ketones **18**, 1,2-carbonyldioxybenzene (**20**), and γ-butyrolactone **21** gave the corresponding α-ylidene-γ-butyrolactones **19**, **22**, and **23**, respectively.

The development of facile methods for introduction of the γ-butyrolactone moiety to organic molecules has become one of the targets of organic chemists because of the occurrence in nature of many compounds of this class having significant biological activity.[1]

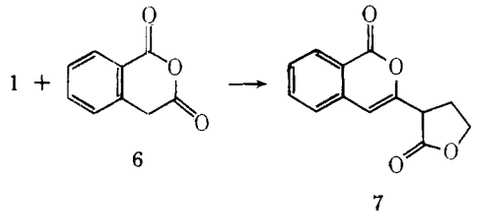
We have previously reported the synthesis of various α-ylidene-γ-butyrolactones from an α-(*O,O*-diethylphosphono)-γ-butyrolactone carbanion (**1**) and simple carbonyl reagents such as aldehydes and ketones.[2] In an attempt to explore further synthetic utility of the phosphonate carbanion **1**, we have investigated the reaction titled above.

Results and Discussion

Acid Anhydrides. The phosphonate carbanion **1** easily reacted with phthalic (**2**) and thiophthalic anhydrides (**3**) in refluxing benzene for 3 h to give a mixture of (*Z*)-3- (**4a**, 58%) and (*E*)-3-(2-oxotetrahydrofuran-3-ylidene)phthalide (**4b**, 42%) and (*Z*)-3-(2-oxotetrahydrofuran-3-ylidene)thiophthalide (**5**), respectively, in quantitative yields.



Although the reaction with homophthalic anhydride (**6**) required relatively vigorous conditions (at 140 °C for 4 h in a sealed tube), 3-(2-oxotetrahydrofuran-3-yl)isocoumarin (**7**)



was obtained in good yield. However, treatment of maleic and succinic anhydrides with **1** under similar conditions gave no corresponding product. This result suggests that the carbonyl group of the acylated phosphonates derived from attack of **1** on these acid anhydrides could not have an appropriate configuration for being subsequently attacked by the generated carboxylate anion due to easy rotation of the anionic moiety.

On the other hand, the reaction products of isatoic **8** and *N*-methylisatoic anhydrides **11** with **1** were drastically solvent dependent. The reaction of **8** in refluxing benzene for 3 h led to 4*H*-2-(2-oxotetrahydrofuran-3-yl)benz[*d*][1,3]oxazin-4-one (**9**, 91%) corresponding to **7**, but the reaction in *N,N*-dimethylformamide (DMF) at 110 °C gave only *N*-ethylisatoic anhydride in 79% yield. The structural assignment of product **9** was made by spectral data and elemental analysis and by alkaline hydrolysis of the product **9** yielding 2-*N*-(2-oxotetrahydrofuran-3-carboxyamido)benzoic acid (**10**) (Scheme I). Whereas the reaction of **11** in benzene solvent at 140 °C for 7 h in a sealed tube gave 2*H*,4*H*-1-methyl-(*E*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]oxazin-2-one (**12a**, 43%) along with 2*H*,3*H*,4*H*-9-methylfuro[2,3-*b*]quinolin-4-one (**13**, 5%), the reaction in DMF at 110 °C for 4 h produced only **13** in high yield with the accompanying evolution of carbon dioxide gas. Heat of the separated (*E*) isomer **12a** in refluxing ethanol containing NaOH for confirmation of its stereochemistry led to the corresponding (*Z*) isomer **12b**.

Thus, the phosphonate anion **1** was observed to react with isatoic anhydride **8** with the less reactive carbonyl group at

Scheme I

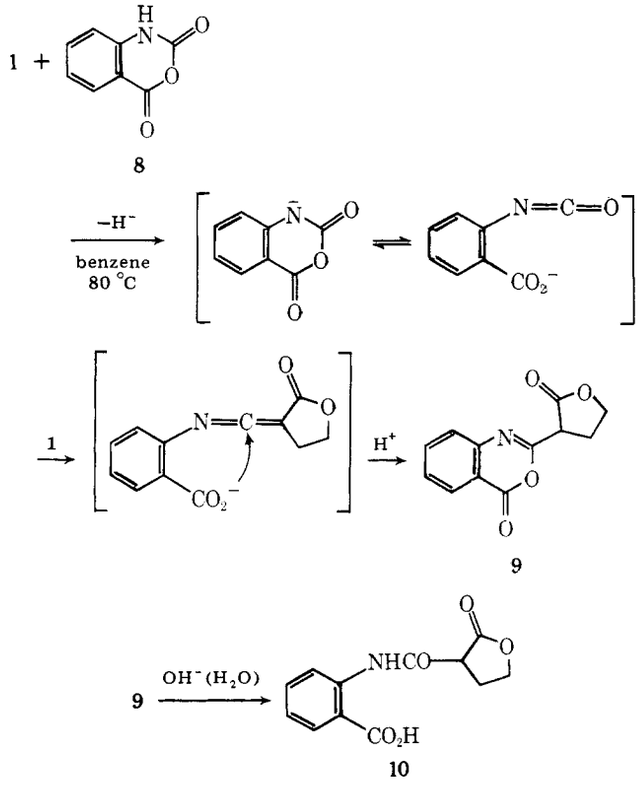


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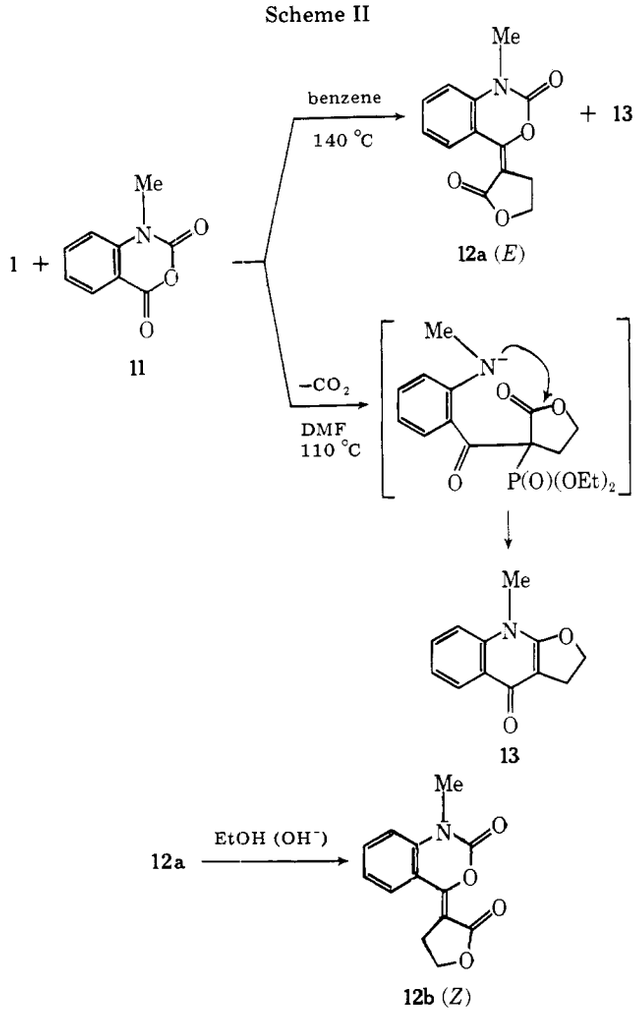
Table I. Reaction of the Phosphonate Anion 1 with Epoxides 14

Epoxides			Registry	Reaction conditions[a]		Products,[e] 15 + 16				Anal., %			
										Calcd		Found	
14	R^1	R^2	no.	Temp, °C	Time, h	Yield,[b] %	Ratio[c] of 15:16	bp °C (1 mmHg)	Empirical formula	C	H	C	H
14a	Ph	H	96-09-3	150	3	44	1:1	105–109	$C_{12}H_{12}O_2$	76.57	6.43	76.71	6.56
14b	Me	H	75-56-9	160	2	61	2:1	44–45	$C_7H_{10}O_2$	66.64	7.99	66.29	8.04
14c	Me	Me	558-30-5	180	5	60	1:3	44–46	$C_8H_{12}O_2$	68.54	8.63	68.21	8.90
14d	$-(CH_2)_5-$		185-70-6	180	5	60	1:2	100–105	$C_{11}H_{16}O_2$	73.30	8.95	73.11	9.10
14e[d]	H	H	75-21-8	180	5	55		40–41	$C_6H_8O_2$	64.27	7.19	63.78	7.86

[a] The reactions were carried out in a benzene solution in a sealed tube. [b] All yields are for distilled products. [c] Based on VPC and NMR. [d] Ethylene carbonate was used. [e] Registry No.—**15a**, 65652-07-5; **15b**, 65652-08-6; **15c**, 65652-09-7; **15d**, 65652-10-0; **15e**, 65652-11-1; **16a**, 65652-12-2; **16b**, 65652-13-3; **16c**, 65652-10-0; **16d**, 65652-14-4.

Scheme II

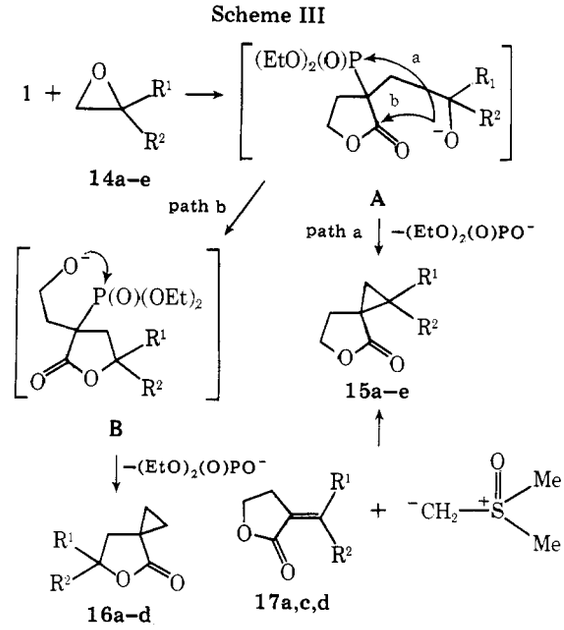


the 2 position to yield 9 and with *N*-methylisatoic anhydride 11 with the relatively reactive carbonyl group at the 4 position to afford **12a** and **13**. To the phosphonate anion **1**, **8** is more reactive than **11** as shown in the reactions using benzene as solvent. The difference in reactivities between **8** and **11** could be due to the presence of a labile hydrogen at the 1 position of **8**. That is, hydrogen abstraction of the 1 position of **8** by the phosphonate anion **1** would cause cleavage of the anhydride ring to produce a reactive intermediate isocyanate[3] in benzene solvent, which could easily react with **1** to yield a ketenimine[2] followed by cyclization to the product **9** (Scheme I). On the other hand, the formation of *N*-ethylisatoic anhydride in DMF could be similarly explained by *N*-ethylation of the solvent stabilized intermediate isatoic anhydride anion with **1** and/or α-diethylphosphono-γ-butyrolactone, as *N*-alkylation of nitrogen heterocycles with alkyl esters of phosphorus oxy acids has been already reported.[4] In contrast, the reaction between **1** and **11** in DMF would be reasonably explained by a sequence of the nucleophilic attack of **1** on the 4-position carbon atom of the anhydride ring, successive elimination of CO_2, and the nucleophilic attack of the resulting nitrogen anion on the carbonyl group of the lactone ring, followed by elimination of sodium diethylphosphate to the product **13**, as shown in Scheme II.

Such one step synthesis of the furoquinoline **13** suggests applicability to total synthesis of natural furoquinoline alkaloids such as lunacrine and balfourodine.[5]

Epoxides, Carbonates, a Lactone. Interestingly, treatment of epoxides **14a–d** in benzene solution with **1** gave a mixture of two isomers, spirolactones **15a–d** and **16a–d** in 40–60% yields, although the reaction required heating in a sealed tube at 150–180 °C for 2–5 h (Table I). In the example using propylene oxide (**14b**), separation of individual pure samples, **15b** and **16b**, was carried out by a gas chromatographic technique. The structures of **15b** and **16b** were assigned to be 1-methyl-4-oxo-5-oxaspiro[2,4]heptane and 6-methyl-4-oxo-5-oxaspiro[2,4]heptane, respectively, by elemental analysis and spectral data (see Experimental Section). The structures of the products **15a,c,d**, one of the isomers, were identified as 1-substituted 4-oxo-5-oxaspiro[2,4]heptane derivatives by comparison of their spectral data with authentic samples alternatively prepared from corresponding α-yli-

Scheme III



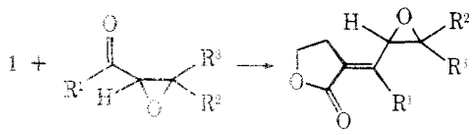
14a, 15a, 16a, 17a, R^1 = Ph; R^2 = H
14b, 15b, 16b, R^1 = Me; R^2 = H
14c, 15c, 16c, 17c, R^1 = R^2 = Me
14d, 15d, 16d, 17d, R^1, R^2 = $-(CH_2)_5-$
14e, 15e, R^1 = R^2 = H

dene-γ-butyrolactones[2,15] and dimethyloxosulfonium methylide. The structural assignments of the other isomers **16a,c,d** were similarly made by elemental analyses and spectral data of the mixtures.

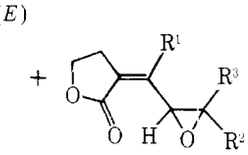
In the case where ethylene carbonate as a precursor of ethylene oxide was used under similar conditions, an anticipated single product, 4-oxo-5-oxaspiro[2,4]heptane (**15e**), was obtained in 55% yield.

Based on these results, it is reasonable to consider that the initial intermediate oxy anions A generated by nucleophilic attack of **1** on the unsubstituted carbon of epoxides **14a–d** would competitively attack the phosphonate moiety to give one of the isomers **15a–d** (path a) and the carbonyl group of the lactone ring following by the formation of the other intermediate B to yield the other isomers **16a–d** (path b) (Scheme III).

On the other hand, similar treatment of epoxy ketones **18** containing two reactive sites under mild conditions (80 °C, 1 h) selectively led to products **19**, which were derived from



18a,b **19a (*E*)**

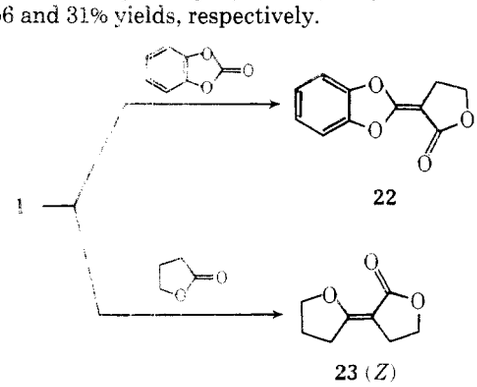


19b (*Z*)

18a, 19a, $R^1 = R^2 = R^3 = Me$
18b, 19b, $R^1 = R^2 = Ph$; $R^3 = H$

the reactions in only the carbonyl site of **18**, in good yields. Thus, to the phosphonate anion **1**, the carbonyl group was observed to be more reactive than the epoxy group.

Furthermore, we found that less reactive carbonyl compounds such as 1,2-carbonyldioxybenzene (**20**) and γ-butyrolactone (**21**) likewise reacted with the phosphonate anion **1** to produce the corresponding α-ylidene-γ-butyrolactones **22** and **23** in 56 and 31% yields, respectively.



22

23 (*Z*)

In conclusion, the α-phosphono-γ-butylrolactone anion can serve as a versatile reagent not only for the introduction of the γ-butyrolactone ring, but for syntheses of furoquinoline alkaloids and of related compounds consisting of furan ring systems.

Experimental Section

General. All melting points of products were determined with a Yanagimoto micromelting apparatus and are uncorrected. The NMR spectra were recorded with a JEOL JNM-PS-100 or JNM-PMX-60 spectrometer with tetramethylsilane as an internal standard. The IR spectra were obtained with a Jasco IRA-1 spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

Materials. α-(*O,O*-Diethylphosphone)-γ-butyrolactone,[2,6] thiophthalic[7] (**3**), homophthalic[8] (**6**), and *N*-methylisatoic anhydrides[9] (**11**), isobutylene[10] (**14c**) and methylenecyclohexane oxides[10] (**14d**), 3,4-epoxy-4-methyl-2-pentanone[11] (**18a**), chalconepoxide[11] (**18b**), and 1,2-carbonyldioxybenzene[12] (**20**) were prepared according to the established procedures.

3-(2-Oxotetrahydrofuran-3-ylidene)phthalide (4a and 4b). To a solution of an α-phosphono-γ-butyrolactone carbanion[2] (**1**) (0.02 mol) in 100 mL of dry benzene was added phthalic anhydride (**2**) (2.96 g, 0.02 mol) in 30 mL of THF with stirring and then the reaction mixture was refluxed for 3 h. The resulting solid was filtered and washed with water, and the residual solid (2.51 g, 58%) was recrystallized from a large amount of ethanol–benzene to give pure (*Z*)-**3-(2-oxotetrahydrofuran-3-ylidene)phthalide (4a):** mp 255–260 °C dec; IR (Nujol) 1775 and 1745 (C=O) and 1670 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.44 (t, J = 7.5 Hz, 2 H, methylene protons), 4.52 (t, J = 7.5 Hz, 2 H, OCH_2), and 7.80–8.20 (m, 4 H, aromatic protons); mass spectrum (70 eV) *m/e* 216 (M^+). Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.55; H, 3.37.

The filtrate was concentrated and the resulting solid (1.81 g, 42%) was recrystallized from benzene–hexane to yield pure (*E*)-**3-(2-oxotetrahydrofuran-3-ylidene)phthalide (4b):** mp 222 °C; IR (Nujol) 1775 and 1735 (C=O) and 1660 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.36 (t, J = 7.5 Hz, 2 H, methylene protons), 4.60 (t, J = 7.5 Hz, 2 H, OCH_2), 7.80–8.20 (m, 3 H, aromatic protons), and 9.15 (d, J = 7.5 Hz, 1 H, aromatic proton); mass spectrum (70 eV) *m/e* 216 (M^+). Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.42; H, 3.42.

(*Z*)-3-(2-Oxotetrahydrofuran-3-ylidene)thiophthalide (5). This derivative was similarly obtained from **1** and thiophthalic anhydride (**3**). After similar treatment, crude **5** was isolated in quantitative yield. Recrystallization of crude **5** from benzene–hexane gave the pure sample: mp 230–232 °C; IR (Nujol) 1720 and 1680 (C=O) and 1605 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.65 (t, J = 7.5 Hz, 2 H, methylene protons), 4.65 (t, J = 7.5 Hz, 2 H, OCH_2), and 7.85–8.30 (m, 4 H, aromatic protons); mass spectrum (70 eV) *m/e* 232 (M^+). Anal. Calcd for $C_{12}H_8O_3S$: C, 62.07; H, 3.47. Found: C, 61.93; H, 3.59.

3-(2-Oxotetrahydrofuran-3-yl)isocoumarin (7). The reaction of **1** with homophthalic anhydride (**6**) was carried out in a sealed tube at 140 °C for 4 h. After removal of sodium diethyl phosphate by filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel to give 3.40 g (74%) of **7:** mp 174–175 °C (from acetonitrile); IR (Nujol) 1760 and 1715 (C=O) and 1650 cm^{-1} (C=C); NMR (CD_3CN) δ 2.64 (m, 2 H, methylene protons), 3.84 (t, J = 9 Hz, 1 H, methine proton), 4.42 (m, 2 H, OCH_2), 6.65 (s, 1 H, vinylic proton), 7.30–7.90 (m, 3 H, aromatic protons), and 8.24 (d, J = 8 Hz, 1 H, aromatic proton); mass spectrum (70 eV) *m/e* 230 (M^+). Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.55; H, 4.25.

Reaction of 1 with Isatoic Anhydride (8). A. A mixture of **1** (0.02 mol) and **8** (3.26 g, 0.02 mol) in benzene (50 mL) was heated at 80 °C for 3 h. The organic layer was concentrated to give 4.20 g (91%) of crude **4*H*-2-(2-oxotetrahydrofuran-3-yl)benz[*d*][1,3]oxazin-4-one (9),** which was recrystallized from benzene–hexane to provide the pure sample: mp 176–177 °C; IR (Nujol) 1765 and 1705 (C=O) and 1660 cm^{-1} (C=N): NMR ($CDCl_3$) δ 2.83 (m, 2 H, methylene protons), 4.00 (t, J = 9 Hz, 1 H, methine proton), 4.30–4.66 (m, 2 H, OCH_2), and 7.50–8.30 (m, 4 H, aromatic protons); mass spectrum (70 eV) *m/e* 231 (M^+). Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.16; H, 3.65; N, 6.12.

B. In a similar reaction (0.02 mol scale) at 110 °C for 3 h, using DMF (50 mL) as solvent, *N*-ethylisatoic anhydride was obtained in a yield of 3.02 g (79%) together with recovered **8** (0.60 g, 18%). *N*-Ethylisatoic anhydride had mp 124–125 °C (lit.[13] mp 123–124 °C): IR (Nujol) 1760 (C=O) and 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.51 (t, 3 H, methyl protons), 4.15 (q, 2 H, methylene protons), 7.18–7.39 (m, 2 H, phenyl protons), 7.66–7.90 (m, 1 H, phenyl proton), and 8.09 (d, 1 H, phenyl proton).

Alkaline Hydrolysis of 9. A solution of **9** (2.31 g, 0.01 mol) in ethanol (50 mL) was stirred with NaOH (0.88 g, 0.022 mol) in water (20 mL) at room temperature for 5 h. After the reaction mixture was neutralized with hydrochloric acid (5%) and extracted with ether, the ether extract was distilled to remove solvents. The residue was chromatographed on silica gel using benzene–ethanol (95:5) as eluent to give 2.0 g (80%) of **2-*N*-(2-oxotetrahydrofuran-3-carboxyamido)benzoic acid (10),** which was recrystallized from acetonitrile to provide a pure sample: mp 181–183 °C; IR (Nujol) 3160 (NH), 2500 (broad, OH), 1770 (lactone C=O), 1680 (C=O), and 1660 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) δ 2.40–2.80 (m, 2 H, methylene protons), 3.96 (t, J = 8.0 Hz, 1 H, methine proton), 4.22–4.52 (m, 2 H, OCH_2), 7.06–8.52 [m, 5 H, aromatic protons (4 H) and NH], and 11.56

(s, 1 H, COOH). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.54; N, 5.62. Found: C, 58.04; H, 4.29; N, 5.60.

Reaction of 1 with *N*-Methylisatoic Anhydride (11). A. A mixture of 1 (0.03 mol) and 11 (5.31 g, 0.03 mol) in benzene (200 mL) was heated at 140 °C in a sealed tube for 7 h. The organic layer was separated and concentrated to give **2*H*,4*H*-1-methyl-(*E*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]oxazin-2-one (12a)** (2.70 g). The filtrate was chromatographed on silica gel using benzene–hexane and benzene as eluent to give **12a** (0.50 g) and **2*H*,3*H*,4*H*-9-methylfuro[2,3-*b*]quinolin-4-one (13)** (0.32 g, 5%). The combined yield of **12a** was 3.20 g (43%). The crude product **12a** was recrystallized from benzene–hexane, giving a pure sample: mp 182–183 °C; IR (Nujol) 1760 and 1710 (C=O) and 1640 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.12 (t, 2 H, methylene protons), 3.36 (s, 3 H, NMe), 4.36 (t, 2 H, OCH_2), 7.13–7.68 (m, 3 H, aromatic protons), and 8.72 (d, J = 8 Hz, 1 H, aromatic proton); mass spectrum (70 eV) m/e 245 (M^+). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.83; H, 4.43; N, 5.51.

A pure sample of **13**, which was obtained by recrystallization of the crude **13** from benzene–hexane, had mp 141–142 °C: IR (Nujol) 1660 (C=O) and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.17 (t, J = 9.0 Hz, 2 H, methylene protons), 3.63 (s, 3 H, NMe), 4.77 (t, J = 9.0 Hz, 2 H, OCH_2), and 7.03–7.80 (m, 4 H, aromatic protons); mass spectrum (70 eV) m/e 201 (M^+), 172 ($M^+ - C_2H_4 - H$), 134 ($M^+ - C_4H_4O + H$), and 132 ($M^+ - C_4H_4O - H$). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.90. Found: C, 71.62; H, 5.54; N, 6.86.

B. In a similar reaction (0.02 mol scale) at 110 °C for 4 h, using DMF (90 mL) as solvent, **13** was obtained in a yield of 3.35 g (83%) along with *N*-methylanthranilic acid (0.50 g).

Base-Catalyzed Isomerization of 12a to 2*H*,4*H*-1-methyl-(*Z*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]oxazin-2-one (12b). A solution containing **12a** (1.0 g, 4.0 mmol) and NaOH (0.32 g, 8.0 mmol) in 100 mL of ethanol was refluxed for 4 h. The solution was concentrated to give 0.51 g of recovered starting material **12a** (from acetonitrile). The filtrate was neutralized with hydrochloric acid and extracted with ether. The ether extract gave 0.40 g (40%) of **12b**, which was recrystallized from benzene–hexane to afford a pure sample: mp 123–125 °C; IR (Nujol) 1760 and 1695 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.07 (t, 2 H, methylene protons), 3.50 (s, 3 H, NMe), 4.60 (t, 2 H, OCH_2), and 7.03–8.10 (m, 4 H, aromatic protons); mass spectrum (70 eV) m/e 245 (M^+). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.58; H, 4.73; N, 5.35.

Reaction of 1 with Propylene Oxide (14b). The reaction of 1 (0.03 mol) with propylene oxide (**14b**) (3.48 g, 0.06 mol) in benzene (60 mL) was heated at 160 °C in a sealed tube for 2 h. After removal of the resulting salt by filtration, the organic layer was concentrated and distilled to give 2.31 g (61%) of a 2:1 mixture of **15b** and **16b**. Analytically pure samples of each were obtained by preparative VPC. The product **15b** had the following properties: IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.55–0.64 (dd, J = 5.4 Hz, 2.2 Hz, 1 H, cyclopropyl CH), 1.10 (d, J = 5.4 Hz, 3 H, cyclopropyl CMe), 1.35–1.60 (m, 2 H, cyclopropyl CH), 1.98–2.44 (m, 2 H, lactone CH_2), and 4.36 (t, 2 H, OCH_2).

The product **16b** had the following properties: IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90–1.04 (m, 2 H, cyclopropyl CH), 1.10–1.34 (m, 2 H, cyclopropyl CH), 1.46 (d, J = 6.2 Hz, 3 H, OCHMe), 1.88–2.08 (dd, 1 H, one proton of lactone CH_2), 2.24–2.44 (dd, 1 H, other proton of lactone CH_2), and 4.52–4.88 (m, 1 H, methine proton). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found for a mixture of **15b** and **16b**: C, 66.29; H, 8.04.

Reactions of 1 with Epoxides 14a,c,d and Ethylene Carbonate. The reactions were carried out in a similar manner. After similar treatments, mixtures of **15a,c,d** and **16a,c,d** and **15e** were obtained by distillation. The results are summarized in Table I. The mixtures of **15a,c,d** and **16a,c,d** and **15e** had the following properties.

1-Phenyl-4-oxo-5-oxaspiro[2,4]heptane (15a) and 6-phenyl-4-oxo-5-oxaspiro[2,4]heptane (16a): IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.94 (t, J = 3.0 Hz, 1 H), 1.16 (t, J = 3.0 Hz, 1 H), 1.20–2.75 (m, 4.5 H), 4.00–4.35 (m, 1 H, OCH_2), 5.45 (t, J = 7.8 Hz, 0.5 H, OCHPh), and 6.90–7.40 (m, 5 H, phenyl protons).

1,1-Dimethyl-4-oxo-5-oxaspiro[2,4]heptane (15c) and **6,6-dimethyl-4-oxo-5-oxaspiro[2,4]heptane (16c):** IR (neat) 1753 cm^{-1} (C=O); NMR spectrum ($CDCl_3$) δ 0.80–1.00 (m, 7/4 H, cyclopropyl CH), 1.20–1.36 (m, 13/4 H, cyclopropyl CH and Me), 1.50 (s, 9/2 H, $-CMe_2-$), 2.00–2.40 (m, 2 H, lactone CH_2), and 4.00–4.40 (m, 1/2 H, $-OCH_2-$).

1-Oxo-2-oxadispiro[4,0,5,1]dodecane (15d) and **4-oxo-5-oxadispiro[2,2,5,1]dodecane (16d):** IR (neat) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.77–1.05 (m, 5/3 H, cyclopropyl CH), 1.15–2.05 (m, 34/3 H, cyclopropyl and cyclohexyl protons), 2.10 (s, 4/3 H, lactone CH_2 of **16d**), 2.30 (t, J = 7.2 Hz, 2/3 H, lactone CH_2 of **15d**), and 4.00–4.50 (m, 2/3 H, OCH_2).

4-Oxo-5-oxaspiro[2,4]heptane (15e): IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90–1.10 (m, 2 H, cylopropyl CH), 1.10–1.30 (m, 2 H, cyclopropyl CH), 2.32 (t, J = 7.4 Hz, 2 H, lactone CH_2), and 4.36 (t, J = 7.4 Hz, 2 H, OCH_2).

Preparation of Authentic Spirolactones 15a,c,d. To a dimethylsulfoxide solution containing dimethyloxosulfonium methylide (0.04 mol) prepared according to the established procedure[14] was added α-benzylidene-γ-butyrolactone[2,15] (**17a**) (6.96 g, 0.04 mol) and the mixture was stirred at room temperature for 12 h; then the reaction was poured into water and extracted with ether. The ether extract was concentrated and chromatographed on silica gel using benzene and benzene–alcohol as eluent to give **15a** (2.0 g, 27%) and 1.10 g (16%) of a dimeric product of starting **17a** whose structure was tentatively assigned as 6,12-diphenyl-1,8-dioxo-2,9-dioxadispiro[4,1,4,1]dodecane on the basis of spectral data shown below. Distillation of crude **15a** gave the pure sample: bp 106–109 °C (1 mm); IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25–2.20 [m, 4 H, cyclopropyl CH (2 H) and lactone CH_2 (2 H)], 2.65 [dd, J = 9.0, 7.5 Hz, 1 H, cyclopropyl C(Ph)H], 4.05–4.40 (m, 2 H, OCH_2), and 6.90–7.45 (m, 5 H, phenyl protons). The dimeric product had mp 195–197 °C (from benzene–alcohol): IR (Nujol) 1740 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 2.0–3.0 (m, 4 H, methylene protons), 3.65–4.25 (m, 4 H, OCH_2), 4.40 (s, 2 H, –CHPh–), and 7.15–7.40 (m, 10 H, phenyl protons); mass spectrum (70 eV) m/e 348 (M^+) and 174 ($M^+ - C_{11}H_{10}O_2$). Anal. Calcd for $C_{22}H_{10}O_4$: C, 75.84; H, 5.79. Found: C, 75.53; H, 5.66.

Other authentic samples of **15c** and **15d** were prepared in the same way as **15a**, from α-isopropylidene-[2] (**17c**) and α-cyclohexylidene-γ-butyrolactone[2,15] (**17d**). The yields of authentic **15c** and **15d** were obtained in 50 and 74% yields.

15c had bp 54–56 °C (1 mm): IR (neat) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, 1 H, cyclopropyl CH), 1.20 (s, 3 H, methyl protons), 1.30 (d, 1 H, cyclopropyl CH), 1.35 (s, 3 H, methyl protons), 2.08–2.45 (m, 2 H, lactone CH_2), and 4.15–4.50 (m, 2 H, OCH_2); mass spectrum (70 eV) m/e 140 (M^+). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.36; H, 8.91.

15d had mp 51–52 °C (from benzene–hexane): IR (Nujol) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.79 (d, J = 3.6 Hz, 1 H, cyclopropyl CH), 1.29 (d, J = 3.6 Hz, 1 H, cyclopropyl CH), 1.30–2.20 (m, 10 H, cyclohexyl CH_2), 2.28 (dd, J = 6.1, 9.1 Hz, 2 H, lactone CH_2), and 4.04–4.50 (m, 2 H, OCH_2); mass spectrum (70 eV) m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.35; H, 8.79.

α-(1,3-Dimethyl-(*E*)-2,3-epoxybutylidene)-γ-butyrolactone (19a). The reaction was carried out at 80 °C for 1 h with **1** (0.03 mol) and 3,4-epoxy-4-methyl-2-pentanone (**18a**) (3.42 g, 0.03 mol) in benzene (60 mL). After similar treatment, distillation of the residue gave 4.20 g (77%) of **19a**: bp 88–90 °C (1 mm); IR (neat) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.18 (s, 3 H, epoxy Me), 1.44 (s, 3 H, epoxy Me), 2.05–2.30 [m, 3 H, cis Me of –(CO)C=C(Me)–], 2.70–3.20 (m, 2 H, lactone CH_2), 3.20–3.40 (m, 1 H, epoxy methine proton), and 4.25 (t, 2 H, OCH_2). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.98.

Since the (*Z*)- and (*E*)-methyl protons of **17c** were observed at δ 2.15–2.30 and 1.80–1.92 in the NMR spectrum ($CDCl_3$), the assignment of the stereochemistry of **19a** could be clearly decided as above.

α-(1,3-Diphenyl-(*Z*)-2,3-epoxypropylidene)-γ-butyrolactone (19b). This derivative was similarly obtained in a 7.55-g (86%) yield by using **1** (0.03 mol) and *trans*-chalconepoxide (**18b**) (6.72 g, 0.03 mol). Recrystallization of crude **19b** from benzene–hexane gave the pure sample: mp 118–119 °C; IR (Nujol) 1731 (C=O) and 1636 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.50–2.95 (m, 2 H, lactone CH_2), 3.43 (d, J = 2.2 Hz, 1 H, epoxy methine proton), 4.22 (t, 2 H, OCH_2), 5.20 (d, J = 2.2 Hz, 1 H, epoxy methine proton), and 7.10–7.45 (m, 10 H, phenyl protons); NMR (C_6D_6) δ 1.70–2.15 (m, 2 H, lactone CH_2), 3.25–3.60 [m, 3 H, OCH_2 (2 H) and epoxy methine proton (1 H)], 5.17 (d, J = 2.2 Hz, 1 H, epoxy methine proton), and 6.90–7.35 (m, 10 H, phenyl protons). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.13; H, 5.45.

2*H*-2-(2-Oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]dioxole (22). The reaction of **1** (0.03 mol) with 1,2-carbonyldioxybenzene (**20**) (4.10 g, 0.03 mol) in benzene (80 mL) was carried out at 170 °C for 12 h in a sealed tube. After similar treatment, **22** was obtained in a 3.41-g (56%) yield along with unreacted **20** (1.20 g, 29%). **22** had mp 208–209 °C (from benzene–hexane): IR (Nujol) 1740 and 1690 (C=O) and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.05 (t, J = 7.5 Hz, 2 H, lactone CH_2), 4.40 (t, J = 7.5 Hz, 2 H, OCH_2), and 7.20 (broad s, 4 H, phenyl protons); mass spectrum (70 eV) m/e 204 (M^+). Anal. Calcd for $C_{11}H_8O_4$:

C, 64.70; H, 3.95. Found: C, 64.35; H, 3.80.

α-(Z)-(Tetrahydrofuran-2-ylidene)-γ-butyrolactone (23). The reaction of 1 (0.03 mol) and γ-butyrolactone (**21**) (2.58 g, 0.03 mol) in 50 mL of benzene at 150 °C for 8 h in a sealed tube gave 1.42 g (31%) of **23**: mp 81–82 °C (from benzene–hexane) (lit.[16] mp 86.5 °C); IR (Nujol) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.85–2.39 (m, 2 H, methylene protons), 2.70–3.30 [m, 4 H, C=C(-O-)CH_2 + C=C(CO)CH_2], and 4.30 (t, 4 H, OCH_2); NMR (C_6D_6) δ 1.05–1.62 (m, 2 H, methylene protons), 2.25–2.66 [m, 2 H, C=C(-O-)CH_2], 2.70–3.05 [m, 2 H, C=C(CO)CH_2], and 3.40–3.80 (m, 4 H, OCH_2); mass spectrum (70 eV) *m/e* 154 (M^+). Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.98; H, 6.29.

The stereochemistry of **23** was determined on the basis of upfield shifts of all protons by a change of solvent from $CDCl_3$ to benzene-d_6 in the NMR spectrum.[2]

Registry No.—**1**, 52217-10-4; **2**, 85-44-9; **3**, 5698-59-9; **4a**, 65652-15-5; **4b**, 65652-16-6; **5**, 65652-17-7; **6**, 703-59-3; **7**, 65652-18-8; **8**, 118-48-9; **9**, 65652-19-9; **10**, 65701-66-8; **11**, 10328-92-4; **12a**, 65701-67-9; **12b**, 65682-25-9; **13**, 65652-20-2; **17a**, 6285-99-0; **17c**, 24186-31-0; **17d**, 21681-63-0; **18a**, 4478-63-1; **18b**, 7570-86-7; **19a**, 65652-21-3; **19b**, 65652-22-4; **20**, 2171-74-6; **21**, 96-48-0; **22**, 65652-23-5; **23**, 65652-24-6; *N*-ethylisatoic anhydride, 50332-68-8; 6,12-diphenyl-1,8-dioxo-2,9-dioxadespiro[4.1.4.1]dodecane, 65652-25-7.

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Chemistry of Carbanions. 32. Formation of the Perhydroazulene System by Intramolecular Alkylation[1]

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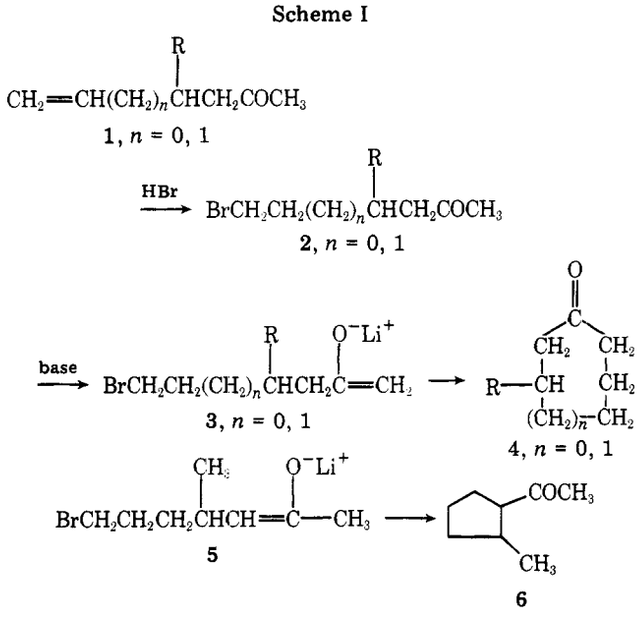
A synthetic route (Schemes II and III) for the formation of the perhydroazulene derivative **10** has been developed based upon the intramolecular cyclization of the bromo enolate **8** formed by the kinetic deprotonation of the bromo ketone **7**. Reaction of this bromo ketone with base under equilibrating conditions (KOBu-*t* in *t*-BuOH) yields the alternative cyclization product **19**. In seeking efficient synthetic routes to the intermediate unsaturated ketone **14**, we attempted to prepare the reagent $Br(CH_2)_3Li$; although this reagent could apparently be generated even at −110 °C in Et_2O–hexane solution, the material decomposed too rapidly to be useful.

In previous papers,[2,3] we have described general procedures for the formation of unsaturated ketones **1** (Scheme I) and the conversion of these intermediates **1**, via the bromo ketones **2** and the enolates **3**, to six- and seven-membered cyclic ketones **4**. In this earlier study, the cyclization of the bromo ketone **2** (R = CH_3, n = 1) to the seven-membered ketone **4** was complicated by the competing formation of the cyclopentyl ketone **6** (40% of the monomeric product). This competing cyclization **2** → **6** was attributed to a combination of three factors: (1) kinetically controlled deprotonation of methyl *n*-alkyl ketones with the hindered base *i*-Pr_2NLi typically forms 80–85% of the terminal enolate (e.g., **3**) accompanied by 15–20% of the internal enolate (e.g., **5**);[4] (2) the reaction of internal enolates (e.g., **5**) with alkyl halides is usually more rapid than the corresponding reaction with terminal enolates (e.g., **3**) that are presumably more highly aggregated;[4,5] (3) intramolecular alkylation to form five-membered rings is more rapid than the analogous reaction to form seven-membered rings.[6] This latter unfavorable rate factor is further enhanced in the present case because the cyclization **3** → **4** (n = 1) requires the additional strain of incorporating a planar enolate system into the cyclic transition state[3] while the cyclization **5** → **6** does not have this unfavorable requirement. The relatively slow rate of cyclization **3** → **4** (n = 1) allowed sufficient time for competing enolate equilbration **3** ⇌ **5** so that a significant amount of the unwanted cyclopentane by-product **6** was produced.

Scheme I



It was apparent that certain of the aforementioned difficulties associated with an intramolecular cyclization to form a cycloheptanone derivative could be mitigated by cyclization of a bromo ketone of the type **7** (Scheme II). In such cases,

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