Photochemical Cleavage of the Cyclopropane Ring of 6,20-Epoxylathyrol {1,11-Diacetoxy-3,6,6,14-tetramethyl-13-phenylacetoxy(tricyclo-[10.3.0.0^{5,7}]pentadec-3-ene-10-spiro-2′-oxiran)-2-one}

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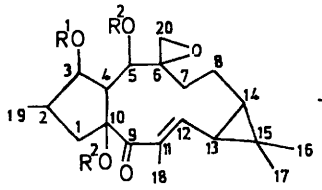
The products of direct and triplet-sensitized irradiation of 6,20-epoxylathyrol (1a) and the corresponding parent alcohol (1b) have been investigated. The major product of direct irradiation is a furan derivative, arising from *cis–trans*-isomerisation of the 11,12-double bond followed by cleavage at the cyclopropane ring and insertion of the resulting carbene into the carbonyl group. The nature of the electronic species involved in this reaction scheme is discussed.

THE naturally occurring diterpenoid epoxylathyrol, isolated from the caper spurge, *Euphorbia lathyris* L.,[1] has been shown to have structure (1a) containing a 3-oxoprop-1-enylcyclopropane system within an 11-membered ring.[2,3] The interesting electronic properties



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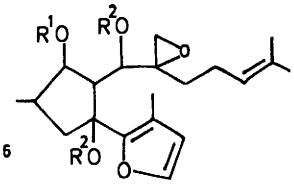

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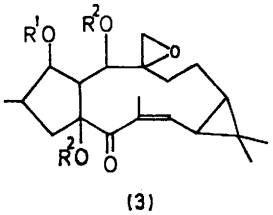

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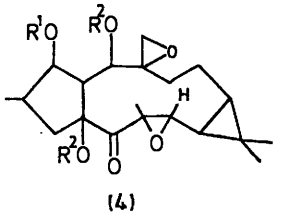
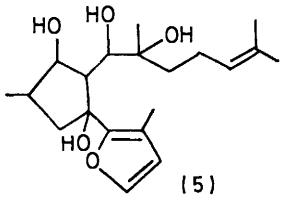


(4)

a; R^1=PhCH$_2$CO R^2=CH$_3$CO
b; R^1=R^2=H



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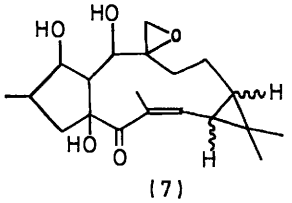

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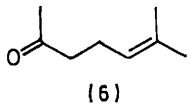

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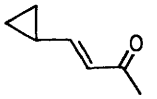

(8)

of the cyclopropyl conjugated carbonyl chromophore [4,5] have caused it to be the subject of numerous photochemical investigations using both cyclic [6] and acyclic [7] systems. Among the plethora of reaction products which have been obtained on irradiation of this chromophore system or its component parts are those arising from geometrical isomerisation,[7,8] rearrangement to cyclopentenes [6a,9] or to bicyclo[2.1.0]pentanes,[7] and fragmentation to carbenes.[7,10]

We have now investigated the response of this extended conjugated system to u.v. irradiation when contained in the ring system of 6,20-epoxylathyrol.[11]

EXPERIMENTAL

Irradiations were carried out, unless otherwise stated, on a 1% solution (100 ml) using a Philips HPK-125 mercury lamp inserted into a water-cooled, Pyrex immersion probe. Solutions were stirred and purged with a slow stream of nitrogen for 30 min prior to irradiation. Solvents (methanol, benzene, acetone) were dried and distilled before use. Naphthalene was recrystallised from methanol before use, and acetophenone was distilled under reduced pressure, b.p. 91° at 36 mmHg.

Hydrolysis of 6,20-*Epoxylathyrol* (1a).—6,20-Epoxylathyrol (700 mg) was dissolved in methanol (50 ml) containing 1% KOH (w/v) and left at room temperature under N_2 for 24 h. Most of the solvent was removed under reduced pressure, the residue was neutralised with acetic acid, and the product extracted with methylene chloride. The organic phase was washed several times with brine, dried, and evaporated to leave a gummy residue (480 mg). The hydrolysis product (1b) crystallized from MeOH–H_2O as needles, m.p. 203—204°, $\lambda_{max.}$ (MeOH) 193.5 (ε 4.800) and 273 nm (15 200), $\nu_{max.}$ (KBr) 3 470, 3 075, 2 970, 2 950, 2 930, 2 870, 1 638, and 1 628 cm^{-1} (Found: C, 68.65; H, 8.65. Calc. for $C_{20}H_{30}O_5$: C, 68.5; H, 8.65%).

Irradiation of 6,20-*Epoxylathyrol* (1a).—(a) *Direct irradiation.* A 1% solution of epoxylathyrol (1a) in benzene was irradiated in the Pyrex apparatus under nitrogen for 1.5 h. The gummy 2-[1-*acetoxy*-2-(1-*acetoxy*-6-*methyl*-2-*methyleneoxyhept*-5-*enyl*)-4-*methyl*-3-*phenylacetoxycyclopentyl*]-3-*methylfuran* (2a) obtained on evaporation of the solvent was chromatographed on Merck ready-made plates [Kieselgel H_{254}; layer thickness 2.0 mm; cyclohexane–ethyl acetate (60 : 40)], $\lambda_{max.}$ 260 nm (ε 1 200) (Found: M^+, 552. $C_{32}H_{40}O_8$ requires M, 552), $\nu_{max.}$ ($CHCl_3$) 1 732, 1 440, 1 380,

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1 235, 1 140, 1 010, and 960 cm^{-1}, δ 1.99 and 2.03 (each 3H, s 2 × CH_3CO_2), 5.30 (d, *J* 7 Hz, C*H*OAc), 5.50 (t, *J* 3 Hz, C*H*OCOCH$_2$Ph), and 0.75 (3H, d, *J* 6 Hz, C*H*$_3$CH).

(b) *Irradiation of* (1a) *with acetophenone as sensitiser.* To a solution of (1a) (100 mg) in benzene (100 ml) was added freshly distilled acetophenone (1.2 g) to give a solution which was 0.0018M in (1a) and 0.1M in acetophenone.[12] Irradiation was carried out for 15 min. Most of the solvent was evaporated *in vacuo* and the remaining acetophenone was removed by short path-distillation at 35° and 0.1 mmHg. The crude residue was purified by passing over a column of silica gel (8 g), using 15% ethyl acetate–benzene as eluant. This provided the gummy cis-*enone* (3a) (64 mg) (Found: *M*$^+$, 552. $C_{32}H_{40}O_8$ requires *M*, 552), $\nu_{max.}$ ($CHCl_3$) 1 730, 1 710, 1 460, 1 380, 1 235, 1 140, 1 065, 1 025, 970, and 945 cm^{-1}, c.d. 268, 330, and 335 nm (Δ*E* +1.80, +0.04, and −0.06), δ 0.72 (d, *J* 6 Hz, C*H*$_3$CH), 1.0br (6H, s, 2 × CH_3C), 1.98 (6H, s, 2 × CH_3CO_2), 2.03br (3H, s, C*H*$_3$C=CH), 2.59 (ABq, CH_2–O–), 3.63 (2H, s, PhC*H*$_2$CO$_2$), 5.52 (3H, m, 2 × C*H*OAc, C*H*=C), and 7.24 (5H, s, Ph).

A sample of the *cis*-enone (3a) in benzene was irradiated for 1 h without sensitiser. The sole product was the furan (2a), identical in all respects with that prepared by direct irradiation of (1a) as described above.

(c) *Irradiation of* (1a) *with acetone as sensitiser.* A solution of (1a) was irradiated in acetone for 2 h under normal conditions. Preparative chromatography in 15% ethyl acetate–benzene provided enone (3a) (85 mg), identical in all respects with that obtained as described in (b).

(d) *Irradiation of* (1a) *with naphthalene as triplet quencher.* Freshly crystallised naphthalene (1.8 g) was added to a solution of (1a) (140 mg) in benzene (100 ml) giving a solution which was 0.0025M in (1) and 0.14M in naphthalene. Irradiation was carried out for 2 h, after which the reaction mixture was evaporated to dryness and the naphthalene removed by passing over a silica gel column (10 g), using 5% ether–hexane as eluant. Further elution with 10% ethyl acetate–benzene provided a product (112 mg) which was spectroscopically identical with the furan (2a).

Irradiation of Parent Alcohol (1b).—(a) *Direct irradiation.* The alcohol (1b) was irradiated in methanol–benzene (50 : 50) for 1.5 h. The solvent was removed under reduced pressure and the residue chromatographed over silica gel (7 g), the major *product* (2b) (60 mg) being eluted with 20% ethyl acetate–benzene (Found: *M*$^+$, 350. $C_{20}H_{30}O_5$ requires *M*, 350), $\lambda_{max.}$ 3 400, 2 900, 1 603, 1 495, 1 425, 1 380, 1 035, 905, and 865 cm^{-1}, δ 7.14 and 6.12 (2 × d, *J* 2 Hz, furan H), 4.96 (m, C*H*=C), 4.22 (2H, m, 2 × C*H*OH), 3.02 and 2.71 (ABq, *J* 5 Hz, CH_2–O–), 2.19 (3H, s, furan Me), and 1.66 and 1.55 (6H, 2 × s, Me_2C=). Further elution of the column with 30% ethyl acetate–benzene provided the more polar minor *enone* (7) isomeric with (3b) (15 mg), m.p. 160—162°, $\lambda_{max.}$ 250 nm, (ε 1 100), $\nu_{max.}$ ($CHCl_3$) 3 420, 2 900, 1 675, 1 370, 1 140, 1 070, 1 000, 950, and 885 cm^{-1}, δ 5.28 (dq, *J* 9 and 1.5 Hz, C*H*=CCH$_3$), 4.27 (2H, m, 2 × C*H*OH), 3.25 and 2.58 (ABq, *J* 5 Hz, CH_2–O–), 1.98 (3H, d, *J* 1.5 Hz, CH_3C=C), and 1.01 and 1.07 (6H, s, 2 × CH_3), c.d. 317 (Δ*E* = +0.47) and 250 nm (+3.38) (Found C, 68.35; H, 8.5. $C_{20}H_{30}O_5$ requires C, 68.55; H, 8.65%).

(b) *Irradiation of* (1b) *with acetophenone as sensitiser.* A solution of (1b) (150 mg) in benzene (100 ml) was irradiated as described above in the presence of acetophenone (1.6 ml). The main product of the reaction was the ring-isomerised substance (7), obtained in pure form (104 mg) after chromatography over silica gel. The product thus isolated was identical (t.l.c., m.p., n.m.r.) with the minor product of the direct irradiation of (1b).

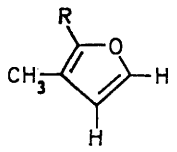
Epoxidation of the cis-*Enone* (3a). The enone (3a) (43 mg) in ethyl acetate (3 ml) was treated with *p*-nitroperbenzoic acid (25 mg) in ethyl acetate (1 ml) and the mixture was left at room temperature for 24 h, then washed with 5% sodium hydrogen carbonate solution and brine, and passed over a small plug of alumina. The *epoxide* (4a) was quickly eluted with chloroform as a gum which crystallised slowly from ether, m.p. 192—194° (Found: *M*$^+$, 568. $C_{20}H_{40}O_9$ requires *M*, 568), c.d. 320, 311, 301, and 293 nm (Δ*E* = +1.04, +2.04, +2.23, and +1.81), $\nu_{max.}$ ($CHCl_3$) 2 900, 1 735, 1 460, 1 380, 1 235, 1 160, 1 125, 1 060, 1 030, 990, and 865 cm^{-1}, δ 0.75 (3H, d, *J* 6 Hz, C*H*$_3$CH), 1.07 and 1.19 (6 H, 2 × s, 2 × CH_3C), 1.99 and 2.03 (6H, 2 × s, 2 × CH_3CO_2), 3.06 (2H, s, PhC*H*$_2$CO$_2$), 5.46 (d, *J* 3 Hz, C*H*OAc), 5.63 (d, *J* 3.2 Hz, C*H*OOCCH$_2$Ph), and 7.26 (5H, m, Ph).

Reduction of Furan (2b).—The fragmentation product (2b) (80 mg) was dissolved in dry ether (5 ml) and stirred at room temperature for 1 h with $LiAlH_4$ (60 mg). The reaction was stopped by dropwise addition of ethyl acetate. Water was then added and the product extracted several times with ethyl acetate. Preparative scale chromatography of the crude product in 50% ethyl acetate–benzene furnished the *tetraol* (5) (56 mg) (Found: *M*$^+$, 352. $C_{20}H_{32}O_5$ requires *M*, 352), δ 7.13 and 6.10 (2 × d, *J* 2 Hz, furan H), 2.16 (3H, s, furan CH_3), 1.10 (3H, s, C*H*$_3$COH), 5.01 (1H, m, CH=C), 4.50 and 3.84 (2H, 2 × m, 2 × C*H*OH), 1.53 and 1.63 (6H, 2 × s, Me_2C=C), and 1.13 (3H, d, *J* 6 Hz, C*H*$_3$CH).

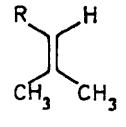
Cleavage of Tetraol (5) *with* $NaIO_4$.—The tetraol (5) (30 mg) was dissolved in methanol (3 ml) to which was added $NaIO_4$ (34 mg) in water (1 ml) and the mixture was left at room temperature for 20 h. The product was extracted with ethyl acetate and chromatographed over silica gel (3 g) using benzene as eluant. Two fractions were obtained containing a total of *ca.* 5 mg of 6-methylhept-5-en-2-one (6). This substance was identified by its behaviour on g.l.c. by comparison with that of an authentic sample (1% SE30 at 80°; co-injection of the product with the authentic ketone gave one peak under several sets of conditions).

RESULTS

Irradiation of epoxylathyrol led, after 1 h, to its quantitative conversion into a single photoproduct. The n.m.r. spectrum of this product showed, in addition to signals attributable to the ester and epoxide groups of the starting material, a pair of doublets (*J* 2 Hz) situated at δ 7.15 and 6.06 (each 1H) and a singlet at 2.04 (3H). These data are compatible with the presence of a *cis*-disubstituted furan system as in part-structure A. In addition, the appearance



A



B

of a trisubstituted double bond of type B could be inferred from the presence of singlets at δ 1.62 and 1.51 (each 3H) together with a multiplet at 4.87 (1H) for an olefinic proton. The u.v. and i.r. spectra showed that the cyclopropyl

[12] *Cf.* H. E. Zimmerman and K. G. Hancock, *J. Amer. Chem. Soc.*, 1968, **90**, 3749.

conjugated enone system had disappeared, and this together with the above data leads to the formulation of structure (2a) for the photoproduct.

When photolysis of (1) was monitored by t.l.c. at 5 min intervals, it could be seen that the fragmentation product (2a) was not formed directly from (1a), but *via* a transient intermediate, the structure of which on chemical and spectroscopic evidence can be formulated as (3a). Isolation of (3a) was facilitated by triplet sensitised irradiation of (1a) using acetone (E_T 82 kcal mol^{-1}) or acetophenone (E_T 74 kcal mol^{-1}) under conditions in which the sensitiser absorbed the major part of the incident radiation. This led to the quantitative isolation of (3a) in 10—15 min. Further irradiation of isolated and purified (3a) in the absence of sensitiser gave rise as expected to the furan (2a).

In the n.m.r. spectrum of (3a) the signal for the β-proton of the enone system had moved upfield by 1.06 p.p.m. with respect to that for the equivalent proton in epoxylathyrol, suggesting a decrease in the extent of conjugation between the carbonyl group and the adjacent double bond. This conclusion was further borne out by the u.v. spectrum, which showed that the extensively conjugated system of (1a) [$\lambda_{max.}$ 273 nm (ε 15 000)] had disappeared. Moreover, the i.r. spectrum did not show any carbonyl absorption below 1 705 cm^{-1}. The continued presence of the carbonyl group in (3a) was demonstrated by the c.d. spectrum. These data are explicable in terms of a twisted conformation for the enone grouping, hindering the efficient overlap of the π-orbitals of the C=O and C=C bonds. Such situations are known to obtain under certain conditions for medium ring enones.[13]

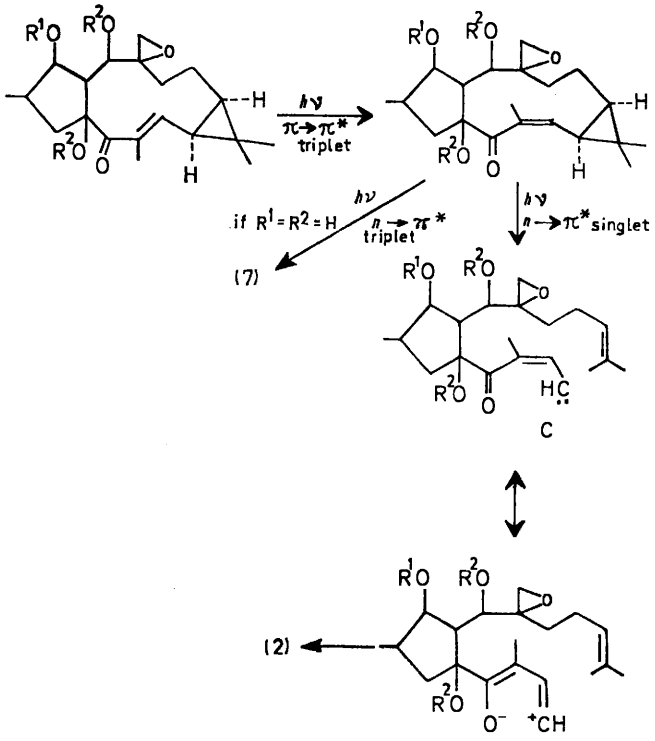
Direct chemical evidence for the lack of conjugation is obtained in the formation of an epoxide (4a) on treatment of (3a) with *p*-nitroperbenzoic acid in ethyl acetate. Mass spectral analysis showed the addition of one oxygen function, whereas from the n.m.r. spectrum it could be seen that the signals for the 11-CH_3 and 12-H had shifted upfield to δ 1.56 (s) and 3.10 (m) respectively. The other spectral characteristics of this compound were in accord with the assigned structure.

When direct irradiation was carried out on the parent alcohol (1b), obtainable from (1a) by mild base hydrolysis, two products were obtained in the approximate ratio 4 : 1. The main product was a non-crystalline gum which exhibited the spectral characteristics expected of the fragmentation product (2b). This structure was subsequently confirmed by reduction of (2b) with $LiAlH_4$ to give the tetraol (5), cleavage of which with sodium metaperiodate in MeOH–H_2O furnished, as the only isolable fragment, 6-methylhept-5-en-2-one (6). The minor product, subsequently obtained in better yields by triplet sensitised irradiation of (1b) was assigned structure (7) on the basis of spectral evidence. Its u.v. spectrum was similar to that of the *cis*-enone (3a), while the c.d. spectrum indicated the continued presence of the carbonyl group. In addition, the cyclopropane protons of (7) were clearly visible in the n.m.r. spectrum as a 2H multiplet centred at δ 0.51. This is in contrast to observations made with the other compounds of this series, in which these protons resonate at lower fields and are obscured by other signals. These data, taken in conjunction with the fact that (7) is photochemically stable (no fragmentation products are observed either on direct or sensitised irradiation) lead to the conclusion that isomerisation has occurred at the cyclopropane ring, which has consequently moved out of conjugation with the adjacent π-electron system. Geometrical isomerisation of cyclopropane rings on irradiation is a well documentated photochemical process.[7,8] It is not possible from information presently available to define the stereochemical arrangement at the cyclopropane ring in (7).

[13] N. J. Leonard and F. J. Owens, *J. Amer. Chem. Soc.*, 1958, **80**, 6039.

DISCUSSION

Our interpretation of the mechanisms of the above reactions is shown in the Scheme. The rapid *trans–cis*-isomerisation observed as the first step in the photolysis of (1a and b) is a well known photochemical process[14] and is presumed to occur *via* a triplet excited state.



SCHEME

This isomerisation was not susceptible to quenching by substantial concentrations of naphthalene, indicating that the rotation of the triplet biradical occurs faster than diffusion control. The photolysis of (1a) using acetone or acetophenone as a triplet sensitiser led exclusively to the formation of the *cis*-enone (3a). No photostationary *cis–trans*-equilibrium state was attained, a fact which is probably attributable to the higher energy of the π→π* triplet state of (3a) with respect to that of (1a). This means that it will not be susceptible to excitation by the incident light which is cut off at *ca.* 280 nm, by the Pyrex filter. Under triplet sensitised conditions with the sensitiser absorbing almost all of the incident radiation, optical pumping[15] occurs until the *trans*-enone has been completely converted to its *cis*-isomer.

The subsequent fragmentation of the *cis*-enones (3a)

[14] P. E. Eaton and K. Lin, *J. Amer. Chem. Soc.*, 1964, **86**, 2087.
[15] Ref. 6*b*, p. 20.

and (3b) to give furan derivatives has precedent in the work of Jorgenson,[7] who studied this reaction with cyclopropyl olefinic esters. The fragmentation of cyclopropyl derivatives to carbenes has been observed to occur *via* an excited singlet state of the reacting species.[7,16] This is supported by our finding that carrying out the reaction in the presence of substantial concentrations of naphthalene does not affect the progress of fragmentation, whereas triplet sensitised photolysis, in which the singlet state is by-passed, does not give any fragmentation products. The cleavage of the cyclopropane bonds which are suitably disposed to overlap with the adjacent π-system would lead to a resonance-stabilised carbene C (Scheme) of the appropriate geometry for insertion into the carbonyl group.

Isomerisation of the cyclopropane ring obviously occurs *via* an $n\rightarrow\pi^*$ triplet excited state, as shown by photolysis of the parent alcohol (1b) in the presence of acetophenone. It is noteworthy that no product analogous to (7) could be isolated from the *cis*-enone (3a), even after sensitised irradiation for several hours. The reason for this is not completely clear, but it could be explicable in terms of conformational effects which preclude any rotation of the intermediate biradical which would lead to isomerisation.

The fact that a cyclopropyl conjugated ketone of type (3a) can undergo such a ready fragmentation reaction raises some interesting mechanistic questions as to the nature of the electronically excited species involved. It has been reported [7] that cyclopropyl conjugated ketones such as 4-cyclopropylbut-3-en-2-one (8) do not undergo fragmentation or other photochemically induced reactions apart from *cis–trans*-isomerisation. The corresponding cyclopropyl acrylic esters, on the other hand, are readily amenable to fragmentation on irradiation through a Vycor filter. For these esters, it is known that the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions have comparable, energies [17] and in some cases the energy of the $\pi\rightarrow\pi^*$ transition may be even lower than that of the $n\rightarrow\pi^*$ transition.[18] After consideration of the electronic and conformational effects involved, Jorgenson [7] came out in favour of the $\pi\rightarrow\pi^*$ excited singlet state as the origin of the fragmentation products of these esters. It was further concluded that the non-reactivity of the ketone (8) could be explained in terms of the relative energies of its $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ singlet states. Since, in this case, the $n\rightarrow\pi^*$ transition will be of lower energy, no fragmentation products should be obtained if these can only arise from the $\pi\rightarrow\pi^*$ transition. In the case of the *cis*-enone (3a), however, where the lowest excited singlet is also surely $n\rightarrow\pi^*$ in origin, a quantitative yield of fragmentation product is obtained in what is obviously a very efficient photochemical process. Furthermore, the fact that cleavage of the cyclopropane ring takes place on irradiation of (3a) through a Pyrex filter, *i.e.*, under conditions in which the incident energy will be suitable only for the activation of the $n\rightarrow\pi^*$ transition, supports the conclusion that this particular singlet state is the origin of the fragmentation products.

The quantitative nature of the photochemical cleavage of (3a) is probably due to favourable stereoelectronic factors which ensure maximal overlap of the cyclopropane σ-bonds with the adjacent π-electron system.

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[17] M. J. Jorgenson and T. Leung, *J. Amer. Chem. Soc.*, 1968, **90**, 3769.

[18] W. D. Clossen, S. F. Brady, and P. J. Orenski, *J. Org. Chem.*, 1965, **30**, 4026.