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ON THE MECHANISM OF REACTIONS OF ONCOGENIC N-ACYLOXYPURINES—III
EXTENT OF RADICAL PARTICIPATION[1]

JAMES C. PARHAM* and MARY AGNES TEMPLETON
Memorial Sloan-Kettering Cancer Centre, New York, NY 10021, U.S.A.

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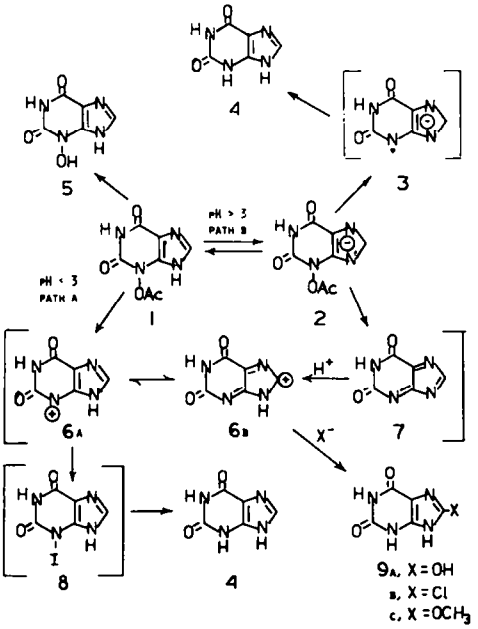
Abstract—UV irradiation of a model "activated ester" of the oncogen 3-hydroxyxanthine induced homolytic cleavage of the N–O bond and gave products arising by reduction of as well as by recombination of the solvent caged amidyl radical intermediate. Identification of the latter product constitutes the first evidence that a distinct product associated specifically with a radical from an acyloxypurine can be formed. The absence of this product among those formed spontaneously from 3-acetoxyxanthine provides the first indication that an amidyl radical is not an intermediate in the spontaneous reactions of N-acyloxy purines.

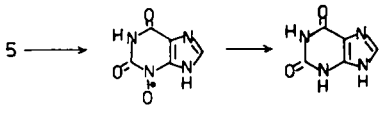
N-Oxidation of N-3 or N-7 of certain purines, including guanine and xanthine, produces potent oncogens.[2-7] Like many related carcinogens,[8] N-oxidized purines require metabolic activation by esterification to a proximate oncogenic form.[9-11] Esters of oncogenic purine N-oxides are highly reactive and undergo at least three competing reactions, including nucleophilic substitution, reduction, and ester hydrolysis.[12-16] Studies[17] on the reactions of one model ester, 3-acetoxyxanthine (**1**; Scheme 1), led to the formulation of two reaction paths (**a** and **b**) for the nucleophilic substitution of **1** at C-8. That reaction was interpreted as proceeding via the delocalized cation (**6**) which could arise directly from **1** slowly or more rapidly from the anion (**2**) depending upon pH.



Scheme 1.

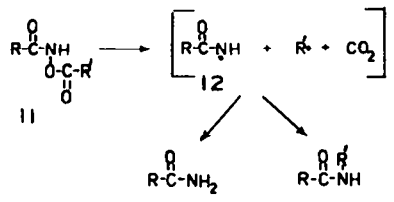
It was suggested[17] that the spontaneous reduction of up to 30% of **1** to xanthine (**4**) observed only in conjunction with path **b** might involve a radical intermediate, for which structure **3** was proposed. The basis for that proposal was the observations (a) that a radical which could be induced photochemically in solid **5** was immediately reduced to **4** upon solution in protic solvents[18] and (b) that iodide ion did not act as a nucleophile toward **1**, but instead reduced it to **4** with concomitant oxidation to iodine.[14,17] The latter evidence suggested that iodide was acting as a radical scavenger. The uptake of oxygen during the reaction of **1** in the presence of bisulfite was also interpreted as being indicative of a radical intermediate.[15] Reduction of the radical photochemically-generated in solid **5** was so rapid when dissolved in protic solvents that ESR of it in solution could not be obtained.[18] Radicals were similarly not detectable in aqueous solutions of reacting,[17] even with the use of a radical trapping agent.[16]

A subsequent study on the structure of the radical photoinduced in solid **5**, however, using oriented single crystals[19] demonstrated that it was not an amidyl radical (**3**), as concluded from studies employing poly crystalline powders,[18] but was instead the acyl nitroxyl (**10**; Scheme 2). Other studies[16,20] showed that, unlike the spontaneous formation of **4**, the oxidation of iodide ion was not unique to path **b** and that the redox reaction with iodide ion was more likely associated with the reaction of **6a** via intermediate **8** (Scheme 1). Since an understanding of the reactivities of esters of purine N-oxides is essential for elucidating the mechanism of tumor induction by these compounds, we have sought other methods that might demonstrate the extent of radical participation in the spontaneous reduction of **1**.



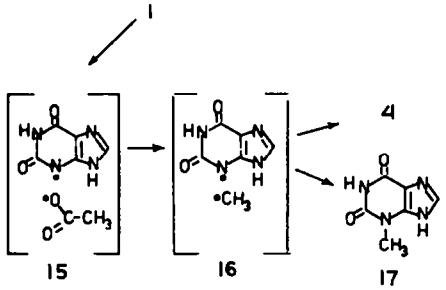
Scheme 2.

For this purpose, we examined the photo-reactions of **1** in solution. The irradiation of di-[21,22] or tri-[23] acyl hydroxylamines, e.g. **11** (Scheme 3), has been reported to induce homolytic cleavage of the N–O bond and both reduction (**13**) and radical recombination (**14**) products have been isolated. The presence of diacylamino radicals following irradiation of triacylhydroxylamines was documented by radical trapping.[23] Since **1** is in essence an N-substituted, cyclic N,O-diacylhydroxylamine, irradiation of it should yield the amidyl radical (**3**) and



Scheme 3.

might also yield a product arising via radical recombination of it. Identification of such a product, e.g. 17 (Scheme 4), would provide a compound that was uniquely associated with the radical (3). Examination of the extent of formation of that product under conditions that 4 is formed from 1 in the *absence* of *irradiation* would provide a measure of the participation of 3 in the spontaneous reactions of 1.



Scheme 4.

RESULTS AND DISCUSSION

The rate of reaction of 1 and the products derived from it are highly dependent upon experimental conditions, particularly the pH.[16,17] This requires that conditions for photochemical studies be selected to minimize spontaneous reactions of 1 during the time of irradiations. The reactions of the ester (1) are slowest ($t_{\frac{1}{2}} \sim 2$ hr) in acid solution (pH < 3) and under those conditions are primarily ester hydrolysis to 5 (85%) with 8-substitution observed to a small extent (5%)[17] (Expt #1, Table 1). Irradiation of 1 in 1 N HCl (Expt #2) caused some decomposition, decreased the formation of 5 sharply, reduced the yield of 8-chloroxanthine (9b) slightly and yielded xanthine (4) as a major product. It also produced a small amount of a new product that was identified as 3-methylxanthine (17; Scheme 4) (8.5%). The formation of 4 and 17 is consistent with the reported photoreactions of N,O-di-[21,22] and N,N,O-tri-[23] acyl hydroxylamines. Although N-hydroxypurines are known to be photoreduced,[18,24,25] xanthine does not arise by photoreduction of 5; 5 was not appreciably reduced under the same conditions but was partially degraded to non-UV-absorbing compounds (Expt #4). 3-Methylxanthine (17) presumably arises via a route similar to that leading to the formation of N-alkylamides following irradiation of diacylhydroxylamines[21,22] which involves recombination of solvent caged amidyl and Me radicals (16; Scheme 4). The latter must arise by decarboxylation of the acetoxy radicals initially formed by homolytic cleavage of the N–O bond of 1, as in 15.

Table 1.

		Conditions			Product Yield,[a] %				
Compound	Expt #	Solvent	$+h_\nu$	Time[b]	3-OH-xan (5)	Xan (4)	3-CH_3-xan (17)	8-R-Xan (9)(R=)	Total Recovery
3-Acetoxy-xanthine (1)	1	1 N HCl	-	24 h	85	-	-	5 (Cl)	90
	2	1 N HCl	h_ν	55 m	21	30	8.5	3 (Cl)	63
3-Hydroxy-xanthine (5)	3	1 N HCl	-	24 h	98	-	-	-	98
	4	1 N HCl	h_ν	45 m	83	2	-	-	85
3-Acetoxy-xanthine·HCl	5	CH_3OH	-	24 h	41	22	-	-	63
	6	CH_3OH	h_ν	43 m	-	59	6	5 (OCH_3)	73
								3 (OH)	
	7	CH_3OH[c]	-	43 m	unchanged				
3-Hydroxy-xanthine (5)	8	CH_3OH	-	45 m	99	-	-	-	99
	9	CH_3OH	h_ν	45 m	98	0.5	-	-	99
3-Acetoxy-xanthine·HCl	10	CH_3CN	h_ν	8 m	-	57	7	4 (Cl)	68
	11	HOAc	h_ν	51 m	-	53	11	5 (Cl)	69
	12	n-PrOH	h_ν	35 m	-	49	15	2 (OPr)	66
	13	n-BuOH	h_ν	21 m	-	50	21	2 (OBu)	73
3-Acetoxy-xanthine (1)	14	H_2O (pH 5)	-	24 h	17	16	-	44 (OH)	77
	15	H_2O (pH 5)	h_ν	47 m	-	49	15	5 (OH)	69

a/ Yields are based on the initial weights of 1 or 5; all reactions of 1 were carried to completion before analysis.

b/ h = hours, m = minutes

c/ No reaction detectable during time of irradiation of Expt #6.

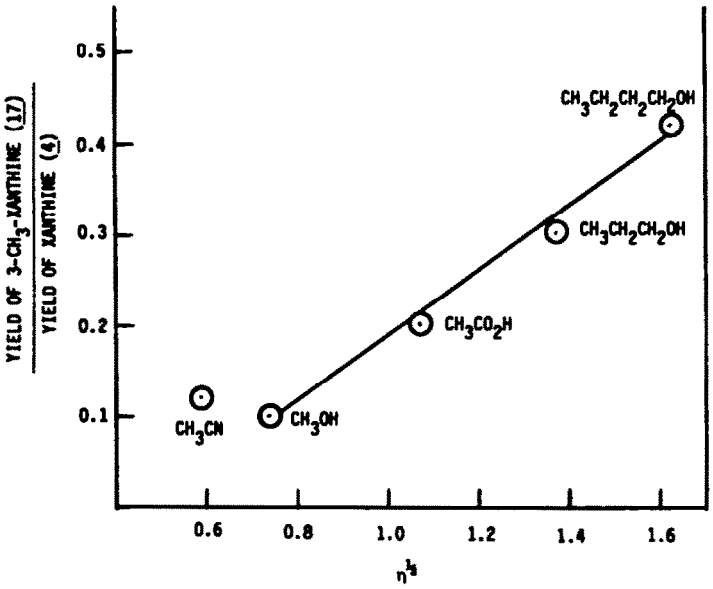


Fig. 1. Ratio of cage to non-cage product as a function of viscosity.

To verify this mechanism for the formation of 17, photolyses of the hydrochloride salt of 1 were performed in a series of organic solvents of varying viscosity. Although 1 as the free base exhibits limited solubility in only a few polar organic solvents, when dissolved it usually reacts rapidly with the solvent to afford an 8-substitution product (9). The hydrochloride salt of 1, however, proved to be significantly less reactive in organic solvents, which permitted a study of the effect of solvent viscosity on its photochemistry. The salt also formed a different set of products than the free base. While the free base of 1 reacts in methanol within minutes to afford 8-methoxyxanthine (9c) almost exclusively,[14] 1·HCl in methanol afforded no 9c. Instead it reacted very slowly to yield mainly the hydrolysis product (5) and the reduction product (4; Expt #5). The slow reactivity of 1·HCl and formation of 5 in methanol is comparable to the reaction of 1 in aqueous acid,[17] but the production of 22% of 4 and the lack of conversion to 9c were unexpected.

Irradiation of 1·HCl in methanol (Expt #6) afforded 5% of 9c (comparable to the 3% yield of 9b from the irradiation in 1 N HCl, Expt #2) as well as 3% of uric acid (9a) and gave xanthine (4) as the major product with some 3-methylxanthine (17; 6%). A control solution of 1·HCl in methanol (Expt #7) showed little change in UV spectrum during the time required for the irradiation in Expt #6. Irradiation of 5 under the same conditions (Expt #9) caused only a slight photoreduction (<1%) to 4, indicating that 5 was also not an intermediate in the photochemical formation of 4 in methanol. Irradiations of 1·HCl in other solvents (Expts #10–13) showed that the yield of 17 varied, depending upon the solvent.

Several studies have demonstrated that the observed rate of decomposition[26,27] as well as the rate of diffusion[28–30] of a radical pair are inversely proportional to the square root of the viscosity of the medium. Ratcliff and Kochi[31] demonstrated that following photochemical dissociation to a radical pair, the ratio of solvent-caged radical recombination product to "non-cage" product also varies as a function of the square root of viscosity of the medium. If 4 and 17 arise from a common intermediate and the latter results from the reaction of solvent-caged radical pair, then the ratio of the yields of 17 ("cage") and 4 ("non-cage") should exhibit a linear dependence on $\eta^{1/2}$. A plot of 17/4 *vs* $\eta^{1/2}$ (Fig. 1) showed that in a series of hydroxylic solvents there was such a dependence over a wide viscosity range. Thus the formation of 4 and 17 displays a dependence on the fluidity of the medium that is consistent with the intermediacy of a solvent-caged pair for one of the products. These data complement earlier "cross-over" experiments which first indicated that N-alkyl amides were generated from solvent-caged radical pairs[22] and indicate that 17 is formed by a similar route.

To evaluate the extent of formation of 17 from 1 under conditions where 4 is formed spontaneously from 1 (path b), pH 5 was selected. Xanthine is not formed in aqueous solution below pH 3,[17] while at pH's near neutrality the rapid rate of spontaneous reaction of 1 would complicate the photochemical study. The $t_{\frac{1}{2}}$ of 1 at pH 5 is also dependent on the buffer concentration;[16] in 0.01 M acetate buffer it was 26 min. A close examination of the product composition arising from 1 spontaneously at pH 5 did not reveal the presence of any 3-methylxanthine (17; Expt #14). To demonstrate the extent to which it might be formed, 1 was irradiated in 0.01 M acetate buffer (Expt #15). Under those conditions 5 was not formed, the yield of the 8-substitution product, uric acid (9a) was decreased sharply and the yield of xanthine was tripled, compared to the spontaneous reaction; 3-methylxanthine (17) was formed in 15% yield. This product composition is comparable to that from irradiations in other hydroxylic solvents. Based on the yield of 17 produced via 3 photochemically at pH 5, a yield of 17 about one third of 4 might be expected in the spontaneous reduction of 4, if that reaction also proceeded via the radical 3. From the yield of 4 at pH 5 of 16% (Expt #14), a yield of about 5% of 17 might be expected. The complete absence of any detectable 17 without UV irradiation under two conditions in which 4 is formed spontaneously and 17 can be produced photochemically

in readily detectable quantities, i.e. in methanol and at pH 5, suggests that the amidyl radical (3) is not present as an intermediate in the spontaneous reduction of 1, as originally proposed.[17]

In agreement with other studies,[21,22] one reaction of the photochemically-generated non-caged amidyl radical, 3, is reduction to 4. The fact that 17 can be produced from 1 only photochemically, while 4 is formed both spontaneously and photochemically raises the question whether one electronic state of 3 might be produced thermally, accounting for the formation of only 4, while two† are produced in the photochemical reaction and lead to 4 and 17. The evidence that both the Π_N ground and Σ_N excited states are readily accessible thermally for the structurally-related succinimidoyl radicals[35,41] and that there is ready mixing between the two states in amidyl radicals,‡[40] suggests that the lack of formation of 17 in the spontaneous reaction of 1 is unlikely to be due to the inability of 3 to attain the requisite electronic state thermally to produce 17. Instead, the absence of 17 in the spontaneous reaction of 1 considered with the negative ESR data[16,17] and the evidence that oxidation of iodide ion is associated with the cation 6[16] provides a strong indication that the amidyl radical (3) is not an intermediate in the spontaneous reduction of 1 and that 4 must arise by another mechanism.§

The present studies also provide evidence against a radical cation as a possible intermediate in the reactions of 1.¶ The formation of 4 and 17 following UV irradiation of 1 is consistent with the presence of a radical intermediate. It is therefore noteworthy that irradiation under acidic conditions, e.g. Expt #2 (Table 1), where a radical cation would be most likely to be found, does not lead to an enhancement in the 8-substitution reaction. That would be the expected result if a radical cation were an intermediate in the substitution reaction. The present data thus argue against a radical or radical cation intermediate in the substitution, reduction and redox reactions of 1.

EXPERIMENTAL

NMR spectra were determined with a JEOL PFT-100 NMR Spectrometer and UV spectra with a Unicam SP-800 Recording Spectrophotometer. Irradiations were performed in quartz flasks in a Rayonet Photochemical reactor equipped with eight low pressure Hg lamps emitting primarily at 254 nm and a magnetic stirrer. Most experiments were performed with deoxygenated (N_2/20 min) ~4×10^{-4} M solns (5 mg/50 ml) of 3-acetoxyxanthine hydrochloride, which was prepared as described.[16] Progress of the photochemical reactions was followed by monitoring the UV spectra of aliquots removed with a syringe. When no further change occurred, the solvent was removed under vacuum and the residue was chromatographed over a 9×150 mm column containing Dowex 50 (H^+) ion exchange resin. Water eluted **9b**,[53] **9a**,[54] **5**,[55] and **17**,[56] in that order, with good resolution; 1 N HCl eluted 4. Yields were calculated from elution volumes and known extinction constants.[53-57] The ϵ 8-ethoxyxanthine (11,000 at 274 nm)[57] was used to estimate the yields of 8-propoxy- and 8-butoxyxanthines in Table 1.

A sample of 17 for structure studies was obtained by irradiation of a soln of 80 mg of 1·HCl in 800 ml of 1-propanol, followed by chromatography over a 9×200 mm Dowex 50 (H^+) column once to separate 4 and 17 from the other products, than again to resolve 4 and 17. The assignment of structure as 3-methylxanthine was confirmed by the similarity in the UV spectral values at pH's 6 and 10;[56] by the identity of the NMR values[58] between the photoproduct and those of an authentic sample of 3-methylxanthine; and by comparative silica gel tlc's in two solvent systems (*n*-BuOH–H_2O–HOAc, 4:1:1, $R_f = 0.76$ and MeCN–H_2O–28% NH_4OH, 7:2:1, $R_f = 0.76$).

Because of the high reactivity of 1 at pH 5, solns of 1 in acetate buffer could not be degassed prior to irradiation. For Expt #15 (Table 1) the solvent was degassed first, then the sample was introduced with N_2 flushing and irradiation was initiated immediately with degassing continued throughout the irradiation.

Values for the viscosity used in Fig. 1 were those at 25° taken directly from or calculated from reported viscosity data.[59]

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†Theoretical studies indicate that the Π_N structure of amidyl and the related imidoyl radicals[32-35] is more stable than the Σ_N state and corresponds to the ground state.[36,37] The Π_N state was also indicated by ESR[33,36,38] and CIDNP[39] studies. However, products can be formed from both the ground state Π_N and excited Σ_N states. These are usually distinguishable by the extent of reactivity[35] or by the type of product formed,[40] but the difference in reactivity between the two states is *quantitative*, not *qualitative*.

‡For example, photochemical generation of amidyl radicals by homolysis of N-iodoamides can lead to γ and to δ lactams by intramolecular electrophilic cyclizations of the Σ_N and Π_N radicals, respectively, when there is no constraint on free rotation in the system.[40] The extent of formation of each product is dependent on the degree of overlap of reacting orbitals in the two states of the amidyl radical with those of the aromatic system. In rigid planar systems, however, only δ lactams are produced, indicating that there is ready hybridization between the two energy levels.

§An attractive candidate for an alternate intermediate in the spontaneous formation of 4 from 1 is the triplet state of the electron-deficient nitrogen in the resonance contributor (**6a**) since nitrenium triplets have been reported to undergo hydrogen abstraction and reduction to the corresponding amine.[42,43] However, efforts to demonstrate the presence of the triplet state of **6a** by the use of heavy atoms to promote spin inversion of the singlet to the triplet state[44,45] and increase the yield of 4 were unsuccessful.[15,17] Thus the mechanism of the spontaneous reduction of 1 to 4 must be regarded as unknown.

¶The nucleophilic substitution, reduction and redox reactions of 1 show a striking similarity to the substitution, reduction and electron transfer reactions of radical cations,[46,47] such as perylene,[48-50] thianthrene[51,52] and phenothiazine.[52] However, in contrast to the reactions of the non-radical (1), which occur spontaneously in the dark in aqueous solution, radical cations must be generated by a chemical, electrolytic or photochemical process prior to undergoing other reactions.[46]

REFERENCES

[1]This investigation was supported in part by Grants Number CA-08748 and CA-23622, awarded by the National Cancer Institute, DHEW. Ref. 20 is now designated as II in the series and Ref. 16 is designated as I.
[2]G. B. Brown, K. Sugiura and R. M. Cresswell, *Cancer Res.* **25**, 986 (1965).
[3]K. Sugiura and G. B. Brown, *Ibid.* **27**, 925 (1967).
[4]M. N. Teller, G. Stohr and H. Dienst, *Ibid.* **30**, 179 (1970).
[5]K. Sugiura, M. N. Teller, J. C. Parham and G. B. Brown, *Ibid.* **30**, 184 (1970).
[6]G. B. Brown, M. N. Teller, I. Smullyan, N. J. M. Birdsall, T.-C. Lee, J. C. Parham and G. Stöhrer, *Ibid.* **33**, 1113 (1973).
[7]M. N. Teller, J. M. Budinger, G. Zvilichovsky, A. A. Watson, J. J. McDonald, G. Stöhrer and G. B. Brown, *Ibid.* **38**, 2038 (1978).
[8]E. C. Miller, *Ibid.* **38**, 1479 (1978), and refs therein.
[9]G. Stöhrer and G. B. Brown, *Science* **167**, 1622 (1970).
[10]G. Stöhrer, E. Corbin and G. B. Brown, *Cancer Res.* **32**, 637 (1972).

[11]J. J. McDonald, G. Stöhrer and G. B. Brown, *Ibid.* **33**, 3319 (1973).
[12]U. Wölcke, W. Pfleiderer, T. J. Delia and G. B. Brown, *J. Org. Chem.* **34**, 981 (1969).
[13]U. Wölcke, N. J. M. Birdsall and G. B. Brown, *Tetrahedron Letters* 785 (1969).
[14]N. J. M. Birdsall, U. Wölcke, T.-C. Lee and G. B. Brown, *Tetrahedron* **27**, 5969 (1971).
[15]G. Stöhrer and G. Salemnick, *Cancer Res.* **35**, 122 (1975).
[16]M. A. Templeton and J. C. Parham, *J. Org. Chem.* **43**, 544 (1978).
[17]N. J. M. Birdsall, J. C. Parham, U. Wölcke and G. B. Brown, *Tetrahedron* **28**, 3 (1972).
[18]J. C. Parham, I. Pullman and G. B. Brown, *Ibid.* **29**, 3329 (1973).
[19]M. S. Jahan and C. Alexander, *Radiat. Res.* **74**, 251 (1978).
[20]J. C. Parham, M. A. Templeton and M. N. Teller, *J. Org. Chem.* **43**, 2325 (1978).
[21]B. Danieli, P. Manitto and G. Russo, *Chem. & Ind.* 329 (1969).
[22]B. Danieli, P. Manitto and G. Russo, *Ibid.* 203 (1971).
[23]F. R. Stermitz and D. W. Neiswander, *J. Am. Chem. Soc.* **95**, 2630 (1973).
[24]F. L. Lam and J. C. Parham, *J. Org. Chem.* **38**, 2397 (1973).
[25]F. L. Lam, G. B. Brown and J. C. Parham, *Ibid.* **39**, 1391 (1974).
[26]W. A. Pryor and K. Smith, *J. Am. Chem. Soc.* **92**, 5403 (1970).
[27]K. Sugiyama, T. Nakaya and M. Imoto, *Bull. Chem. Soc. Jap.* **48**, 941 (1975).
[28]T. Koenig, J. Huntington and R. Cruthoff, *J. Am. Chem. Soc.* **92**, 5413 (1970).
[29]T. Koenig, *Ibid.* **91**, 2558 (1969).
[30]T. Koenig and M. Deinzer, *Ibid.* **90**, 7014 (1968).
[31]M. A. Ratcliff and J. K. Kochi, *J. Org. Chem.* **37**, 3275 (1972).
[32]R. S. Neale, *Synthesis* 1 (1971).
[33]W. C. Danen and F. A. Neugebauer, *Angew. Chem.* Int. Ed. **14**, 783 (1975).
[34]P. Mackiewicz and R. Furstoss, *Tetrahedron* **34**, 3241 (1978).
[35]P. S. Skell and J. C. Day, *Accts. Chem. Res.* **11**, 381 (1978).
[36]T. Koenig, J. A. Hoobler, C. E. Klopfenstein, G. Hedden, F. Sunderman and B. R. Russel, *J. Am. Chem. Soc.* **96**, 4573 (1974).
[37]N. C. Baird and H. B. Kaphtal, *Ibid.* **98**, 7532 (1976).
[38]W. C. Danen and R. W. Gellert, *Ibid.* **94**, 6853 (1972).
[39]C. Brown and A. J. Lawson, *Tetrahedron Letters* 191 (1975).
[40]S. A. Glover and A. Goosen, *J. Chem. Soc.* Perkin I 1348 (1977).
[41]P. S. Skell and J. C. Day, *J. Am. Chem. Soc.* **100**, 1951 (1978).
[42]P. G. Gassman, *Accts. Chem. Res.* **3**, 26 (1970).
[43]P. G. Gassman and G. D. Hartman, *J. Am. Chem. Soc.* **95**, 449 (1973).
[44]P. G. Gassman and R. L. Cryberg, *Ibid.* **91**, 5176 (1969).
[45]A. G. Anastassiou, *Ibid.* **88**, 2322 (1966).
[46]A. J. Bard, A. Ledwith and H. J. Shine, *Adv. Phys. Org. Chem.* **13**, 156 (1976).
[47]L. Eberson, Z. Blum, B. Helgee and K. Nyberg, *Tetrahedron* **34**, 731 (1978).
[48]H. J. Shine, B. K. Bandlish and M. T. Stephenson, *Tetrahedron Letters* 733 (1978).
[49]T. R. Evans and L. F. Hurysz, *Ibid.* 3103 (1977).
[50]H. J. Shine and C. V. Ristagno, *J. Org. Chem.* **37**, 3424 (1972).
[51]K. Kim and H. J. Shine, *Ibid.* **39**, 2537 (1974).
[52]H. J. Shine, J. J. Silber, R. J. Bussey and T. Okuyama, *Ibid.* **37**, 2691 (1972).
[53]R. K. Robins, *Ibid.* **26**, 447 (1961).
[54]W. Pfleiderer, *Liebigs Ann.* 2030 (1974).
[55]J. C. Parham, T. G. Winn and G. B. Brown, *J. Org. Chem.* **36**, 2639 (1971).
[56]W. Pfleiderer and G. Nubel, *Liebigs Ann.* **647**, 155 (1961).
[57]G. Stöhrer and G. B. Brown, *Biochemistry* **15**, 2772 (1976).
[58]D. Lichtenberg, F. Bergmann and Z. Neiman, *J. Chem. Soc.* (C) 1939 (1971).
[59]*CRC Handbook of Chemistry and Physics*, (Edited by R. C. Weast) 55th Edn, pp. F50–55. CRC Press, Cleveland, Ohio (1975).