Journal of Photochemistry, *38* (1987) 357 - 363

GENERAL SYNTHESIS OF NEW ROSE BENGAL DERIVATIVES WITH ETHER FUNCTIONAL GROUPS

DANIAN XU†, ADRIAAN VANLOON, SHWN-MEEI LINDEN and D. C. NECKERS‡

Center for Photochemical Sciences, Bowling Green State University, Bowling Green, OH 43403 (U.S.A.)

(Received October 21, 1986; in revised form December 18, 1986)

Summary

All combinations of functionalization in the C-2′ and C-6 positions of rose bengal are reported. Derivatives obtained are the C-2′ ester, C-6 ether, the C-2′ ester, C-6 salt and the C-2′ salt, C-6 ether. Strategies for manipulating the reactive functional groups in the presence of one another are reported.

1. Background

Save for chlorophyll, no energy transfer donor is likely to be as important as tetrachlorotetraiodofluorescein (rose bengal), the Indian Happiness Wart. (The history of rose bengal has been published previously [1].)

From pesticidal action and pesticides [2] to tumor phototherapy [3], rose bengal's applications and potential applications are wide ranging. No less than 500 papers were published last year in which rose bengal was used for some photochemical purpose.

Until recent work [4], the organic chemistry of rose bengal has received no attention. In view of the complexity of this old [5] dye this neglect is easy to understand. After all, in even the most contemporary organic texts, important organic dyestuffs are displaced to chapters behind the index [6].

The work reported herein focuses on selectively functionalizing the two anionic positions of the dye, the C-2′ position and the C-6 position. The C-6 position is a center not routinely functionalized using ordinary nucleophilic displacement processes and it is not trivial to do so. This center is highly hindered and the negative charge highly delocalized. The ultimate purpose of our work is to develop new ways to carry xanthenes such as rose bengal to active sites in specific biological molecules [7].

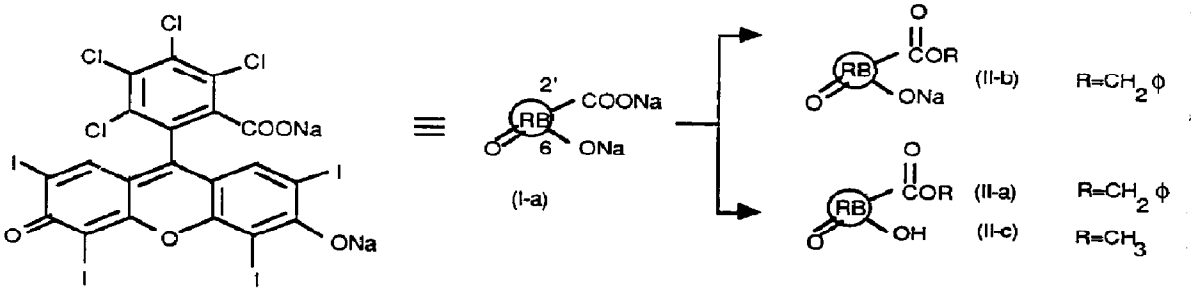
As shown in our previous papers [4], it is possible to prepare rose bengal esters by alkylating the disodium salt (I-a) at the C-2′ position (carboxylate

†Visiting Scholar, Institute for Photographic Sciences, Beijing, China.

‡Author to whom correspondence should be addressed.

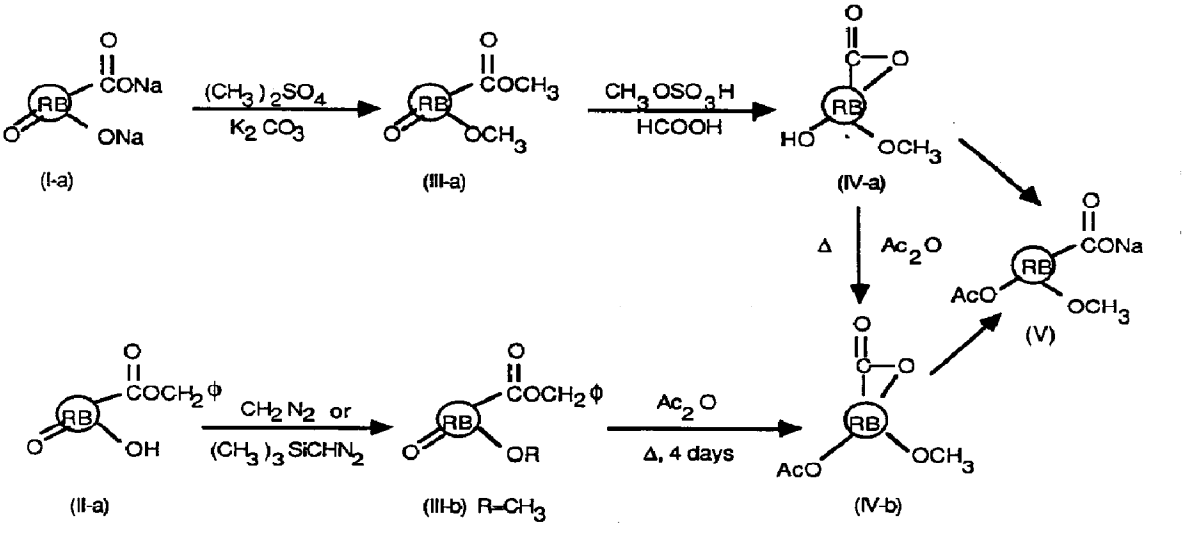
0047-2670/87/$3.50

group). The C-2′ position is by far the more nucleophilic in all polar solvents studied, and no C-6 substitution is observed. Both the molecular form (II-a) and the monosodium salt form (II-b) of the rose bengal ester can be obtained by simply choosing different solvents (Scheme 1). In contrast, alkylation at the C-6 position (phenolate group) fails to materialize even under rather severe conditions. Thus using a large excess of alkyl halide or even using the alkyl halide as solvent fails to alkylate the dye at C-6. No C-6 alkylation is observed by lengthening the reaction time from 18 h to 3 days, and using the 15-crown-5-ether complex of the disodium salt did not help.



Scheme 1.

The successful preparation of three new general rose bengal systems is reported in Scheme 2. These are the RB ester, ether (III-a - III-c), the RB lactone, ether (IV-a and IV-b) and the RB acid salt, ether (V).



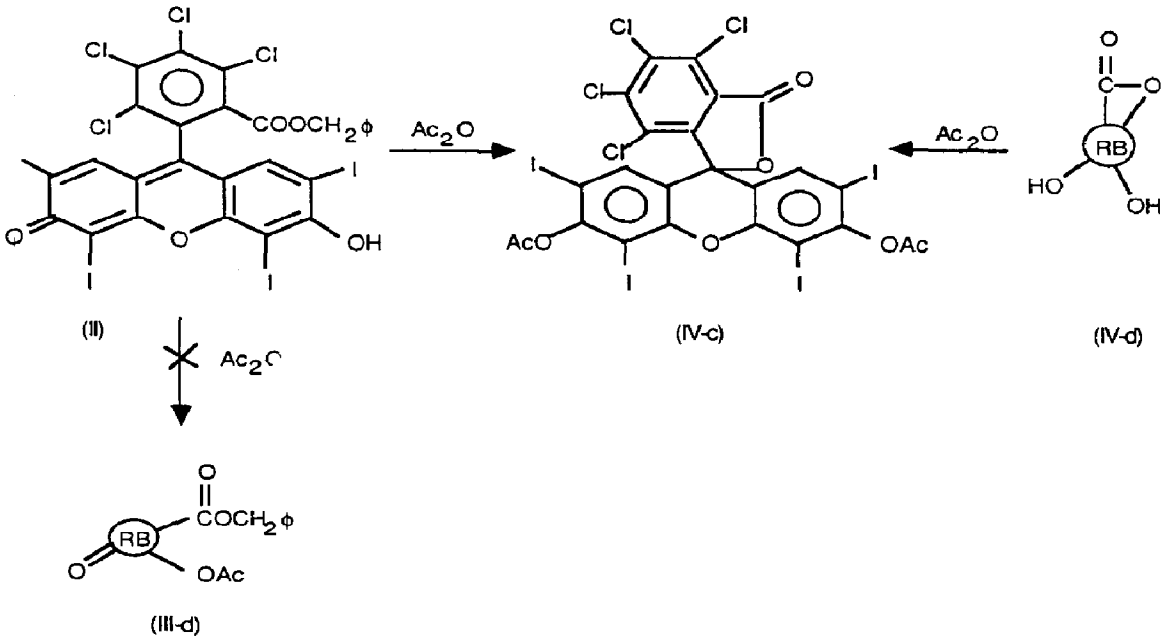
Scheme 2.

2. Results

RB methyl ester, methyl ether (III-a) was obtained in 78% yield from I-a and dimethyl sulfate in the presence of a weak base using either chloroform

or 1,2-dimethoxyethane as the solvent. When a polar solvent such as methanol or water was used, the product obtained was the molecular form of RB methyl ester (II-c). II-c did not undergo further alkylation. The absorption spectra of orange III-a in either methylene chloride or methanol and compound II-c in methylene chloride are similar. Both possess the characteristic λ_{max} at 490 nm and 400 nm [3, 4]. The absorption spectrum of compound II-c in methanol, however, is totally different. It has λ_{max} at 560 nm and 520 nm [4]. This latter spectrum is due to the dissociation of the phenolic O—H bond in the more polar solvent and is typical for a C-6 dissociated C-2′ rose bengal ester. RB benzyl ester, methyl ether (III-b) was obtained almost instantaneously from adding diazomethane to a solution of II-a. In contrast, trimethylsilyldiazomethane required 24 h before the reaction was completed. This reactivity difference reinforces the observation that the C-6 position is extremely sensitive to steric factors in alkylation. The advantage of the diazomethane route, however, is that one can synthesize different combinations of the C-2′ ester and C-6 ether by choosing the desired alkyl halide first to alkylate C-2′ and then the appropriate diazo compound to alkylate C-6.

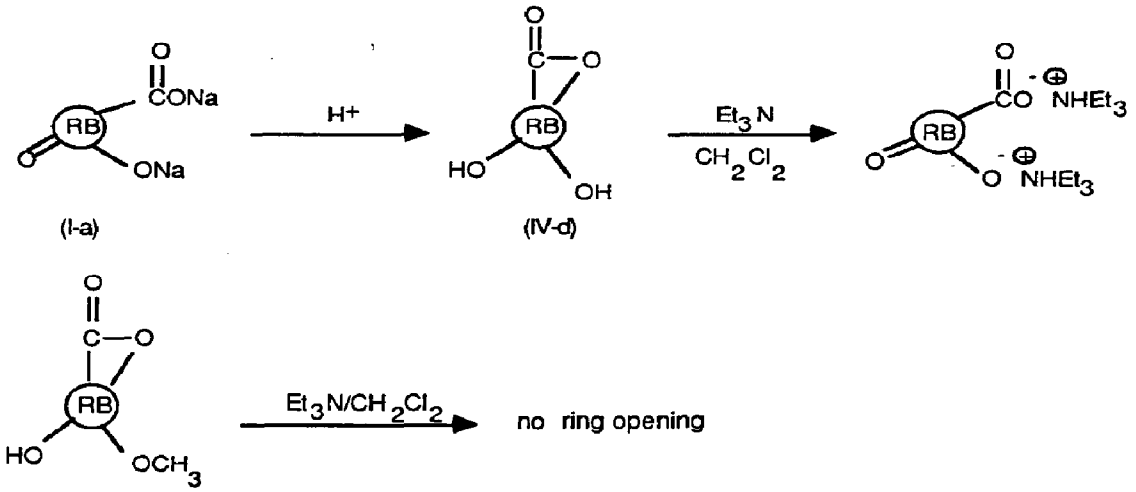
Removal of only the ester group from III-a or III-b is not an easy task. Saponifying reagents, such as sodium hydroxide in ethanol, hydrolyze not only the ester function but also the phenol ether. From previous work it was known that RB benzyl ester, when heated with acetic anhydride, eliminated the benzyl group and IV-c was obtained instead of the expected *O*-acetyl RB benzyl ester (III-d) (Scheme 3) [5]. Acetic anhydride removed the benzyl ester function from III-c, but even under conditions where



Scheme 3.

lactonization was observed, greater than 50% of the starting RB ester, ether III-b still remained in the solution after 24 h at reflux in acetic anhydride. C-3 *O*-acetyl RB lactone C-6 methyl ether (IV-b) was eventually obtained but only after 4 days at reflux. Unfortunately, its formation was also accompanied by decomposition. A better lactonization procedure was found to be refluxing either III-a or III-b in a mixture of methanesulfonic acid and formic acid [8]. Using these conditions the slightly yellow RB lactone methyl ether (IV-a) was obtained in high yield. This can then be easily converted to IV-b by refluxing in acetic anhydride.

The RB lactone ring was opened to yield the desired C-2′ salt, C-6 ether by stirring either IV-a or IV-b with sodium carbonate monohydrate suspended in 1,2-dimethoxyethane. The main product, the rose bengal C-2′ sodium salt, C-6 methyl ether (V) was obtained by column separation. Minor products were identified as unopened lactone and I-a. Even under conditions which were mildly basic, not only did the lactone hydrolyze, but so, too, did the phenol ether. Stronger bases, such as NaOH–EtOH and NaOH–EtOH–CH_2Cl_2, facilitate the opening of the lactone ring. However, these basic systems also increase the loss of the methyl ether group at C-6. In contrast, triethylamine in methylene chloride, which easily converts the RB lactone IV-d into the RB di(triethylamine) salt (Scheme 4), gives no sign of ether lactone ring opening or C-6 demethylation.



Scheme 4.

We summarize several of the unusual chemical properties of these rose bengal systems as follows: (1) C-6 is difficult to alkylate, (2) the RB ester ether (III-a and III-b) is remarkably resistant toward acid compared with the RB benzyl ester (II-a and II-b) and (3) the methyl ether group in RB lactone IV-a or IV-b is lost easily by the action of base under conditions of basic ester hydrolysis. In view of the important applications of this rather old dye, work is continuing to develop new and different derivatives.

3. Experimental details

Rose bengal (dye content, 92%) and all the other reagents were used as received. IR spectra were obtained by using a Nicolet 20DX FT IR spectrometer and electronic absorption spectra were taken by using a Varian Cary 219 UV–visible instrument. All the nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 NMR spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Tennessee. (In the past, we have used elemental analysis for iodine in the presence of chlorine. Analysis for carbon has been found to be more sensitive. Rose bengal contains virtually no hydrogen so this elemental analysis was not performed.) Most of the rose bengal derivatives decomposed at around 230 °C and no distinct melting point was observed.

3.1. Rose bengal benzyl ester molecular form (II-a)

II-a was synthesized according to the procedure of Lamberts and Neckers [4]. When the reaction was scaled up 15-fold (about 15 g of compound I-a) more than two thirds of the product obtained was in the monosodium salt form (II-b).

IR(KBr): 1735 cm^{-1}, 3415 cm^{-1}. NMR(DMSO-d_6): δ 4.98 (s, 2H, $CH_2\phi$), 7.67 - 6.76 (m, 7H). Visible(CH_2Cl_2): λ_{max} 496 nm ($\epsilon = 1.55 \times 10^4$ M^{-1} cm^{-1}), 407 nm ($\epsilon = 1.55 \times 10^4$ M^{-1} cm^{-1}).

3.2. Rose bengal benzyl ester monosodium form (II-b)

II-b was prepared according to the Lamberts–Neckers procedure [4] with the following modification in the purification step: the crude product was washed with methylene chloride to remove the small amount of II-a produced. The molecular form is obtained if the dimethylformamide solvent is not perfectly dry.

IR(KBr): 1735 cm^{-1}. NMR(DMSO-d_6): δ 4.99 (s, 2H, $CH_2\phi$), 7.41 - 6.80 (m, 7H). Visible(MeOH): λ_{max} 564 nm ($\epsilon = 1.02 \times 10^5$ M^{-1} cm^{-1}), 524 nm ($\epsilon = 3.16 \times 10^4$ M^{-1} cm^{-1}). Carbon analysis: found, 29.94%; calculated, 29.87%.

3.3. Rose bengal benzyl ester methyl ether (III-b)

II-a (2 g, 1.88 mmol) was dissolved in CH_2Cl_2 (30 ml) and an ethereal diazomethane solution (30 ml) was added. The resulting solution was stirred for 5 min. The reaction was completed in 20 s as monitored by thin-layer chromatography. After removal of the excess diazomethane by bubbling N_2 gas through the solution for 1 h, the solution was dried over anhydrous $MgSO_4$ and filtered. Compound III-b (2.01 g, 99%) was obtained after removing the solvent under reduced pressure.

IR(KBr): 1735 cm^{-1}. NMR(DMSO-d_6): δ 3.88 (s, 3H, —OCH_3), 4.96 (m, 2H, —$CH_2\phi$), 7.93 (s, 1H), 7.73 (s, 1H), 7.60 - 6.70 (m, 5H). NMR($CDCl_3$): δ 3.99 (s, 3H, —OCH_3), 5.02 (s, 2H, —$CH_2\phi$), 7.34 (s, 1H), 7.47 (s, 1H), 7.49 - 6.83 (m, 5H). Visible($CHCl_3$): λ_{max} 497 nm ($\epsilon = 1.28 \times 10^4$ M^{-1} cm^{-1}),

403 nm ($\epsilon = 1.79 \times 10^4\ M^{-1}\ cm^{-1}$). Visible(EtOH:acetone (1:1)): λ_{max} 494 nm ($\epsilon = 2.17 \times 10^4\ M^{-1}\ cm^{-1}$), 403 nm ($\epsilon = 2.91 \times 10^4\ M^{-1}\ cm^{-1}$). Carbon analysis: found, 33.70%; calculated, 31.20%.

3.4. Rose bengal benzyl ester trimethylsilyl methyl ether (III-c)

III-c was prepared in the same way as III-b. Trimethylsilyldiazomethane was used instead of diazomethane and the reaction time required was 24 h.

IR(KBr): 1735 cm^{-1}. NMR($CDCl_3$): δ 0.15 (s, 9H, $-Si(CH_3)_3$), 3.99 (s, 2H, $-OCH_2Si-$), 5.03 (s, 2H, $-OCH_2\phi$), 7.30 (s, 1H), 7.48 (s, 1H), 7.49 - 6.83 (m, 5H). Visible(CH_2Cl_2): λ_{max} 497 nm ($\epsilon = 1.74 \times 10^4\ M^{-1}\ cm^{-1}$), 403 nm ($\epsilon = 2.41 \times 10^4\ M^{-1}\ cm^{-1}$). Visible(EtOH:acetone (1:1)): λ_{max} 494 nm ($\epsilon = 1.58 \times 10^4\ M^{-1}\ cm^{-1}$), 403 nm ($\epsilon = 2.20 \times 10^4\ M^{-1}\ cm^{-1}$). Carbon analysis: found, 32.22%; calculated, 32.38%.

3.5. Rose bengal methyl ester methyl ether (III-a)

III-a was prepared by refluxing a mixture of I-a (3.21 g, 3.1 mmol), dimethyl sulfate (3 ml, 31 mmol) and potassium carbonate (4.5 g) in 1,2-dimethoxyethane (DME) (50 ml). After 5 h the precipitates were filtered and washed with methylene chloride. The filtrate and CH_2Cl_2 washings were combined and dried and the solvent was removed *in vacuo*. The product obtained weighed 2.24 g (71% yield).

IR(KBr): 1736 cm^{-1} (C=O), 1051 cm^{-1} and 1128 cm^{-1} (O—CH_3). NMR($CDCl_3$): δ 3.61 (s, 3H, CO_2CH_3), 3.99 (s, 3H, $-OCH_3$), 7.64 (s, 1H), 7.40 (s, 1H). Visible($CHCl_3$): λ_{max} 497 nm ($\epsilon = 1.19 \times 10^4\ M^{-1}\ cm^{-1}$), 403 nm ($\epsilon = 1.69 \times 10^4\ M^{-1}\ cm^{-1}$). Visible(EtOH:acetone (1:1)): λ_{max} 492 nm ($\epsilon = 1.71 \times 10^4\ M^{-1}\ cm^{-1}$), 402 nm ($\epsilon = 2.37 \times 10^4\ M^{-1}\ cm^{-1}$). Carbon analysis: found, 26.10%; calculated, 26.37%.

3.6. Rose bengal lactone methyl ether (IV-a)

III-a (1.02 g, 1 mmol) in a mixture of formic acid (25 ml) and methanesulfonic acid (1.8 ml, 25 mmol) was refluxed for 15 h. The pale orange precipitates formed were collected, washed with water (3 × 20 ml) and methanol (2 × 10 ml), and dried in a vacuum overnight (at about 60 °C). The yield was 0.91 g (91%). This compound had also been synthesized in 89% yield by replacing III-a by III-b.

IR(KBr): 1771 cm^{-1}. NMR($CDCl_3$): δ 3.91 (s, 3H, $-OCH_3$), 6.22 (broad s, 1H, OH), 7.19 (s, 1H), 7.13 (s, 1H). UV–visible(CH_2Cl_2): λ_{max} 242 nm ($\epsilon = 1.27 \times 10^5\ M^{-1}\ cm^{-1}$) and no absorption in the visible. Visible(EtOH: acetone (1:1)): λ_{max} 565 nm ($\epsilon = 5.23 \times 10^3\ M^{-1}\ cm^{-1}$), 525 nm ($\epsilon = 2.22 \times 10^3\ M^{-1}\ cm^{-1}$) indicating 5% IV-d existed.

3.7. O-Acetyl rose bengal lactone methyl ether (IV-b)

A mixture of IV-a (0.5 g) and acetic anhydride (4 ml) was refluxed for 5 h. A white precipitate was collected, washed with water and dried in a vacuum oven (60 °C) overnight. The yield was 0.5 g (97%).

IR(KBr): 1785 cm^{-1}. NMR($CDCl_3$): δ 2.43 (s, 3H, CH_3CO-), 3.91 (s, 3H, $-OCH_3$), 7.24 (s, 1H), 7.21 (s, 1H). UV–visible($CHCl_3$): no absorption

in the visible region. Visible(EtOH:acetone (1:1)): no absorption in the visible region. Carbon analysis: found, 27.24%; calculated, 26.83%.

3.8. Rose bengal acid sodium salt, methyl ether (V)

A mixture of IV-a (0.10 g, 0.10 mmol) and sodium carbonate monohydrate (0.18 g) in DME (3 ml) was stirred at room temperature for 12 h. During that period, the color of the solution gradually turned darker and darker red. After filtration, the condensed filtrate was subjected to column chromatographic separation (silica gel). The light yellow compound collected from the first band with CH_2Cl_2 as the eluting solvent (IR, 1771 cm^{-1}) indicated that the lactone ring still remained. The main product was collected from the second band, using THF as an eluting solvent, and it weighed 0.068 g. The third band was then eluted with EtOH.

The following results were obtained for band 2 (mainly compound V). IR: 1602 cm^{-1}. NMR(DMSO-d_6): δ 3.77 (s, 3H, $-OCH_3$), 7.12 (s, 1H) and 7.58 (s, 1H). Visible(EtOH): λ_{max} 493 nm ($\epsilon = 5.85 \times 10^3\ M^{-1}\ cm^{-1}$), 403 nm ($\epsilon = 6.61 \times 10^3\ M^{-1}\ cm^{-1}$). Visible(EtOH:acetone (1:1)): λ_{max} 486 nm ($\epsilon = 5.43 \times 10^3\ M^{-1}\ cm^{-1}$), 394 nm ($\epsilon = 5.93 \times 10^3\ M^{-1}\ cm^{-1}$).

The following results were obtained for band 3 ([V]:[I-a] = 70:30). IR: 1602 cm^{-1}. NMR(DMSO-d_6): δ 3.79 (s) for V, 7.06 (s) and 7.58 for V, 7.32 (s) for I-a.

Acknowledgments

This work was supported by the National Science Foundation (CHE-8503551). The authors are grateful for this support. We thank Mrs. Mary Fieser for providing us with the name "Indian Happiness Wart".

References

1 J. Paczkowski, J. J. M. Lamberts, B. Paczkowska and D. C. Neckers, Photophysical properties of rose bengal and its derivatives (XII), *J. Free Rad. Biol. Med., 1* (1985) 341.
2 R. L. Rawis, Light-activated pesticides, *Chem. Eng. News*, (September 22, 1986) 21 - 25.
3 T. Hasan, R. Rodenhouse and D. C. Neckers, unpublished results, 1986.
4 J. J. M. Lamberts and D. C. Neckers, Rose bengal and non-polar derivatives: the birth of dye sensitizers for photooxidation, *Z. Naturforsch., Teil B, 39* (1984) 474.
J. J. M. Lamberts and D. C. Neckers, Rose bengal and nonpolar derivatives, *J. Am. Chem. Soc., 105* (1983) 7465.
5 A. Von Baeyer, *Ber., 8* (1875) 146.
6 A. Streitwieser and C. H. Heathcock, *Introduction to Organic Chemistry*, MacMillan, New York, 1981, 2nd edn.
R. T. Morrison and R. N. Boyd, *Organic Chemistry*, Allyn and Bacon, Boston, 1983, 4th edn.
D. C. Neckers and M. P. Doyle, *Organic Chemistry*, Wiley, New York, 1979.
7 D. C. Neckers, *J. Chem. Educ.*, in the press.
8 B. Loev, *Chem. Ind.*, (1964) 193.