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Substituent Effects on the Product Distribution in Diazo Amide Photochemistry. Role of Ground-State Conformational Populations

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Effects of substituents on the photochemical processes of several α-diazo amides (**1a**–**f**) have been studied [$RCN_2CONR'R''$ (**1**): **a**, R = H, R′ = R″ = Et; **b**, R = H, R′ = R″ = Me; **c**, R = H, R′ = Ph, R″ = Me; **d**, R = H, R′ = Ph, R″ = Et; **e**, R = $COCH_3$, R′ = R″ = Et; **f**, R = $COCH_3$, R′ = Ph, R″ = Et]. Irradiation of **1b** in ethyl ether and acetone afforded, in addition to a β-lactam, the reaction products with the solvents, i.e., $EtOCH_2CONMe_2$ and 1,3-dioxolane, respectively, whereas similar irradiation of **1a** in these solvents gave only intramolecular reaction products, i.e., β- and γ-lactams. Displacement of one of the alkyl groups on the amide nitrogen with a Ph group markedly changed its photochemical processes. Thus irradiations of **1c** and **1d** in MeOH gave oxindole almost exclusively. Introduction of an acetyl group on the diazo carbon also caused a change in the product distributions. Photolysis of **1e** in methanol gave, for example, the Wolff rearrangement (WR) product of Me migration and a β-lactam, whereas similar irradiation of **1f** afforded WR product and oxindole. The results are interpreted as indicating that the β-lactam, the oxindole, and the WR product are derived from the excited singlet state of *s-Z* form of the diazo amide itself, whereas that of *s-E* form dissociates nitrogen to generate singlet carbene, and that populations of each conformers in the ground state are important in determining the photochemical processes of the α-diazo amide.

It has been reported[1] that the photolysis of *N,N*-diethyldiazoacetamide (**1a**) gives two possible intramolecular C–H insertion products, β- and γ-lactams, in a roughly equal ratio. It was generally believed that the key and common intermediate leading to both lactams in this reaction was free carbene and that intramolecular lactam formation readily occurred since one ethyl group must remain adjacent to the incipient carbene as a consequence of the planar peptide bond. The examination of the effect of sensitizer and quencher on the product distributions revealed[2] that, although carbene presumably generated from the *s-E* form of **1a** is indeed involved in the formation of the γ-lactam, the key intermediate leading to the β-lactam is the excited singlet-state *s-Z* conformer of the diazoamide itself rather than free carbene (Scheme I). The reaction patterns of each reacting state are suggested[2] to be affected by a conformational effect, i.e., the closest approach distance to the carbene center, for the carbene process, and an electronic one, i.e., stabilization in the transition state, for the excited **1a** reaction.

The intramolecular β-lactam formation in the photolysis of α-diazo amide has attracted much attention also from the synthetic standpoint since the reaction has been shown[3] to be a general method to synthesize families of β-lactam antibiotics, e.g., penicilins, and hence many efforts[4] have been made to generate other structures containing the β-lactam unit by the diazo amide approach. Thus, it is very important to elucidate the general applicability of this on method for generation of lactams. In the light of these intensifying interests, we investigated the effect of the precursor diazo structure (**1a**–**f**) on its photochemical processes.

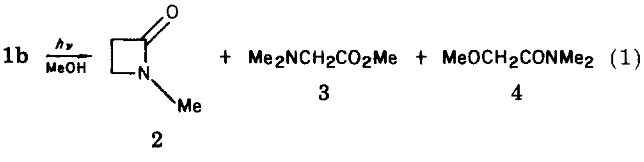
Results and Discussion

Effect of Substituents on Amide Nitrogen. From the reaction mechanism outlined in Scheme I, one can

$$\overset{N_2}{\overset{\|}{RC}}CONR'R''$$

1a, R = H; R′ = R″ = Et
b, R = H; R′ = R″ = Me
c, R = H; R′ = Ph; R″ = Et
d, R = H; R′ = Ph; R″ = Me
e, R = $COCH_3$; R′ = R″ = Et
f, R = $COCH_3$; R′ = Ph; R″ = Et

easily expect that displacement of ethyl groups on the amide nitrogen of **1a** with methyl groups would lead to the intermolecular carbene reaction with surrounding molecules upon direct irradiation since the relative populations of *s-E* and *s-Z* conformers are not changed so much in going from *N,N*-diethyl to *N,N*-dimethyldiazo amide, and singlet carbene generated from the *s-E* form of **1b** would have no available intramolecular C–H bonds to insert. Photolysis of **1b** in methanol gave OH insertion product **4** in addition to the β-lactam **2** and the Wolff rearrangement (WR) product **3** (eq 1). This is not so surprising,



however, since methanol is known[5] to be an efficient quencher for singlet carbene, and similar quenching of the intramolecular pathway, i.e., γ-lactam formation, from singlet carbene by methanol has been also observed[1,2] in the photolysis of **1a**. More intriguing results are obtained in the photolysis of **1b** in ethyl ether and acetone, in which

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(1) Rando, R. *J. Am. Chem. Soc.* **1970**, *92*, 6706; **1972**, *94*, 1629.

(2) Tomioka, H.; Kitagawa, H.; Izawa, Y. *J. Org. Chem.* **1979**, *44*, 3072.

(3) Corey, E. J.; Felix, A. M. *J. Am. Chem. Soc.* **1965**, *87*, 2093.

(4) (a) Lowe, G.; Ramsay, M. V. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 479. (b) Golding, R. T.; Hall, D. R. *Ibid.* **1975**, 1517. (c) Lowe, G.; Parker, J. *Chem. Commun.* **1971**, 577. (d) Brunwin, D. M.; Lowe, G.; Parker, J. *Ibid.* **1971**, 865. (e) Oida, S.; Yoshida, A.; Ohki, E. *Chem. Pharm. Bull.* **1978**, *26*, 448.

(5) (a) Tomioka, H.; Izawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 6128. Similar quenching of the intramolecular pathway of singlet carbene by methanol has been demonstrated in the 1,2 hydrogen shift of $PhCCH_3$: Tomioka, H., unpublished observation. (b) There is a possibility that under certain conditions some diazo compounds are protonated by alcohols and, therefore, that the reactions take place in the diazonium ion. See for example: Bartz, W.; Regitz, M. *Chem. Ber.* **1970**, *103*, 1463. However, the possibility may be removed in the present system by the findings that (1) OH insertion products, possible reaction products from diazonium ion, were not suppressed appreciably in the photolysis of **1a**,**b** in frozen MeOH at −196 °C, where proton donor activities of alcohols are greatly suppressed and that (2) the sensitized decompositions of **1a**,**b** also lead to the OH insertion.

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Scheme I

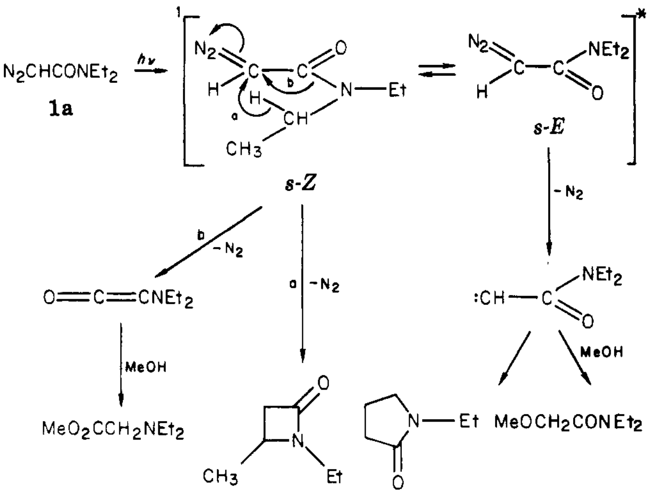


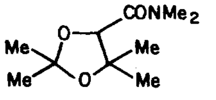
Table I. Photolysis of 1b in Various Solvents[a]

solv	[Ph_2CO], mM	rel yield, %[b] 2	3	4-6
MeOH	0	10.2	32.3	57.5
	125	0	~2	98
Et_2O	0		28.0	72.0
	125		3	97
Me_2CO	0		36.2	63.8
	125		~1	99

[a] Irradiations were performed on a 25 mM solution of **1b** in Pyrex. [b] Yields were determined by GC. Absolute yields were 50–60% for direct photolytic runs but dropped to 30–40% for sensitized runs.[8]

no intermolecular reaction products were detected in the photolysis with **1a**. Thus, irradiation of **1b** in ether gave **5**, which apparently arose from a C–O displacement reaction of singlet carbene[6] with ether, in addition to the β-lactam **2**. Similar irradiation of **1b** in acetone also resulted in the formation of solvent-incorporated products, i.e., 1,3-dioxolane (**6**,[7] Table I). When irradiation was carried out in the presence of benzophenone as a triplet sensitizer, the β-lactam formation was almost completely suppressed whereas the yields of intermolecular reaction products **4–6** were not affected.[8] Dominant formation of singlet products **4–6** even under sensitized conditions is understood as indicating that rapid intersystem crossing of the initially formed triplet carbene to the singlet is significant as has been frequently observed[2,9] in the other similar carbene systems. The fact that addition of piperylenes, an efficient quencher for both triplet excited-state and triplet carbene,[10] caused no change in the product ratio also supports the above assignment. These results can be explained in terms of the reaction mechanism outlined in Scheme I, in which singlet carbene generated from **1b** is not able to undergo intramolecular C–H insertion into the methyl group to form the β-lactam and hence is forced to react with the solvents. The results also imply that the intramolecular C–H insertion is quite sensitive to the simple proximity of the hydrogen to the carbene center in the trianglar transition state in this special carbene system.[11]

$EtOCH_2CONMe_2$
5



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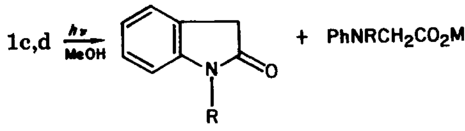

(2)

	7	8
R = Me	64%	3%
R = Et	54%	2%

Displacement of one of the alkyl groups on the amide nitrogen with a phenyl group caused a change in the photochemical processes of the α-diazo amide. Thus, irradiation of **1c** in methanol gave *N*-methyloxindole (**7**, 64%) as the sole isolable product. GC analysis of the reaction mixture showed the presence of a small amount (3%) of the WR product (**8**, eq 2). Similar irradiation of **1d** also resulted in the almost exclusive formation of **7** (54%) along with lesser amounts of **8** (2%) and β-lactam (1.5%). Neither OH insertion product nor other lactams were isolated in each of the reaction mixtures. Attempts to examine the effect of sensitizer on the reaction modes from **1c** and **1d** were unsuccessful since sensitization of **1c,d** led to complex mixtures apparently as a result of extremely rapid photodecomposition[12a] of **7** under these conditions. Formation of **7** was not appreciably quenched, however, even in the presence of a high concentration of piperylenes. The origin of the observed change in the reaction modes caused by phenyl substitution is quite interesting. Obviously, introduction of a phenyl group should displace the fractional population of the *s-E* and *s-Z* conformers in favor of the *s-Z* form due to increased steric repulsion between the diazo and phenyl groups. If the mechanism shown in Scheme I is applied, the formation of **7** might involve a concerted process with nucleophilic attack of the π electrons of phenyl ring on the diazo carbon, with loss of N_2 occurring simultaneously in the excited singlet state. Inspection of the Dreiding models indicates that such a process is geometrically more favorable than a competing 1,4 hydrogen shift forming β-lactam (path a in Scheme I), which explains the almost complete suppression of β-lactam formation from the *s-Z* form. Since we can not assign the exact intermediate leading to each reaction product at present, a carbenic mechanism is not eliminated. However, the fact that neither OH insertion products nor γ-lactams were detected

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[6] (a) Iwamura, H.; Imahashi, Y.; Kushida, K.; Aoki, K.; Satoh, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1690. (b) Agopian, G. K.; Brown, D. W.; Jones, M., Jr. *Tetrahedron Lett.* **1976**, 2931.

[7] Formation of dioxolane has been reported in the photolysis of CH_2N_2 in acetone. See for example: Bradley, J. N.; Ledwith, A. *J. Chem. Soc.* **1963**, 3480.

[8] Control experiments showed that reaction products were not unduly reactive under these conditions. GC analysis of the reaction mixtures indicated the presence of several byproducts including *N,N*-dimethylacetamide and *N,N,N′,N′*-tetramethylmaloamide, characteristic product of triplet carbene, in small amounts, which accounts for the balance of products. See for example: Moss, R. A.; Jones, M., Eds. "Carbenes"; Wiley: New York, 1973; Vol. I; *Ibid.*, 1975; Vol. II.

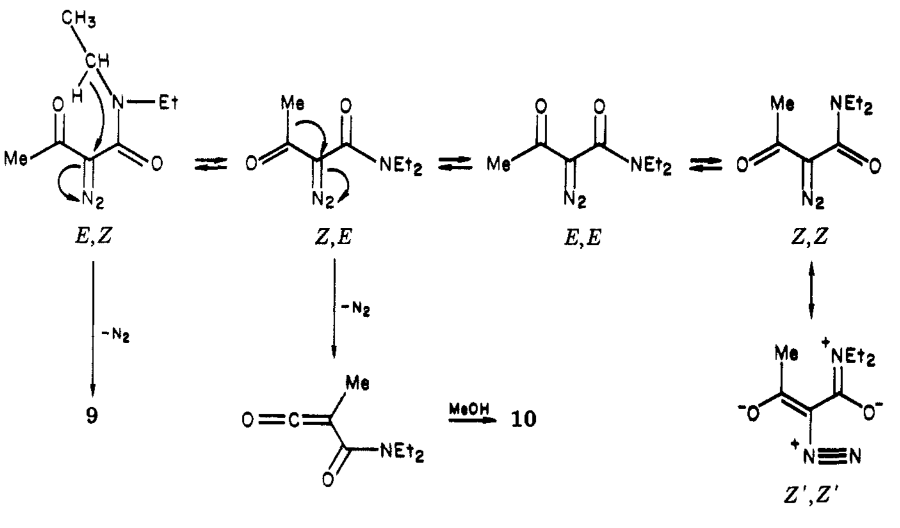
[9] (a) Roth, H. D.; Manion, M. L. *J. Am. Chem. Soc.* **1976**, *98*, 3392. (b) Roth, H. D. *Acc. Chem. Res.* **1975**, *10*, 85. (c) Creary, X. *J. Am. Chem. Soc.* **1980**, *102*, 1611. (d) Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* **1980**, *45*, 5278.

[10] Moss, R. A., ref 8, Vol. I, p 153ff.

[11] The intramolecular C–H insertion of carbene generated from (2-*n*-butylphenyl)diazomethane has been shown to be relatively insensitive to the distance between divalent center and C–H bonds: Baer, T. A.; Gutsche, C. D. *J. Am. Chem. Soc.* **1971**, *93*, 5180; Gutsche, C. D.; Bachman, G. L.; Udel, W.; Bäuerlein, S. *Ibid.* **1971**, *93*, 5172.

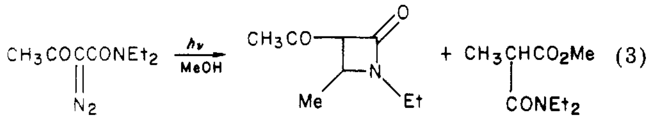
[12] (a) Döpp, D.; Weiler, H. *Chem. Ber.* **1979**, *112*, 3950 and references cited therein. (b) We tentatively assign **9** as a *trans*-β-lactam on the basis of the characteristic coupling constant (2.0 Hz): Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941; Sparrow, K. D.; Spotswood, T. M. *Ibid.* **1965**, 3325. Although other isomers may be contained in the total reaction product, isolation has not been possible thus far.

Scheme II



suggest that free singlet carbene is not generated in the photolysis of **1c,d**, since methanol is known[5] to quench even a very rapid 1,2 hydrogen shift of singlet carbene.

Effect of Substituents on the Diazo Carbon. Substituents on the diazo carbon are expected to have a profound effect not only on the fractional populations of conformers but also on the reactivity of generated carbene and hence on the reaction patterns. With this in mind, we photolyzed *N,N*-diethyldiazoacetoacetamide (**1e**) in methanol (eq 3) to see what effect this would have on the



1e **9** **10**

	9	10
direct	16%	30%
sensitized	25%	trace

intramolecular insertion processes. Direct irradiation of **1e** gave β-lactam **9**[12b] and ester **10**, apparently arising from the Wolff rearrangement of the methyl group on the acetyl function. No detection of OH insertion product and γ-lactam again implies that singlet carbene is not involved in the photochemical process of **1e** either. If one assumes a coplanar molecule for **1e** as a result of contribution of resonance contributors, e.g., *Z′,Z′*, one would expect four possible rotamers for **1e** (Scheme II). The influence of steric and electrostatic effects exerted between the Me, NEt_2, C=O, and C=N=N groups and the above factor cause variations in the relative energy of four conformers and, therefore, in their populations.[13] Electrostatically, conformers *E,Z* and *Z,Z* are favorable as a result of electrostatic attraction whereas *E,E* is less stable due to the repulsion between two C=O groups, as is predicted from the canonical form *Z′,Z′*. Sterically, on the other hand, *E,E* would suffer from steric repulsion in the $Me-N_2-NEt_2$ group, all in a *Z* relationship, and in *Z,Z* the nonbonding repulsion between Me and NEt_2 would be severe. Thus, one would expect that conformers *E,Z* and *Z,E* would be more stable than *E,E* and *Z,Z*. Thus, by analogy to the behavior of **1a** (Scheme I), the formation of **9** can be explained in terms of 1,4 hydrogen shift in the excited state of the more stable *E,Z* conformer, which presents the desirable situation of the migrating H atom group being trans to the leaving N_2 group. In the *Z,E* conformer, on the other hand, dissociation of N_2 to generate singlet carbene leading to the γ-lactam would be expected. However, this conformer also presents a favorable situation for Me migration to form **10** (path b in Scheme I) since migrating and leaving groups in *Z,E* are situated in positions with respect to each other which permit the migration. Moreover, there has been accumulating evidence[9,14] that supports Kaplan and Meloy's mechanism[15] in which the photochemical WR takes place directly through the excited singlet state of the rotamer which is cis with respect to C=O and $C=N_2$. Preferential formation of **10** over the γ-lactam indicates, then, that a smooth, concerted process with migration of the Me group and loss of N_2 occurring simultaneously is favored by a lower activation energy than the dissociation to give carbene followed by C–H insertion. Similar predominance of the migration process over insertion is also observed[16] in the photolysis of 2-diazo-1,3-dicarbonyl compounds in methanol. Furthermore, a similar explanation pointing out the importance of the population of the conformers has been presented[17] to account for the relative migratory aptitude in the photo-WR of 2-diazo-1,3-dicarbonyl compounds which are analogous to the present system.

Sensitized photolysis of **1e** gave somewhat surprising results. Thus, irradiation of **1e** in the presence of benzophenone afforded β-lactam **9** almost exclusively. This is unexpected from the mechanism advanced above because the sensitization has been shown[9b,18] to circumvent the formation of the singlet excited state of **1e**, a precursor leading to **9** as well as **10**. The fact that dominant formation of the products from singlet carbene has been frequently observed[9] in the sensitized decomposition of diazocarbonyl compounds as a result of efficient intersystem crossing of the triplet carbene to singlet manifolds would suggest that **9** is derived from singlet carbene. However, the above results with **1a,b** imply that an intramolecular C–H insertion process of carbene generated from a diazo amide is sensitive to the bond distance between carbene center and the C–H bond, and, hence, γ-lactam rather than β-lactam should be formed preferentially from the carbene. No formation of γ-lactam and OH

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[13] Sorrio, S. In "The Chemistry of Diazonium and Diazo Groups"; Patai, S., Ed.; Wiley: New York, 1978; Vol. I, pp 96–135.

[14] Kaplan, F.; Mitchell, M. L. *Tetrahedron Lett.* **1979**, 759.

[15] Kaplan, F.; Meloy, G. K. *J. Am. Chem. Soc.* **1966**, *88*, 950.

[16] See for review: Meier, H.; Zeller, K.-P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32.

[17] Heyes, G.; Holt, G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1206.

[18] Roth, H. D.; Manion, M. L. *J. Am. Chem. Soc.* **1975**, *97*, 779.

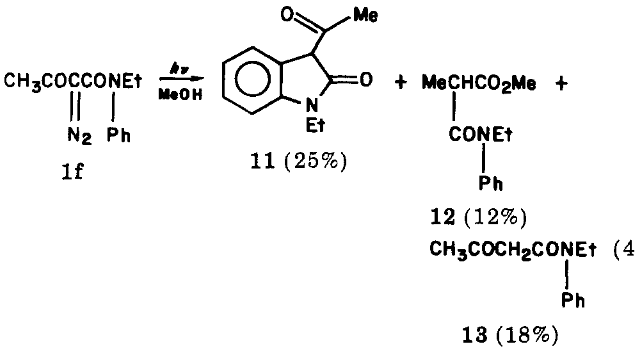
Table II. Effect of Temperature on the Product Distributions in Photolysis of 1a and 1b in Methanol[a]

diazo amide	temp, °C	rel yield, %[b] WR prodt	β-lactam	γ-lactam	OH
1a	0	11.9	37.5	16.8	33.8
	−78	8.8	42.2	17.0	32.0
	−110	7.0	43.4	15.0	34.6
	−155	6.5	44.0	13.7	35.8
	−196	4.6	49.4	7.8	38.2
1b	0	12.8	35.9		51.3
	−78	10.6	36.0		53.4
	−110	6.8	40.6		52.6
	−155	5.0	48.4		46.6
	−196	0.5	54.3		45.2

[a] Irradiations were performed on a 25 mM solution of diazo amide in a Pyrex tube. [b] Yields were determined by GC. Absolute yields were not appreciably altered with temperature.

insertion product might imply that singlet carbene is not generated in the present sensitized decomposition. A plausible explanation would be that **9** is derived from triplet carbene, which is stabilized by the resonance interaction with neighboring carbonyl groups. Such stabilization allows the triplet to undergo intramolecular H abstraction from the weaker methylene C–H bonds, followed by recombination.

Displacement of one of the alkyl groups in **1e** with a phenyl group also caused changes in the photochemical processes of the diazo amides. Thus, photolysis of **1f** in methanol gave **11–13** (eq 4), and lactams were not detected in the reaction mixture.



1f

11 (25%)

12 (12%)

(4)

13 (18%)

Effect of Temperature. It has been reported[19] that photolysis of diazo ketones of the type $RCOC(CH_2R')N_2$ yields the α,β-unsaturated ketone as the major product at room temperature; however, at higher temperature, the ketene rearrangement product is obtained. The results are explained[15] by assuming that the higher energy conformations are more populated as the temperature is raised. The preference of the *s-E* form at room temperature as a result of steric interaction leads to the α,β-unsaturated ketone. On the other hand, when the temperature is raised, enough energy may be available to overcome the steric interaction and give an appreciable amount of the *s-Z* form which leads to the rearrangement product. Thus, the importance of the ground-state conformation would be established by studying the influence of temperature upon the product distributions. Accordingly, we carried out a temperature study on the photochemical processes of **1a,b** in methanol, and the results are summerized in Table II. Accepting that the WR product and β-lactam are formed directly from the *s-Z* form, whereas the OH insertion product and γ-lactam are derived from the *s-E* form via singlet carbene, these results indicate that the relative populations of the conformers are not appreciably altered by lowering of the temperature, at least within the temperature ranges studied. This is in accord with the NMR studies[15] of α-diazo carbonyl compounds which show that populations of the *s-E* and *s-Z* forms are not appreciably changed by lowering of the temperature. The product ratios (e.g., β-lactams/WR products and γ-lactams/OH insertion product) from each of the reacting states are, however, appreciably altered with temperature. Thus, as the temperature is lowered, β-lactam formation becomes dominant at the expense of the WR product, and the amount of OH insertion product increases concomitant with the decrease in γ-lactam. These results can be interpreted in terms of the differences in activation energies for competing reactions from each of the intermediates. Presumably there is a finite activation energy for migration of an NR_2 group, which is known[16] to be an inefficient migrating group. Moreover, similar suppression of the migration of the alkoxy group, an equally inefficient migrating group, by lowering of the temperature has been noted[9b] in the photolysis of a diazoacetate. Thus, β-lactam formation gains over the WR as the temperature decreases.

Experimental Section

IR spectra were determined on a JASCO IR-G recording spectrometer. H^1 NMR spectra were determined on a JEOL JNM-MH-100 NMR spectrometer. Gas chromatographic–mass spectral data were obtained on a Shimadzu GC-MS 1000 spectrometer using a column consisting of 5% OV-17 on Shimalite. GC analyses were performed on a Yanagimoto instrument, Model G-180, with a flame-ionization detector. The following columns were used: A, 5.0 mm × 2.0 m, 10% OV-17 on 60–80-mesh Diasolid L; B, 5.0 mm × 2.0 m, 5% PEG 6000 on 60–80-mesh Diasolid L.

Starting Materials. α-Diazoacetoacetamides **1e,f** were prepared[20] by the diazo exchange of acetoacetamide with *p*-tosyl azide, and α-diazoacetamides **1a–d** were obtained[2] by treatment with MeONa of the corresponding α-diazoacetoacetamides and were purified chromatographically on neutral alumina. All diazo compounds showed satisfactory spectroscopic data.

Authentic Samples for Identification of Reaction Products. The following authentic specimens were prepared according to the literature procedures. Glycinates **3** and **8** were prepared[1] by reacting the corresponding amines with methyl bromoacetate. Alkoxyacetamides **4** and **5** were synthesized[1] by reacting alkoxyacetyl chloride with dimethylamines. Oxindoles **7** were prepared[20] by thermolysis of **1c** or **1d** in toluene. Satisfactory spectroscopic data have been obtained for all authentic samples.

Photochemical Reactions and Analyses. All irradiations were conducted through a Pyrex vessel with a Halos, 300-W, high-pressure mercury lamp with water-cooled jacket until all of the diazo compound was destroyed. For product identification, the irradiation mixtures were concentrated on a rotary evaporator below 25 °C, and individual components were isolated by column chromatography and characterized either as described below (**2**, **6**, **9–12**) or by comparison with authentic specimens (**3–5**, **7**, **8**, **13**). The irradiations outlined in Tables I and II were conducted in degassed and sealed Pyrex tubes of 5.0-mL capacity, and the yields were determined by GC analysis. Sensitized irradiations were conducted in a Pyrex tube in the presence of 5-fold excess benzophenone so as to assure absorption of 98% of the light by the photosensitizer. Temperature studies were carried out as described elsewhere.[21] Control experiments excluded possible photoconversions of the product during the irradiation period and also demonstrated that no reaction occurs in the absence of light over the temperature ranges studied.

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[19] Franzen, V. *Justus Liebigs Ann. Chem.* **1957**, *602*, 199.

[20] Franich, R. A.; Lowe, G.; Parker, J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2034.

[21] (a) Tomioka, H.; Inagaki, T.; Nakamura, S.; Izawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 130. (b) Tomioka, H.; Itoh, M.; Yamakawa, S.; Izawa, Y. *J. Chem. Soc., Perkin Trans. 2* **1980**, 603.

Irradiation of 1b in Acetone. In a typical run, a solution of **1b** (200 mg) in acetone (30 mL) was irradiated at room temperature for 10 h. After removal of the solvent under reduced pressure, the residue was chromatographed with chloroform as eluant to afford β-lactam **2** and 1,3-dioxolane **6** (27% and 45% yield, respectively). NMR of **2** ($CDCl_3$ δ 3.22 (2 H, t, *J* = 2 Hz), 2.95 (2 H, t, *J* = 2 Hz), 2.83 (3 H, s). NMR of **6** ($CDCl_3$) δ 4.21 (1 H, s), 3.18 (3 H, s), 2.84 (3 H, s), 1.41 (3 H, s), 1.39 (3 H, s), 1.30 (3 H, s), 1.13 (3 H, s).

Irradiation of 1e in Methanol. A solution of the diazo amide **1e** (200 mg) in methanol (30 mL) was photolyzed and worked up in the usual way to give β-lactam **9** and the ester **10** (16% and 30% yield, respectively). NMR of **9** ($CDCl_3$) δ 4.05 (1 H, q, *J* = 4.2 Hz, of d, *J* = 2.0 Hz), 3.70 (1 H, d, *J* = 2.0 Hz), 3.41 (2 H, m), 2.19 (3 H, s), 1.35 (3 H, d, *J* = 4.2 Hz), 1.17 (3 H, m). NMR of **10** ($CDCl_3$) δ 3.72 (3 H, s), 3.38 (2 H, m), 3.35 (1 H, q, *J* = 4.5 Hz), 1.41 (3 H, d, *J* = 4.5 Hz), 1.21 (3 H, m).

Irradiation of 1f in Methanol. A solution of **1f** (200 mg) in methanol (30 mL) was photolyzed and worked up in the usual way to afford oxindole **11** (mp 99–101 °C), ester **12**, and acetoacetamide **13** (25%, 12%, and 18% yield, respectively). NMR of **11** ($CDCl_3$) δ 7.42–6.89 (4 H, m), 3.90 (2 H, q, *J* = 3.8 Hz), 3.47 (1 H, s), 2.43 (3 H, s), 1.32 (3 H, t, *J* = 3.8 Hz). NMR of **12** ($CDCl_3$) δ 7.60–7.03 (5 H, m), 3.81 (2 H, q, *J* = 3.8 Hz), 3.64 (3 H, s), 3.35 (1 H, q, *J* = 3.7 Hz), 1.30 (3 H, d, *J* = 3.7 Hz), 1.14 (3 H, t, *J* = 3.8 Hz).

Registry No. 1a, 6112-00-1; **1b,** 62285-47-6; **1c,** 76269-81-3; **1d,** 38118-70-6; **1e,** 76269-82-4; **1f,** 76269-83-5; **2,** 2679-13-2; **9,** 76269-84-6; **10,** 76269-85-7; **11,** 76269-86-8; **12,** 76269-87-9.

Antitumor Plants. 11.[1,2] Diterpenoid and Flavonoid Constituents of *Bromelia pinguin* L.

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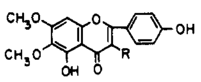
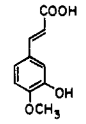
The roots and basal stems of *Bromelia pinguin* L. contain the flavonoids penduletin, cirsimaritin, and casticin, as well as isoferulic acid and three new diterpenoids. Two of these are the novel phyllocladane derivatives 3-oxophyllocladan-16ξ-ol and phyllocladan-16α,19-diol, and the third is 3-oxopimar-15-ene-7β,8β-diol. The major cytotoxic activity of the extracts of *B. pinguin* is probably due to the flavonoids.

The family Bromeliaceae is a mostly tropical group comprising some 45 genera and 1900 species, restricted to the New World except for one West African *Pitcairnia* species. The family has not been thoroughly investigated chemically, except for pineapple (*Ananas comosus*, Bromelioideae) and Spanish moss (*Tillandsia usneoides*, Tillandsioideae). We now report our investigation of the chemical constituents of the roots and basal stems of the pineapple relative *Bromelia pinguin* L. The fruits of this species, known as maya fruit, are a foodstuff throughout the Caribbean area, Mexico, and southward to Panama and Guiana. Aqueous methanolic extracts of the stems and leaves showed cytotoxicity in the KB assay[3] (ED_{50} 2 and 9 μg/mL; two tests) which prompted the present work.

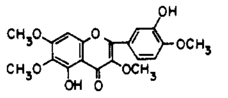
Dried, ground roots and basal stems were extracted with methanol, and the extract was partitioned in the usual manner.[4] The aqueous fraction, which was inactive vs. KB, gave positive tests for tannins and reducing substances. It was not otherwise investigated. The methanolic fraction, which showed activity vs. KB at 2.1 μg/mL, contained flavonoids (Willstätter test) and polyphenolic substances. The polyphenolics were removed with lead(II) acetate,[5] and the fraction was separated into sodium bicarbonate soluble, sodium carbonate soluble, and nonacidic subfractions. The sodium bicarbonate soluble subfraction was inactive vs. KB and yielded no homogeneous characterizable compounds on chromatography, but the sodium carbonate soluble fraction, which showed activity vs. KB at 4.9 μg/mL, yielded the flavonoids penduletin (1) and cirsimaritin (2), as well as a small amount of isoferulic acid (3). Taken together with our recent considerations of the cytotoxicity of flavonoid compounds[6] and in view of the fact that chromatography of the nonacidic subfraction yielded no materials with activity >15 μg/mL, we infer that the cytotoxicity of *B. pinguin* extracts arises mostly from the flavonoids.



(1); R = OCH3
(2); R = H



(3)



(4)

The nonacidic fraction gave the flavonoid casticin (4). The occurrence of compounds 1, 2, and 4 in *B. pinguin* is of considerable chemotaxonomic interest in view of Williams' recent studies of leaf flavonoids of the Bromeliaceae.[7] The occurrence of 6-hydroxylated flavonoids in *B.*

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[1] For part 10 in this series, see: Le Quesne, P. W.; Larrahondo, J. E.; Raffauf, R. F. *J. Nat. Prod.* **1980**, *43*, 353.

[2] The word "antitumor" as used in this title signifies no more than the fact that this plant was regarded by the National Cancer Institute as being of sufficient potential interest in this respect to warrant investigation.

[3] Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep.* **1972**, 3(2), 1.

[4] Ghosh, P. C.; Larrahondo, J. E.; Le Quesne, P. W.; Raffauf, R. F. *Lloydia* **1977**, *40*, 364.

[5] Le Quesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1572.

[6] Edwards, J. M.; Le Quesne, P. W.; Raffauf, R. F. *J. Nat. Prod.* **1979**, *42*, 85.

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