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PHOTOCHEMICAL REACTION OF ETHYL AZIDOFORMATE WITH CYCLIC ETHERS AND ACETALS

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Abstract—Irradiation of ethyl azidoformate dissolved in cyclic ethers (IIIA–VA) and acetals (VIA–VIIIA) yields insertion products (IIIB–VIIIB) of carbethoxynitrenes (II_S and II_T). The attack of the nitrenes occurs exclusively at the C—H bond adjacent to the ether oxygen or adjoining acetal oxygens to produce a single insertion product in each case. Byproducts are urethane (IX) and the dimerization product (X) of amino radicals (XI). The effects of acetophenone as a sensitizer and of methylene chloride as a diluent have been examined and discussed. Reduction of IIIB and IVB with LAH produces 4-methylaminobutan-1-ol and 5-methylaminopentan-1-ol in 62 and 83% yields, respectively.

REACTIONS of carbethoxynitrene (II) as produced by thermal and photochemical decomposition of ethyl azidoformate (I) have been studied extensively.[1] Interest in the behaviour of carbethoxycarbene towards cyclic ethers[2] has motivated the investigation on the action of photochemically produced II upon ethereal substrates (IIIA–VIIIA). This paper comprises the isolation and characterization of insertion products (IIIB–VIIIB) as well as discussions on the nature of the reactive species in this reaction.

A mixture of I and the respective ethereal substrate (1:7 to 1:10 mole ratio) contained in a Vycor cell (N atm) was irradiated at ca. 10° with an external high-pressure mercury lamp (200W) for a period of 200 hr. The insertion products were isolated by distillation *in vacuo* and the major byproduct, ethyl carbamate (IX), was removed as a lower boiling fraction. Each isolated product was homogeneous on GLC and TLC, and the yields and analyses of these novel compounds are summarized in Table 1. The NMR spectral data as recorded in Table 2 support the structures assigned. The IR spectra show N—H absorptions at 3320–3290 and 1540–1518, and carbonyl absorption at 1735–1721 cm^{-1}, respectively. The strictly selective insertion of the intermediary nitrene II to the C—H bond adjacent to ethereal oxygen or the one adjoining acetal oxygens is remarkable. Attack on VIIIA occurs exclusively at the secondary C_2—H bond rather than at the tertiary C_4—H.[3] In contrast to the behaviour of the carbene analogue towards cyclic acetals,[4]

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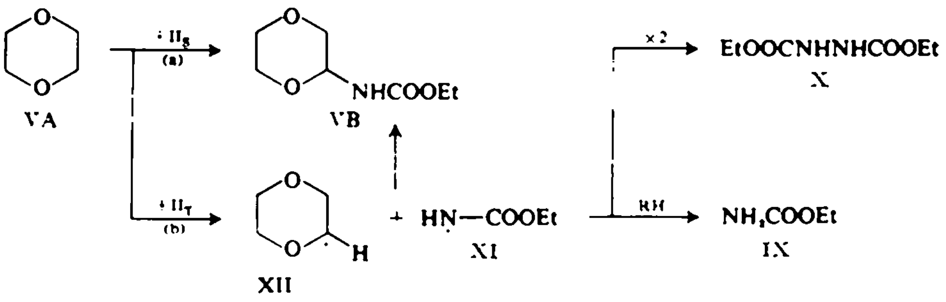
[1] [a] W. Lwowski and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.* **87**, 1947 (1965); [b] R. Huisgen and H. Blaschke, *Chem. Ber.* **98**, 2985 (1965) and Refs cited therein.

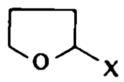
[2] [a] H. Nozaki, H. Takaya and R. Noyari, *Tetrahedron Letters* 2563 (1965); [b] H. Nozaki, H. Takaya and R. Noyori, *Tetrahedron* **22**, 3393 (1966).

[3] NMR spectrum indicated the complete absence of the 4-substituted isomer, which should give an apparent signal near τ 5·0 due to the methylene protons at C_4. See T. A. Crabb and R. C. Cookson, *Tetrahedron Letters* 679 (1964).

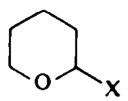
[4] [a] C. D. Gutsche and M. Hillman, *J. Amer. Chem. Soc.* **76**, 2236 (1954); [b] A. W. Johnson, A. Langemann and J. Murray, *J. Chem. Soc.* 2136 (1953); [c] W. Kirmse, *Carbene Chemistry* p. 107, Academic Press, New York (1964).

$$\underset{\text{I}}{N_3COOEt} \xrightarrow[-N_2]{h\nu} \underset{\text{II}_S}{\uparrow\downarrow N{-}COOEt} \xrightarrow{S \to T} \underset{\text{II}_T}{\uparrow\uparrow N{-}COOEt}$$

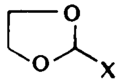




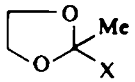
IIIA, B



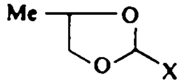
IVA, B



VIA, B



VIIA, B



VIIIA, B

A: X = H   B: X = NHCOOEt

TABLE 1. YIELDS AND ANALYSES OF INSERTION PRODUCTS

Product	B.p., °C/mm (m.p., °C)	Yield[a] %	Formula	Calc. C%	Calc. H%	Calc. N%	Found C%	Found H%	Found N%	Yield of IX, %[a]
IIIB	84–86/0·07	33	$C_7H_{13}NO_3$	52·8	8·2	8·8	52·7	8·4	8·6	10
IVB	108/0·15	41	$C_8H_{15}NO_3$	55·5	8·7	8·1	55·5	8·8	8·2	8
VB	102–103/0·15	34	$C_7H_{13}NO_4$	48·0	7·5	8·0	47·8	7·6	8·0	15
VIB	(55·0–55·5)[b]	64	$C_6H_{11}NO_4$	44·7	6·9	8·7	44·5	7·0	8·7	22
VIIB	107/0·25	62	$C_7H_{13}NO_4$	48·0	7·5	8·0	47·8	7·6	8·0	15
VIIIB	(46·0–47·0)[b]	51	$C_7H_{13}NO_4$	48·0	7·5	8·0	47·9	7·6	8·0	25

[a] Isolation yields.

[b] Recrystallized from ethanol-n-hexane mixture.

no ring enlargement was observed. This photochemical route probably constitutes the only approach at present to a class of compounds such as IIIB-VIIIB. Similar treatment of several open chain ethers yielded a complex mixture of cleavage products, which were not further investigated.[5]

Possible synthetic utilization of the insertion products IIIB and IVB may be illustrated by exhaustive reduction with LAH, which yields 4-methylaminobutan-1-ol and 5-methylaminopentan-1-ol in 62 and 83% yields, respectively.

The formation of the *insertion* products may be ascribed to direct insertion of singlet nitrene II_S as produced initially by photolysis of azide I (path *a*), or alternatively to attack of triplet nitrene II_T producing a radical pair of XI and XII followed by recombination to yield the same product (path *b*).[6] Table 3 summarizes the

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[5] Cleavage of C—O bond in the reaction of carbethoxycarbene with alkyl ethers was recorded. See G. B. R. de Graaf, J. H. van Dijk-Rothuis and G. van de Kolk, *Rec. Trav. Chim.* **74**, 143 (1955).

[6] Initial generation of II_S and subsequent crossing to II_T were reasonably shown. See D. W. Cornell, R. S. Berry and W. Lwowski, *J. Amer. Chem. Soc.* **87**, 3626 (1965) and Ref. 1*a*.

TABLE 2. NMR DATA OF INSERTION PRODUCTS

Product	Shift in τ Value (Intensity, Multiplicity[a]) Assignment
IIIB	3·28 (1H, *d*) NH; 4·45 (1H, *m*) C_2 methine; 5·87 (2H, *q*) OCH_2CH_3; 6·0–6·5 (2H, *m*) C_5 methylene; 7·8–8·2 (4H, *m*) $C_{3,4}$ methylenes; 8·78 (3,H *t*) OCH_2CH_3
IVB	3·60 (1H, *d*) NH; 5·25 (1H, *m*) C_2 methine; 5·95 (2H, *q*) OCH_2CH_3; 6·2–6·7 (2H, *m*) C_6 methylene; 8·0–9·0 (9H, *m* and *t*) $C_{3,4,5}$ methylenes and OCH_2CH_3
VB	3·57 (1H, *d*) NH, 4·90 (1H, *m*) C_2 methine; 5·85 (2H, *q*) OCH_2CH_3; 6·0–6·8 (6H, *m*) $C_{3,5,6}$ methylenes; 8·77 (3H, *t*) OCH_2CH_3
VIB	3·68 (1H, *d*) C_2 methine; 4·13 (1H, *m*) NH; 5·6–6·2 (6H, *m*) OCH_2CH_3 and $C_{4,5}$ methylenes; 8·75 (3H, *t*) OCH_2CH_3
VIIB	3·85 (1H, *s*) NH; 5·8–6·2 (6H, *m*) OCH_2CH_3 and $C_{4,5}$ methylenes; 8·33 (3H, *s*) C_2 methyl; 8·80 (3H, *t*) OCH_2CH_3
VIIIB[b]	3·6–4·0 (2H, *m*) C_2 methine and NH; 5·7–6·2 (5H, *m*) C_5 methylene, OCH_2CH_3 and C_4 methine; 8·6–8·9 (6H, *m*) C_4 methyl and OCH_2CH_3

[a] The multiplicity of signals were indicated in abbreviated form: *s* for singlet, *d* for doublet, *t* for triplet, *q* for quartet, and *m* for multiplet.

[b] Complicated signals in the region of τ 6·5–6·7, which had an integrated area equivalent to 0·8H weight and could not be interpreted reasonably, might indicate contamination with difficultly removable impurities.

TABLE 3. PHOTOSENSITIZED DECOMPOSITION OF I IN VA AS COMPARED WITH DIRECT PHOTOLYSIS

Mole Ratio I:VA:AcPh[a]	Condition[b]	Irradiation time, hr	Conversion[c] %	Yield %[d] VB	Yield %[d] IX	Ratio IX:VB
1:10:1·3	A[e]	9	12	34	65	1·9
1:10:1·3	A[e]	40	33	36	61	1·7
1:10:0	B	40	10	34	18	0·53
1:10:0	C	1	15	37	17	0·46
1:10:0	C	3	31	38	19	0·50
1:10:0	C	268	100	34[f]	15[f]	0·44

[a] AcPh stands for acetophenone added as a sensitizer.

[b] Irradiation was effected with an external high-pressure Hg arc (200W) under condition A: the mixture was placed in a Pyrex tube and a 1·5 cm thick 9% $CuSO_4$ solution was used as a filter; condition B: similarly as A in the absence of the sensitizer; condition C: the mixture was placed in a Vycor tube and no filter was used (the preparative condition).

[c] The conversions were calculated on the basis of the volume of N_2 evolved.

[d] The yields were obtained by GLC and were given on the basis of the consumed I. Products other than VB and IX could not be obtained purely and largely formed non-volatile, and resinous polymer. No detectable amount of X was formed under conditions A–C.

[e] Acetophenone was recovered from the reaction mixture in no less than 93% yield.

[f] Isolation yields.

results of a series of experiments designed for elucidating the spin-multiplicity of carbethoxynitrene II in this reaction. A mixture of I and 1,4-dioxan (VA) in 1:10 molar ratio was irradiated in the presence or absence of acetophenone (1·3 mole) as a triplet sensitizer. It should be noted that the light absorption of I is negligible in comparison with that of the sensitizer under condition A, and accordingly most of the nitrene species involved in this sensitized photolysis must presumably be in the triplet state.[1a] The formation of VB in this case should be ascribed to the species II_T reacting *via* path *b*[7] and the urethane IX should arise by hydrogen abstraction of

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[7] Rigorously, however, the possibility of hydrogen abstraction by triplet azide I followed by elimination of nitrogen molecule to yield amino radicals XI is not excluded.

free amino radicals XI.[8] The molar ratios of IX:VB in the presence of the sensitizer are roughly four-times as large as under the non-sensitized (preparative) conditions, the ratio being neither affected by the wave-length of the exciting light nor by irradiation period. This remarkable change in IX:VB ratios must imply the principal participation of singlet nitrene II_S in the direct photolysis of I in VA.

TABLE 4. THE EFFECT OF DILUTION ON YIELDS

Molar Ratio I:VA:CH_2Cl_2	Yields based on the consumed I[a] in %[b] IX	X	VB
1:50:0	18	0	39
1:28:26	20	4	35
1:7:44	15	11	20
1:3:47	12	15	8
1:1:49	17	12	3
1:0:50	21	28	—

[a] The conversion was determined by means of IR bands at 2185 and 2137 cm^{-1}.

[b] These values were obtained by GLC analyses.

In another series of experiments the photolysis of I was carried out in VA with a varying amount of methylene chloride as a diluent, which had been found by Lwowski *et al.* to be inert towards II_S or II_T in the reaction with olefins.[9] Data in Table 4 show that dilution with the solvent had little effect on the yields of IX, but the yields of recombination product X of amino radicals XI were remarkably increased at the expense of the insertion product VB. Apparently, elastic collisions of II_S with solvent molecules lead to S→T transition to produce II_T species and methylene chloride serves to stabilize the amino radicals XI. It may be safe to conclude that both paths *a* and *b* are operative in the formation of insertion products under conditions of preparative photolysis, the path *a via* II_S predominating over the path *b via* II_T by a factor of 3:1 in crude approximation.[10]

EXPERIMENTAL

All m.ps and b.ps were uncorrected. Microanalyses were performed at the Elemental Analyses Centre of Kyôto University. NMR spectra: in CCl_4 soln on 60 Mc instruments (Varian A-60 and Nippon Denshi JNM-C-60). TLC was performed on silica gel G using benzene-AcOEt (1:1) as a developing agent. GLC was carried out on a 2 m column of Apiezon L or high vacuum silicone grease at 165-170° with He as a carrier gas. Yields of the reaction products were determined by GLC and calibrated by means of standard solutions of the pure samples.

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[8] Dimerization of products of ether radicals such as XII formed as a counterpart of the amino radicals XI were not observed in each solvent used. This is to be ascribed to further ring cleavage of ether radicals, which results in intractable polymers. For instance, see T. J. Wallace and R. J. Gritter, *J. Org. Chem.* **26**, 5256 (1961); D. Elad and R. D. Yousefyeh, *Tetrahedron Letters* 2189 (1963).

[9] [a] W. Lwowski and J. S. McConaghy, Jr., *J. Amer. Chem. Soc.* **87**, 5490 (1965); [b] W. Lwowski and F. P. Woerner, *Ibid.* **87**, 5491 (1965).

[10] The calculation is based on the IX:VB ratios in Table 3 and on the assumption that II_T is the only active species in the photo-sensitized decomposition. We must be careful in discussing the spin-multiplicity of nitrene species based on the data in Table 4, as the hydrogen-abstraction has been observed even in the absence of VA. This could indicate that methylene chloride might not be an indifferent solvent in the present type of reaction.

Materials. Tetrahydrofuran (IIIA) and 1,4-dioxan (VA) used were commercial reagents. Tetrahydropyran (IVA),[11] 1,3-dioxolane (VIA),[12] 2-methyl- (VIIA)[13] and 4-methyl-1,3-dioxolane (VIIIA)[13] were prepared according to accepted procedures. They were purified before use by boiling with Na and fractionation in N_2 atm. Ethyl azidoformate (I) was prepared by the method of Lwowski and Mattingly.[10] Acetophenone was the commercial reagent and distilled before use.

General procedure of photolysis. This is illustrated by the photolysis in 1,4-dioxan. A mixture of the azide I (5·0 g, 0·043 mole) and 1,4-dioxan (38 g, 0·43 mole) was placed in a Vycor tube (25 mm internal diameter), degassed *in vacuo*, covered with N_2 and then irradiated externally with 200W high-press Hg lamp from a distance of 20 mm at ca. 10°. Exposure was continued until N_2 evolution ceased and the characteristic IR bands at 2185 and 2137 cm^{-1} due to azide group disappeared, which required ca. 270 hr. Distillation *in vacuo* gave 0·56 g (15% yield) ethyl carbamate (IX) as large colourless plates, b.p. 55–57°/4 mm, and m.p. 49°. From the higher boiling fraction *ethyl* 1,4-*dioxane*-2-*carbamate* (VB; 2·54 g, 34% yield) was obtained as a viscous colourless liquid, b.p. 102–103°/0·1 mm. Analytical sample was prepared by passing the benzene–ether soln through a silica gel column with ca. 80% recovery.

In the similar manner, *ethyl tetrahydrofuran*-2-*carbamate* (IIIB), *ethyl tetrahydropyran*-2-*carbamate* (IVB), *ethyl* 1,3-*dioxolane*-2-*carbamate* (VIB), *ethyl* 2-*methyl*-1,3-*dioxolane*-2-*carbamate* (VIIB) and *ethyl* 4-*methyl*-1,3-*dioxolane*-2-*carbamate* (VIIIB) were obtained from the corresponding ethers. The details were summarized in Tables 1 and 2.

Acetophenone-sensitized photolysis of I *in* 1,4-*dioxan* (VA). A soln of I (1·5 g, 0·013 mole) and acetophenone (2·0 g, 0·017 mole) in VA (12 g, 0·14 mole) was placed in a Pyrex cell, degassed *in vacuo*, covered with N_2 and irradiated with high-press Hg arc (200W) externally using 9% $CuSO_4$aq as a filter. After 10 to 30% conversion , the irradiation was intercepted, the solvent and unchanged I were removed *in vacuo* below 30° and the residue was analyzed by GCL. The results were summarized in Table 3.

Photolysis of I *in* 1,4-*dioxan–methylene chloride mixture.* A soln of I (1·0 g, 0·0087 mole) in VA and CH_2Cl_2 mixture (total 0·44 mole) in a fused silica tube was irradiated externally as described above. After 9 hr irradiation (ca. 20% conversion), the solvents and unchanged I were removed carefully, and the residue was subjected to GLC analysis. The results were summarized in Table 4.

Reduction of carbamates IIIB *and* IVB *with lithium aluminium hydride.* To a suspension of LAH (3·0 g, 0·079 mole) in anhydrous ether (100 ml) was added dropwise a soln of IVB (1·0 g, 0·0058 mole) in ether (50 ml) in the course of 30 min at room temp and then the mixture was heated at reflux for an additional 2 hr. After treatment with NaOHaq, the slurry was repeatedly extracted with ether. The combined extracts were washed, dried (Na_2SO_4) and concentrated *in vacuo*. Distillation of the residue yielded 5-methylaminopentan-1-ol (0·56 g, 83% yield), b.p. 120°/11 mm, which was identified by comparison of the IR spectrum with one of the authentic specimen.[14]

Similar treatment of carbamate IIIB afforded 4-methylaminobutan-1-ol in 62% yield, b.p. 90°/12 mm, which was characterized by comparison of the IR spectrum with one of the authentic sample.[15]

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[14] I. Scriabine, *Bull. Soc. Chim. Fr.* 454 (1947).

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