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NOVEL SYNTHESIS OF THE TAUTOMERIC ISOMER OF THE AZIRINOMYCIN ETHYL ESTER AND ITS ANALOGUES

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The new and facile syntheses of ethyl 2-azido-2-alkenoate (4) and ethyl 3-azido-2-alkenoate (5), and the subsequent photolysis or pyrolysis of 4 and 5 to 2-alkyl-3-ethoxycarbonyl-2H-azirines and 3-alkyl-2-ethoxycarbonyl-2H-azirines, respectively, were accomplished.

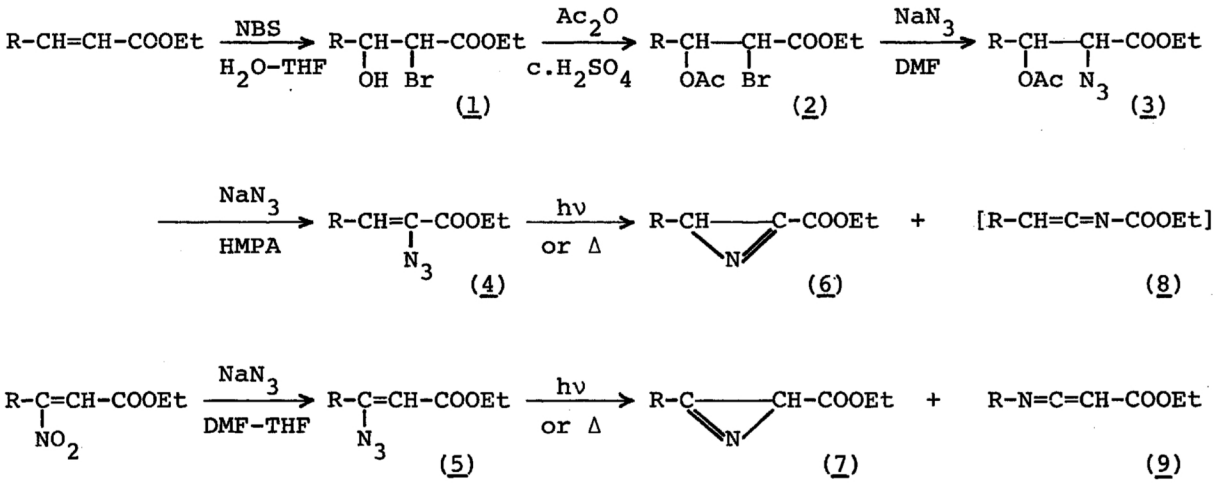
The photochemical transformation of ethyl 3-azido-2-butenoate (5a) to azirinomycin ethyl ester[1] (3-methyl-2-ethoxycarbonyl-2H-azirine (7a)) suggested that ethyl 2-azido-2-alkenoate (4) would be an useful starting material for the tautomeric isomers (2-alkyl-3-ethoxycarbonyl-2H-azirines (6)) of azirinomycin.[2]

In the previous communication,[3] we have reported that ethyl 2- as well as 3-nitro-2-alkenoate reacted with sodium azide to give a mixture of 4, ethyl 3-azido-2-alkenoate (5), and 4-ethoxycarbonyl-1,2,3-triazole derivative as the main product. At present, however, no available method of synthesizing 4 (R=alkyl group) has ever been reported, except for ethyl 2-azido-3-arylacrylate derived from the reaction of ethyl azidoacetate with arylaldehyde[4] and methyl 2-azidoacrylate from methyl 2-azido-3-iodopropionate by the elimination of hydrogen iodide.[5]

Because of the pharmacological and the structural interests in the relation between 6 and 3-alkyl-2-ethoxycarbonyl-2H-azirines (7), the new and facile syntheses of 4 and 5, and the subsequent photolysis or pyrolysis of 4 and 5 to 6 and 7, respectively, were pursued and the general synthetic methods of 4-7 were accomplished in this communication. The two reaction pathways are shown in the Scheme 1.

The yields of each step are reasonable and the reaction conditions are remarkably mild.

Ethyl 2-bromo-3-hydroxyalkanoate (1) was obtained by the reaction of ethyl 2-alkenoate (0.5 mol) with N-bromosuccinimide (NBS) (0.55 mol) in water-THF (300 ml, 1 : 1 V/V) at room temperature, according to the known method.[6] Acetylation of 1 (0.1 mol) with acetic anhydride (0.15 mol) in the presence of one drop of concentrated sulfuric acid at room temperature gave ethyl 3-acetoxy-2-bromoalkanoate (2) as a colorless syrup. Then azidation of 2 (0.02 mol) with sodium azide (0.04 mol) in DMF (50 ml) at 5°C gave ethyl 3-acetoxy-2-azidoalkanoate (3) as a



a; R=CH_3, b; R=C_2H_5, c; R=n-C_3H_7, d; R=i-C_3H_7, e; R=C_6H_5

Scheme 1

Table 1. Yields of 1-6 and 7 (%)

R	1	2	3	4	5	6	7
CH_3	58	83	92	90	88	61 (51)[a]	57 (53)[b]
C_2H_5	51	85	91	81	69	65 (60)[a]	45 (37)[b]
n-C_3H_7	48	86	95	74	38	60 (59)[a]	45 (40)[b]
i-C_3H_7	50	84	92	75	36	60 (68)[a]	40 (38)[b]
C_6H_5	45	90	89	95[c]	35	—	—

a) Pyrolysis of 4 to 6. b) Pyrolysis of 5 to 7. c) Reference 4 (yield 43%).

colorless syrup, which was subsequently treated with 2 equimolar sodium azide in hexamethyl phosphoramide (HMPA) at room temperature to give the expected 4 as a pale yellow syrup, after elimination of acetoxy group.

On the other hand, it was found that the reaction of ethyl 3-nitro-2-alkenoate (0.1 mol) with sodium azide (0.15 mol) at room temperature[7] in DMF-THF (120 ml, 5 : 1 V/V), instead of DMF,[3] underwent selectively to give only 5 in ca. 50% yield. In the previous experiment,[3] a mixture of 4 and 5 obtained could not be separated. Finally, a solution of 4 (0.02 mol) in dry benzene (70 ml) was irradiated in a stream of nitrogen by means of the external 450 W high-pressure

Table 2. Physical constants and spectral data of 4, 6, 7 and 9

Compound	Bp °C/mmHg [Mp °C]	IR spectrum, cm^{-1}, in KBr				NMR spectrum, δ, in $CDCl_3$	
		N_3 [C=C=N][a]	C=N	COOEt [COOEt][a]	C=C	β-H (Hz)	[α-H] [α-H][a]
4a	syrup	2110		1720	1640	6.18q (7.0)	
4b	syrup	2110		1720	1635	6.15t (7.2)	
4c	syrup	2110		1720	1635	6.16t (7.6)	
4d	syrup	2110		1720	1630	5.96d (9.4)	
4e	[42-43][b]	2110		1720	1623	6.96s	
6a	22-25/0.3		1755	1715	1715	2.47q (5.9)	
6b	31-32/0.5		1755	1715		2.44t (5.6)	
6c	45-46/0.2		1755	1715		2.41t (4.5)	
6d	30-31/0.5		1755	1715		2.36d (4.2)	
7a + 9a	34-35/0.5[c]	[2050]	1795	1730 [1700]			2.42s [4.11s]
7b + 9b	38-40/0.5[d]	[2050]	1795	1730 [1700]			2.45s [4.14s]
7c + 9c	50-53/0.2[e]	[2050]	1790	1730 [1710]			2.44s [4.12s]
7d + 9d	45-47/0.5[f]	[2050]	1790	1731 [1706]			2.48s [4.15s]

a) Data in brackets are that of ketenimine (9), except the mp of 4e. b) Reference 4. c) Composed of 7a and 9a in ratio 5 : 1.[g] d) Composed of 7b and 9b in ratio 3 : 5.[g] e) Composed of 7c and 9c in ratio 3 : 4.[g] f) Composed of 7d and 9d in ratio 3 : 4.[g] g) Evaluated from the intensity of ring proton in 7 and vinyl proton in 9.

mercury lamp (above 300 nm) at room temperature for about 3 hr until the azido band at 2110 cm^{-1} had disappeared to give 6 as a colorless oil, without accompanying with the expected N-ethoxycarbonyl-1-alkene-1-imine (8). However, similar treatment of 5 in benzene gave a mixture of colorless oily 7 and ethyl 3-alkyliminoacrylate (9).[2)]

Moreover, according to the method reported,[8)] pyrolysis of 5 (0.02 mol) in refluxing heptane (50 ml) for 2 hr gave only 6, while the same reaction of 4 gave again a mixture of 7 and 9, an almost same ratio as in the case of photolysis (Table 1). Attempt to isomerize to 6 or 7 conversely by alkali was unsuccessful.

The structures of all the new compounds were characterized spectroscopically and gave satisfactory results in elementary analysis. It is noteworthy that 6 and 7 are distingushable by the $\nu_{C=N}$ in IR spectra and the presence and absence of couplings in the ring proton signals in NMR spectra.

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