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Studies on Quinolizine Derivatives. XVI.[1] The Reaction of Azacycl[3,3,3]azine Derivatives. (9)

From the reaction of 1-azacycl[3,3,3]azine derivatives (I) with some dienophiles, the corresponding cycl[3,3,3]azine derivatives (II) and 3,9a-dihydro-3,9a-ethano-1-azacycl-[3,3,3]azine derivatives (IV) were obtained.

As an extension of our studies on azacyclazine derivatives, we have previously described[2] the convertion of 1,3,6-triazacycl[3,3,3]azine derivatives to 1,6-diazacycl[3,3,3]azine derivatives by the Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAC).

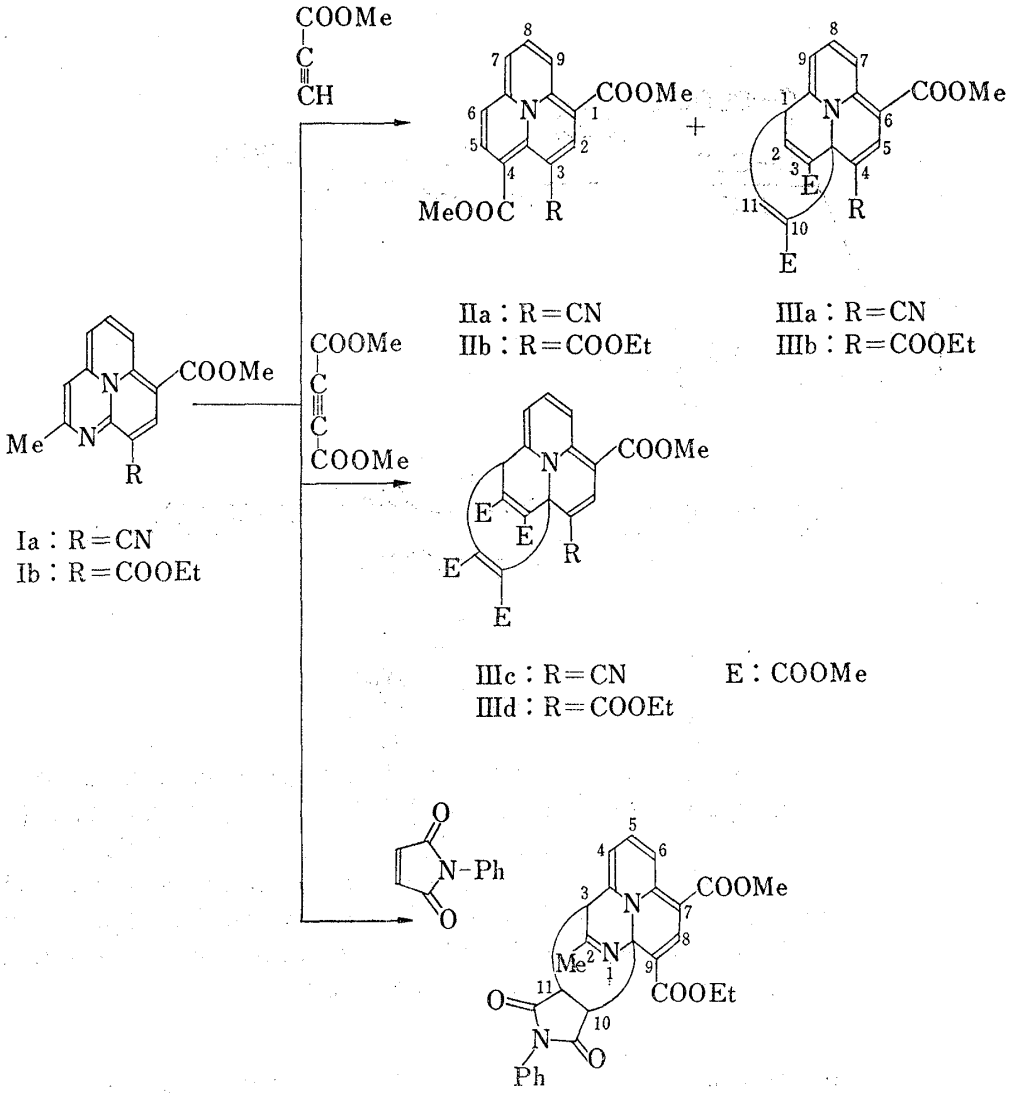

Chart 1

1) Part XV: G. Kobayashi, Y. Matsuda, Y. Tominaga, H. Awaya, and K. Kurata, *Chem. Pharm. Bull.* (Tokyo), **23**, 2759 (1975).
2) K. Kurata, M. Matsuo, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1629 (1975).

Table I. NMR Spectral Data (ppm) for Compounds II, III, IV (Solvent: $CDCl_3$)

Compound	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{11}	OMe	OEt	Me	Coupling constants
IIa		7.00			7.26	5.64	5.36	6.60	6.60			3.68 3.84			$J_{5-6}=J_{7-8}=J_{8-9}=9$Hz
IIb		7.38			7.14	5.56	5.36	6.46	6.64			3.60 3.64	1.24 4.04		$J_{5-6}=J_{7-8}=J_{8-9}=8$ Hz
IIIa	4.60	7.74			7.75		8.46	7.04	6.40			3.76 3.88			$J_{1-2}=J_{1-11}=7$ Hz $J_{7-8}=J_{8-9}=8$ Hz
IIIb	4.44			6.6—7.2 (6H, m, $C_{2,5,7,8,9,11}$-H)								3.60	1.20 4.06		
IIIc	5.63				7.90		8.55	7.20	6.63			3.75 3.90 4.00			$J_{7-8}=J_{8-9}=8$ Hz
IIId	5.43				8.33		8.58	7.14	6.35			3.72 3.73 3.85	1.29 4.13		$J_{7-8}=J_{8-9}=8$ Hz
IV			4.47	6.25	7.10	8.60		8.24		4.19	3.37	3.68	1.37 4.24	2.40	$J_{3-11}=J_{5-6}=10$ Hz $J_{4-5}=7$ Hz $J_{10-11}=3$ Hz

Now, we wish to report the Diels-Alder reaction of azacycl[3,3,3]azine derivatives (I)[3] with some dienophiles; methyl acetylenecarboxylate (MAC), N-phenylmaleimide (PMI) and DMAC. Especially in the reaction of I with MAC, we found a new synthetic method of cycl[3,3,3]azine derivatives (II), which were synthesized by Farquhar and Leaver[4] with their considerable effort and observed the existence of paramagnetic ring-current by NMR spectroscopic study. Dewar[5] concluded II as an antiaromatic compound by PPP–SCF–MO method.

Thus, a mixture of Ia and MAC in acetonitrile was heated in sealed tube at 250° for 20 hr. After evaporation of the solvent, the reaction mixture was chromatographed on silica gel to afford crystals (IIa) in benzene–acetone (20: 1) elution and crystals (IIIa) in benzene–acetone (10: 1) elution. The former crystals (IIa) were recrystallized from $CHCl_3$–MeOH to give dimethyl 3-cyanocycl[3,3,3]azine-1,4-dicarboxylate as brown crystals, mp 155—156°, in 40% yield. The latter crystals (IIIa) were recrystallized from EtOH to give trimethyl 1,3a-dihydro-1,3a-etheno-4-cyanocycl[3,3,3]azine-3,6,10-tricarboxylate as red needles, mp 251—252°, in 30% yield. Similarly, Ib reacted with MAC to give IIb and IIIb, respectively.

On the other hand, the reaction of Ia, b with DMAC in dimethylformamide at 100° for 10 hr gave only the corresponding 1,3a-dihydro-1,3a-ethenocycl[3,3,3]azine derivatives (IIIc, d) in good yield. Cycl[3,3,3]azine derivative (II) was not obtained in this reaction.

In contrast with the reaction with DMAC, 3,9a-dihydro-3,9a-ethano-1-azacycl[3,3,3]-azine derivative (IV) as red needles was obtained by the reaction of Ib with PMI in dimethylformamide at 100° for 10 hr.

Each of the structure of the products (II, III, IV) is confirmed by satisfatory elemental analyses, and infrared, ultraviolet and nuclear magnetic resonance (NMR) spectrum. The data for the products are summarized in Table I. Further works on the investigation of the chemical properties of I and II are in progress.

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Synthesis of (±)-Methyldecamine[1]

The Mannich condensation of the amide (VII) with isopelletierine (VIII) gave stereoselectively the *cis*-quinolizidine (IX), which was converted to (±)-methyldecamine (II) in 4 steps.

Lactonic Lytheaceae alkaloids[2] are classified into two groups, the biphenyl and biphenyl ether type, each of which is further subdivided into the *cis*- and *trans*-quinolizidine type, as shown in I, III, IV, and V. Only the biphenyl-*cis*-quinolizidine type alkaloids have remained unsynthesized, though the other types of alkaloids were already synthesized.[3] This communication deals with the synthesis of (±)-methyldecamine (II), the methyl ether of decamine (I),[4] which is an alkaloid of *Decodon verticillatus* (L.) ELL. and *Lagerstroemia indica* L. and the representative of the biphenyl-*cis*-quinolizidine type alkaloids.

The Mannich condensation of the biphenyl ester (VI)[5] with isopelletierine (VIII)[6] was shown to give stereoselectively the *trans*-quinolizidine derivative, because VI was readily hydrolyzed to the corresponding alkali-soluble carboxylic acid during the reaction.[5,7] In order to get the *cis*-quinolizidine, therefore, VI was converted to the alkali-insoluble amide (VII) [*m/e*: 371 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CHO), 1632 (CON)], which would not be hydrolyzed during the Mannich condensation.

Condensation of VII with VIII in benzene-tetrahydrofuran in the presence of aqueous sodium hydroxide afforded the expected *cis*-quinolizidine (IX) [*m/e*: 494 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O)] and the *trans*-quinolizidine (X) [*m/e*: 494 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2750 (Bohlmann bands), 1715 (C=O)] in the ratio of 6: 1. Reduction of IX with sodium borohydride, followed by the acetylation with acetic anhydride in pyridine furnished the axial acetyl derivative (XI) [*m/e*: 538 (M^+)] and the equatorial acetyl derivative (XII) [*m/e*: 538 (M^+)]. Each of the biphenyl derivatives (IX, X, XI, and XII) was found to be a mixture of two atropisomers from their dynamic nuclear magnetic resonance (NMR) spectra.[5]

Alkaline hydrolysis of XI and subsequent heating of the resulting hydroxy acid (XIII) [*m/e*: 469 (M^+)] with *p*-toluenesulfonic acid in benzene provided (±)-methyldecamine (II) [*m/e*: 451 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1719 (C=O), δ: 5.02 (1H, m, W_H=8 Hz, CHOCO), 4.09 (1H, d-d, J=10; 1 Hz, ArCH), 3.93, 3.88, 3.74 (each 3H, s, $OCH_3 \times 3$)[8]].

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7) M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **23**, 1573 (1975).
8) The published NMR data for methyldecamine[4]: 4.07 (1H, d-d, ArCH), 3.90, 3.86, 3.74 (each 3H, s, $OCH_3 \times 3$).