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Studies on Quinolizine Derivatives. IX.[1] Synthesis of Azacycl[3,3,3]azine Derivatives

In view of the interest in heterocyclic annulenes[2] we have previously reported a new nitrogen-bridged[12]annulene heterocyclic ring system, 1-azacycl[3,3,3]azine derivatives.[1]

We now wish to report a new method for the preparation of 1-azacycl[3,3,3]azine derivatives (Va, b, c) by the reaction of ethyl 6-methyl-2-pyridineacetate (Ia) with ethoxymethylenemalononitrile (II).

Thus, the mixture of Ia (1 mole) and II (1 mole) was heated for one hour on a boiling water bath. After cooling, the reaction mixture was chromatographed on alumina to separate

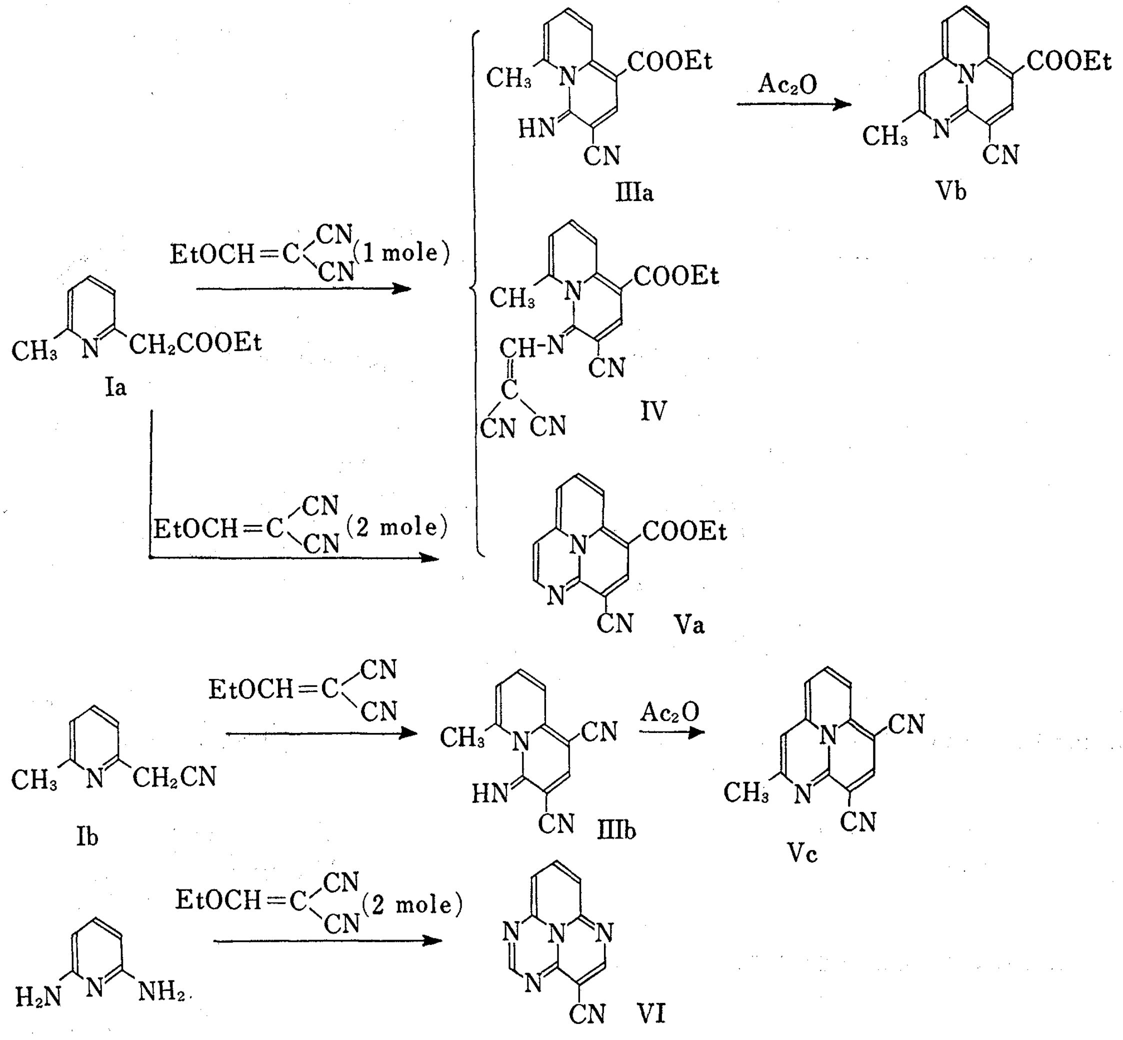

Chart 1

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[1] Part VIII: G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, C. Maseda, and H. Awaya, *Yakugaku Zasshi*, 94, 50 (1974).

[2] *a*) J.T. Shaw, W.M. Westler, and B.D. Stefanko, *Chem. Comm.*, **1972**, 1070; *b*) W.W. Paudler, R.A. Van Dahm, and Y.N. Park, *J. Heterocyclic Chem.*, **9**, 81 (1972); *c*) A.B. Holmes and F. Sondheimer, *Chem. Comm.*, **1971**, 1434; *d*) W.W. Paudler and E.A. Stephan, *J. Am. Chem. Soc.*, **92**, 4468 (1970); *e*) D. Farquhar and D. Leaver, *Chem. Comm.*, **1969**, 24; *f*) W. Flitsh and B. Muter, *Angew. Chem.*, **85**, 543 (1973).

crystals (IIIa) in petroleum benzine–benzene (1: 10) elution, crystals (IV) in benzene elution and crystals (Va) in benzene–acetone (1: 1) elution. The first crystals (IIIa) were recrystallized from acetone–petroleum benzine to give ethyl 3-cyano-6-methyl-4-imino-4H-quinolizine-1-carboxylate as yellow needles, mp 142—144°. The second crystals (IV) were recrystallized from EtOH to give ethyl 3-cyano-6-methyl-4-(2,2-dicyanoethylene)imino-4H-quinolizine-1-carboxylate as yellow needles, mp 181—182°. The third crystals (Va) were recrystallized from acetone–EtOH to give ethyl 9-cyano-1-azacycl[3,3,3]azine-7-carboxylate as green needles, mp 217—219°, nuclear magnetic resonance (NMR) (F_3CCOOH) δ: 5.60 (1H, doublet, J=8 Hz, C_3–H), 6.30 (1H, doublet, J=8 Hz, C_2–H), 6.52 (1H, doublet, J=8 Hz, C_4–H or C_6–H), 7.50 (1H, triplet, J=8 Hz, C_5–H), 7.86 (1H, singlet, C_8–H), 8.16 (1H, doublet, J=8 Hz, C_4–H or C_6–H). The compound (Va) was easily obtained by an alternative synthesis from the reaction of Ia (1 mole) and II (2 mole) for 3 hours on a boiling water bath.

A cycl[3,3,3]azine derivative, 4-cyano-1,3,6-triazacycl[3,3,3]azine (VI)[3] as blue needles, mp 266—267°, NMR (DMSO-d_6) δ: 5.86 (1H, doublet, J=8 Hz, C_7–H or C_9–H), 6.10 (1H, doublet, J=8 Hz, C_7–H or C_9–H), 7.02 (1H, singlet, C_5–H), 7.24 (1H, triplet, J=8 Hz, C_8–H), 7.45 (1H, singlet, C_2–H), was obtained by the reaction of 2,6-diaminopyridine (1 mole) and II (2 mole) for 30 minutes at 150°. When 6-methyl-2-pyridineacetonitrile (Ib) (1 mole) reacted with II (1 mole) for 30 minutes on a boiling water bath, only 6-methyl-1,3-dicyano-4-imino-4H-quinolizine (IIIb) was obtained in good yield.

Furthermore, the reaction of 4-imino-4H-quinolizine derivatives (IIIa, b) with acetic anhydride for 4 hours at 150° or 100° gave the corresponding 2-methyl-1-azacycl[3,3,3]azine derivatives (Vb, c).

The structure of the products are confirmed by satisfactory elemental analyses, and infrared (IR) and ultraviolet (UV) spectra. The data for the products are summarized in Table I.

TABLE I

No.	mp (°C)	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
Va	217—219	$\nu_{C\equiv N}$ 2200 $\nu_{C=O}$ 1680	280(4.58) 386(4.31) 420(4.38) 443(4.53)
Vb	234—235	$\nu_{C\equiv N}$ 2200 $\nu_{C=O}$ 1690	283( )[a] 380( ) 420( ) 445( )
Vc	298	$\nu_{C\equiv N}$ 2200	278( )[a] 388( ) 415( ) 438( )
VI	266—267	$\nu_{C\equiv N}$ 2200	238(4.55) 334(4.49) 375(4.20) 395(4.38)

a) Concentration is unknown because of insufficient solubility.

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Chemistry of Leucomycins. XI. Chemical Transformation of a Basic Macrolide to a Neutral Macrolide

The modification of the 16-membered macrolide antibiotics has been under study in our laboratory for several years.[1a,b] In this course of the study, the aglycone moiety[2] of leucomycin-A_3, leuconolide-A_3 5,18-hemiacetal has been succesfully isolated by applying the modified Polonovski reaction[3] to leucomycin-A_3 N-oxide. While, a new neutral macrolide was obtained from the same reaction product and it's structural determination was mainly investigated by means of proton and carbon-13 nuclear magnetic resonance (NMR) spectroscopy comparing with that of leucomycin-A_3 (I).

The oxidation of I with *m*-chloroperbenzoic acid in chloroform gave leucomycin-A_3 N-oxide (II), $[\alpha]_D^{18}$ -19.0 ($c=0.5$, ethanol) in a high yield (90%). Compound (II) was refluxed with acetic anhydride in chloroform for 1.5 hr and followed the hydrolysis with sodium bicarbonate in order to chemically modify the $NMe_2 \rightarrow O$ group at position-3′ on mycaminose moiety. The product was purified by silica gel column chromatography, obtaining a neutral macrolide, compound (III) as a main product (yield 35%) and aglycone moiety, leuconolide-A_3 5,18-hemiacetal (IV) (yield 10%) as shown in Chart 1. Compound (III) was crystallized from ether to give a colorless needles (mp 129—130°, $[\alpha]_D^{20}$ $-104.2°$ ($c=0.5$, ethanol), UV $\lambda_{max}^{ethanol}$ nm (ε): 232 (10760), $C_{42}H_{64}O_{17}$). The acetylation of III with acetic anhydride and pyridine gave monoacetate (V) ($[\alpha]_D^{20}$ $-106.4°$ ($c=0.5$, ethanol), $C_{44}H_{66}O_{18}$). The mass spectrum of V exhibited the fragmentation peak at m/e 451 due to the aglycone and that at m/e 229 due to isovaleryl mycarose moiety, suggesting that only the mycaminose moiety is subject to modification.

Concerning the structural information for III, NMR spectrometric investigation of I was carried out. The assignment of each proton on I was mainly performed by interpreting the NMR spectra of the α,β-isovaleryl mycarose, α,β-methyl-mycaminoside[4] and IV. The NMR spectrum (251 MHz) (Fig. 1) of I revealed the signals for olefinic proton at δ 5.5—6.8, β-anomeric on mycaminose at δ 4.3 ($J_{1',2'}=7.4$ Hz), α-anomeric on mycarose at δ 5.02 ($J_{1',2'}=2.8$ Hz), and for position-2′,3′,4′ and 5′ on mycaminose at δ 2.7—3.6 region.

In the NMR spectrum (Fig. 2) of III, the signals of each proton based on aglycone and mycarose moiety unchanged comparing with those of I, but the signal of NMe_2 group observed at δ 2.56 in I disappeared, and an OAc group appeared at δ 2.1. Further, the each proton corresponding to position-1′,2′,3′, and 4′ on mycaminose disappeared in III, and the anomeric proton at position-1′ observed at δ 4.3 in I and the proton of the basis of the acetylated hydroxyl group at position-2′ appeared at δ 4.9 and δ 5.1 ($J_{1',2'}=8.0$ Hz) as a doublet, respectively, shifting to lower field. In order to assign the three protons observing at near δ 4.0, III was catalytic hydrogenated over PtO_2, forming tetrahydro compound (VI) ($[\alpha]_D^{22}$ $-118.2°$

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