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STUDIES ON QUINOLIZINE DERIVATIVES XVIII. SYNTHESSES OF
AZABENZOCYCL[3.3.3]AZINE DERIVATIVES ¹⁾

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1,4-Diazabenzocycl[3.3.3]azine derivative (IX) and 1-azabenzocycl[3.2.2]azine derivative (VII) were synthesized by the reaction of dimethyl acetylenedicarboxylate (DMAD) with 3-cyano-4-imino-4H-isoquinolino[1,2-a]pyrimidine (IV). Benzo[g]cycl[3.2.2]azine derivative (VIII) was synthesized using the reaction of DMAD (VI) with methyl 3-cyano-4-imino-4H-isoquinolino[1,2-a]pyridine-1-carboxylate (V).

KEYWORDS—1,4-diazabenzocycl[3.3.3]azine; 1-azabenzocycl[3.2.2]azine; benzo[g]cycl[3.2.2]azine; methyl 1,4-diazabenzocycl[3.3.3]azine-5-carboxylate; benzocyclazine

As an extension of our studies on azacyclazine derivatives, we have investigated the syntheses of 1,4-diazacycl[3.3.3]azine derivatives.²⁾ In this communication, we wish to report methods of synthesizing the benzocyclazine derivatives (VII, VIII, IX) using the reaction of benzoquinolizine derivatives (IV, V) with DMAD (VI).

A mixture of 1-aminoisoquinoline (I) and ethoxymethylenemalononitrile (III) was heated for half an hour in a boiling water bath to give 3-cyano-4-imino-4H-isoquinolino[1,2-a]pyrimidine (IV).³⁾ Likewise by allowing III to react with methyl 1-isoquinolylacetate (II), methyl 3-cyano-4-imino-4H-isoquinolino[1,2-a]pyridine-1-carboxylate (V)³⁾ was obtained.

A solution of IV and VI with Pd-C in xylene was refluxed under N₂ atmosphere for 30 h to give only dimethyl 2-cyano-1-azabenzocycl[3.2.2]azine-3,4-dicarboxylate (VII) as orange needles, mp 198°C. Yield, 32%. Anal. Calcd for C₁₈H₁₁N₃O₄: C, 64.87; H, 3.33; N, 12.61. Found: C, 64.56; H, 3.26; N, 12.71. MS m/z: 333(M⁺). IR (KBr) cm⁻¹: 1720, 1750(C=O), 2220(CN). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 241, 259, 291, 337, 351, 482. NMR(CDCl₃) δ : 4.09(3H, s, OMe), 4.15(3H, s, OMe), 7.73-8.62 (4H, m, aromatic protons), 9.00(1H, s, 5-H).

In a manner similar to the above method, the reaction of V with VI gave the corresponding trimethyl 2-cyanobenzo[g]cycl[3.2.2]azine-1,3,4-tricarboxylate (VIII) as orange needles, mp 285°C. Yield, 35%. Anal. Calcd for C₂₁H₁₄N₂O₆: C, 64.62; H, 3.62; N, 7.18. Found: C, 64.32; H, 3.54; N, 7.26. MS m/z: 390(M⁺). IR (KBr) cm⁻¹: 1708, 1720(C=O), 2210(CN). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 241, 259, 266, 291, 339, 351, 490. NMR(CDCl₃) δ : 3.80(3H, s, OMe), 4.12(3H, s, OMe), 4.16(3H, s, OMe), 7.76(2H, m, 7, 8-H), 8.41(1H, d, J=8Hz, 6-H), 8.72(1H, s, 5-H), 9.25(1H, d, J=7Hz, 9-H).

On the other hand, a solution of IV and VI in N,N-dimethylformamide (DMF) was heated at 150°C for 10 h to give dimethyl 3-cyano-1,4-diazabenzocycl[3.3.3]azine-5,6-dicarboxylate (IX) as green needles, mp 263°C. Yield, 11%. Anal. Calcd for C₁₉H₁₂N₄O₄: C, 63.33; H, 3.36; N, 15.55. Found: C, 63.51; H, 3.31; N, 15.56. MS m/z: 360(M⁺). IR (KBr) cm⁻¹: 1718, 1724(C=O), 2220(CN). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 245, 270, 318, 329, 354, 370, 392, 420, 444, 468. NMR(CDCl₃-TFAA=20:1) δ : 3.88(3H, s, OMe), 3.93(3H, s, OMe), 6.65(1H, s, 7-H), 7.44(1H, d, J=8Hz, 8-H), 7.67(2H, m, 9, 10-H), 7.90(1H, s, 2-H), 8.32(1H, d, J=7Hz, 11-H).

A mixture of IX and polyphosphoric acid (PPA) was heated at 100°C for 10 h to give dimethyl 3-carbamoyl-1,4-diazabenzocycl[3.3.3]azine-5,6-dicarboxylate (X) as green needles, mp 256°C. Yield, 95%. Anal. Calcd for C₁₉H₁₄N₄O₅: C, 60.32; H, 3.73; N, 14.81. Found: C, 60.20; H, 3.79; N, 14.77. MS m/z: 378(M⁺). IR (KBr) cm⁻¹: 1665, 1680, 1740(C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 242, 269, 319, 330, 353, 372, 391, 412, 436, 462. NMR(CDCl₃) δ : 3.80(3H, s, OMe), 3.86(3H, s, OMe), 6.10(1H, s, 7-H), 7.09(3H, m, 8, 9, 10-H), 8.22(1H, d, J=8Hz, 11-H), 8.37(1H, s, 2-H).

A solution of X and 48% HBr was heated at 150°C for 3 h to give 1,4-diazabenzocycl[3.3.3]azine-5-carboxylic acid hydrobromide (XI) as red needles, mp 343°C. Yield, 91%. Anal. Calcd for $C_{15}H_{10}BrN_3O_2$: C, 52.35; H, 2.93; Br, 23.22; N, 12.21. Found: C, 52.25; H, 2.98; Br, 23.25; N, 12.08. MS m/z : 344 (M^+). IR (KBr) cm^{-1} : 1690(C=O). UV λ_{max}^{EtOH} nm(log ϵ): 237(4.43), 303(4.32), 316(4.44), 343(4.03), 359(4.12), 376(3.77), 426(3.60), 442(3.49). NMR(DMSO- d_6) δ : 6.27(1H, d, $J=7$ Hz, 3-H), 6.45(1H, s, 7-H), 7.29-7.63(4H, m, 6, 8, 9, 10-H), 7.77(1H, d, $J=7$ Hz, 2-H), 8.14(1H, d, $J=8$ Hz, 11-H).

A solution of XI in MeOH-HCl was heated at 100°C for 10 h and then treated with potassium carbonate to give methyl 1,4-diazabenzocycl[3.3.3]azine-5-carboxylate (XII) as green needles, mp 215°C. Yield, 97%. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.30; H, 4.00; N, 15.16. Found: C, 69.36; H, 3.90; N, 15.15. MS m/z : 277(M^+). IR (KBr) cm^{-1} : 1700(C=O). UV λ_{max}^{EtOH} nm(log ϵ): 235(4.48), 254(4.37), 262(4.37), 317(4.34), 328(4.28), 340(4.04), 358(4.13), 404(3.91), 426(4.05), 452(3.96). NMR(CDCl $_3$) δ : 3.79(3H, s, OMe), 5.51(1H, s, 6-H), 5.65(1H, d, $J=7$ Hz, 3-H), 6.15(1H, s, 7-H), 6.92(1H, d, $J=8$ Hz, 8-H), 7.04(1H, d, $J=7$ Hz, 2-H), 7.29(2H, m, 9, 10-H), 7.92(1H, d, $J=8$ Hz, 11-H).

XII

XIII

We compared the NMR spectral data of XII and methyl 1,4-diazacycl[3.3.3]azine-5-carboxylate (XIII).⁴⁾ (Table I)

Table I. NMR Spectral Data (ppm) of XII and XIII

Compound(solvent)	2-H	3-H	6-H	7-H	Aromatic protons
XII (CDCl $_3$)	7.04	5.65	5.51	6.15	6.92-7.92
XIII (CDCl $_3$)	6.42	5.43	5.48	4.77	/

In recent years there has been considerable effort to try to rationalize the effect of benzo-fusion on aromatic annulenes. Of central importance has been the question whether benzannulation of a delocalized macrocyclic ring reduced delocalization in the large ring or stopped it all together.^{5a,b)} In the 1,4-diazabenzocycl[3.3.3]azine (XII), the 3-H and 6-H protons appeared in comparatively high fields (δ : 5.51-5.65) which clearly indicated the presence of paramagnetic ring current in comparison with XIII, while the 8-H, 9-H, 10-H and 11-H protons appeared in the usual aromatic fields (δ : 6.92-7.92). The results probably indicate that in the resonance contribution as represented in formulas XII, XII' and XII'', the contribution of formulas XII and XII'' ($12\pi+6\pi$ electron system) are more important than that of formula XII' (16π electron system). Hence, the remarkable lower field shift of 7-H proton signal in XII as compared with that of XIII may also be explainable, in part because the conjugated dienyl ester function (marked by $\circ$ in formula XII) in XII is fixed just as penta-dienoate and in part because this signal is deshielded by the benzene ring current effect since the 7-H proton is directly next to the benzene ring.

We are in the process of preparing other benzocyclazine with the hope of expanding our understanding of these interesting compounds.

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