Communications to the Editor

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

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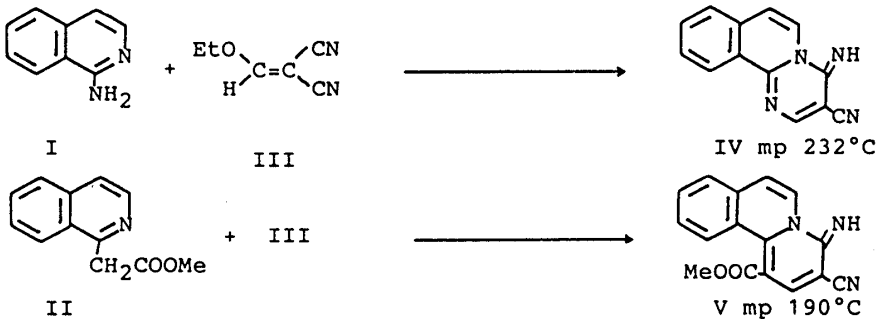
1,4-Diazabenzo[j]cycl[3.3.3]azine derivative (IX) and 1-azabenzo-[h]cycl[3.2.2]azine derivative (VII) were synthesized by the reaction of dimethyl acetylenedicarboxylate (DMAD) with 3-cyano-4-imino-4H-isoquino-lino[1,2-a]pyrimidine (IV). Benzo[g]cycl[3.2.2]azine derivative (VIII) was synthesized using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

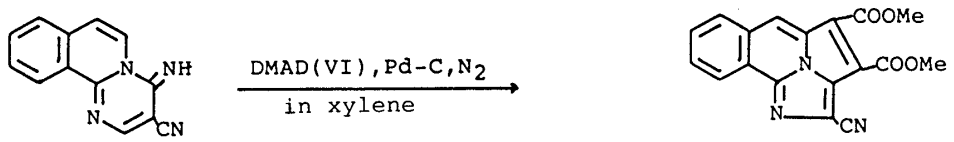
KEYWORDS——1,4-diazabenzo[j]cycl[3.3.3]azine; 1-azabenzo[h]cycl-[3.2.2]azine; benzo[g]cycl[3.2.2]azine; methyl 1,4-diazabenzo[j]cycl-[3.3.3]azine-5-carboxylate; benzocyclazine

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).

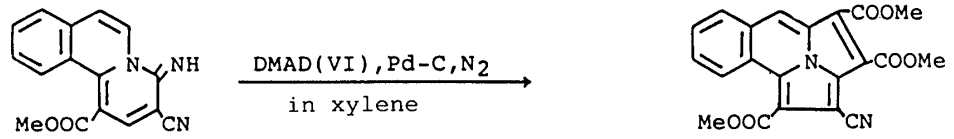
A mixture of 1-aminoisoquinoline (I) and ethoxymethylenemalononitrile (III) was heated for half an hour in a boiling water bath to give 3-cyano-4-imino-4H-isoquinolino[1,2-a]pyrimidine (IV).[3)] Likewise by allowing III to react with methyl 1-isoquinolylacetate (II), methyl 3-cyano-4-imino-4H-isoquinolino[1,2-a]-pyridine-1-carboxylate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



A solution of IV and VI with Pd-C in xylene was refluxed under N_2 atmosphere for 30 h to give only dimethyl 2-cyano-1-azabenzo[h]cycl[3.2.2]azine-3,4-dicarboxylate (VII) as orange needles, mp 198°C. Yield, 32%. Anal. Calcd for $C_{18}H_{11}N_3O_4$: 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 λ_{max}^{EtOH}nm: 241, 259, 291, 337, 351, 482. NMR($CDCl_3$)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).

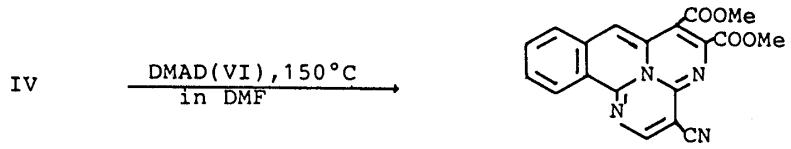


IV VII mp 198°C



V VIII mp 285°C

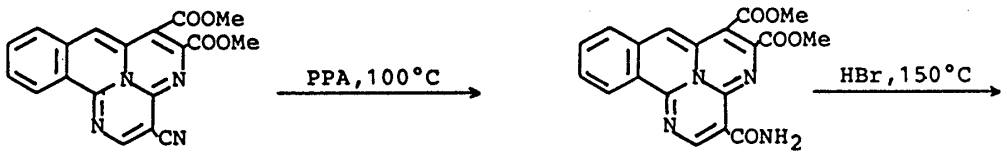
In a manner similar to the above method, the reaction of V with VI gave the corresponding trimethyl 2-cyanobenzo[g]cycl[3.2.2]azine-1,3,4-tricarboxylate (VIII) as orange needles, mp 285°C. Yield, 35%. Anal. Calcd for $C_{21}H_{14}N_2O_6$: C, 64.62; H, 3.62; N, 7.18. Found: C, 64.32; H, 3.54; N, 7.26. MS m/z: 390(M^+). IR (KBr) cm^{-1}: 1708, 1720(C=O), 2210(CN). UV λ_{max}^{EtOH}nm: 241, 259, 266, 291, 339, 351, 490. NMR($CDCl_3$)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).



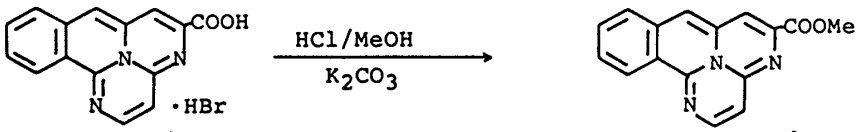
IX mp 263°C

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-diazabenzo[j]cycl-[3.3.3]azine-5,6-dicarboxylate (IX) as green needles, mp 263°C. Yield, 11%. Anal. Calcd for $C_{19}H_{12}N_4O_4$: 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 λ_{max}^{EtOH}nm: 245, 270, 318, 329, 354, 370, 392, 420, 444, 468. NMR($CDCl_3$-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-diazabenzo[j]cycl[3.3.3]azine-5,6-dicarboxylate (X) as green needles, mp 256°C. Yield, 95%. Anal. Calcd for $C_{19}H_{14}N_4O_5$: 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 λ_{max}^{EtOH}nm: 242, 269, 319, 330, 353, 372, 391, 412, 436, 462. NMR($CDCl_3$) 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).



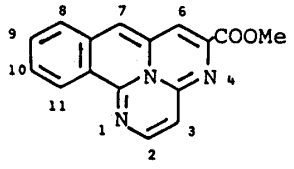
IX X mp 256°C



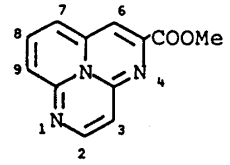
XI mp 343°C XII mp 215°C

A solution of X and 48% HBr was heated at 150°C for 3 h to give 1,4-diazabenzo[j]cycl[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(logε): 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=7Hz, 3-H), 6.45(1H, s, 7-H), 7.29-7.63(4H, m, 6, 8, 9, 10-H), 7.77(1H, d, J=7Hz, 2-H), 8.14(1H, d, J=8Hz, 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-diazabenzo[j]cycl[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(logε): 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=7Hz, 3-H), 6.15(1H, s, 7-H), 6.92(1H, d, J=8Hz, 8-H), 7.04(1H, d, J=7Hz, 2-H), 7.29(2H, m, 9, 10-H), 7.92(1H, d, J=8Hz, 11-H).



XII



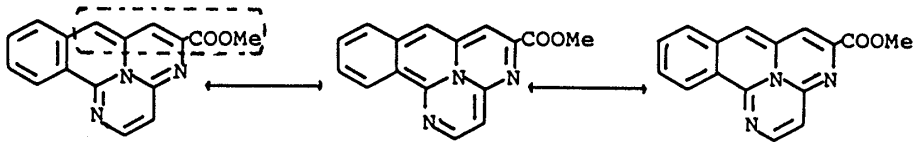
XIII

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 benzannelation of a delocalized macrocyclic ring reduced delocalization in the large ring or stopped it all together.[5a,b] In the 1,4-diazabenzo[j]cycl[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 ⌒) in formula XII) in XII is fixed just as pentadienoate 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.



XII XII' XII"

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

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3) these compounds (IV, V) gave satisfactory spectral/elemental analysis and IV, V correspond to the yields (95%, 90%).
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