A SYNTHESIS OF PYRIDO[1,2-a]QUINOXALINES AND PYRIDO[1,2-a]-PYRAZINES [1)]

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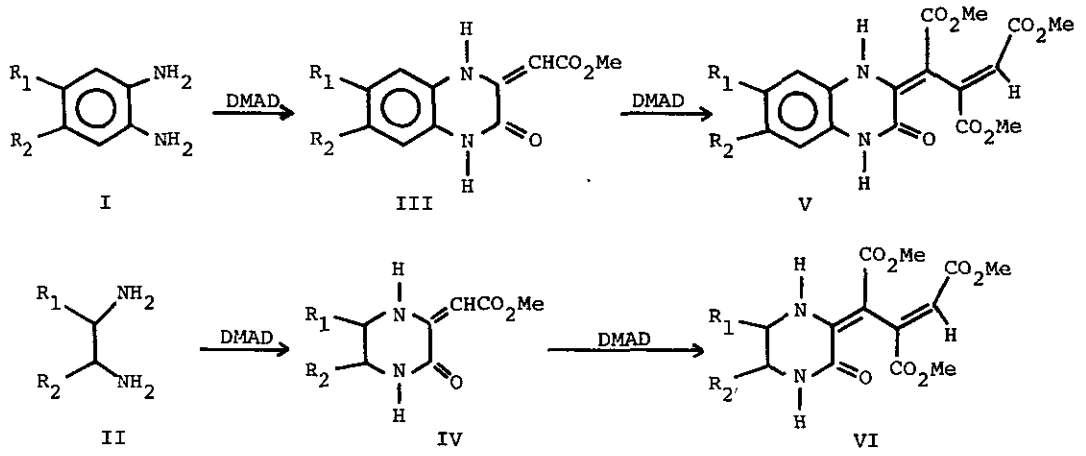
Abstract ---- o-Phenylenediamines and 1,2-diamines reacted with dimethyl acetylenedicarboxylate (DMAD) to afford trimethyl 3-oxo-1,2,3,4-tetrahydroquinoxaline-$\Delta^{2,\gamma}$-aconitates and trimethyl 3-oxo-piperazine-$\Delta^{2,\gamma}$-aconitates which were converted to pyrido-[1,2-a]quinoxalines and pyrido[1,2-a]pyrazines, respectively, by thermal or photochemical reactions.

Acetylenic esters are widely used for the preparation of heterocyclic compounds.[2)] As a part of our studies on heterocyclic compounds, we recently reported the results of the reactions of benzazoles[3)] or nucleic acid bases[4)] with dimethyl acetylenedicarboxylate (DMAD). In this paper, we describe a novel synthesis of pyrido[1,2-a]quinoxalines and pyrido[1,2-a]pyrazines. The reaction of o-phenylene-diamine (Ia) with DMAD in MeOH has been known to produce 3-methoxycarbonyl-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (IIIa).[5)] The further reaction of IIIa (3.0g) with DMAD (5ml) in dioxane (30ml) under reflux overnight provided a crystalline solid which was collected by filtration and recrystallized from CH_2Cl_2-EtOH to afford trimethyl 3-oxo-1,2,3,4-tetrahydroquinoxaline-$\Delta^{2,\gamma}$-aconitate (Va, 1.54g).[6)] From the filtrate, additional Va (1.25g) was isolated by column chromatography on silica gel (total 2.79g, 54.44%).

The compound Va was also obtained directly by the reaction of o-phenylenediamine (Ia, 1.08g) with DMAD (5ml) in refluxing dioxane (30ml) overnight. Evaporation of the reaction mixture afforded crystals, which were collected, washed with EtOH and recrystallized from CH_2Cl_2-EtOH to give Va (1.39g). From the filtrate and washings, additional Va (0.29g) was obtained by preparative TLC on silica gel with benzene-ethyl acetate (4 : 1) as developer (total 1.68g, 46.7%).



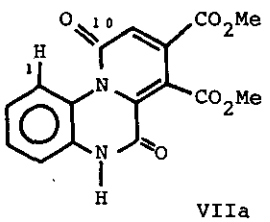
scheme 1

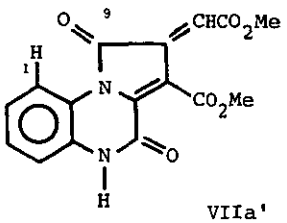
Table 1 The products obtained from the reactions of III and IV with DMAD

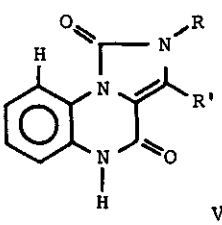
Compound		mp(°C)	MS m/e(M^+)	yield(%)
V a	$R_1 = R_2 = H$	220-221	360	56.4
b	$R_1 = H$, $R_2 = Cl$	170-172	394,396	20.0
VI a	$R_1 = Me$, $R_2 = H$	181-182.5	326	53.1
b	R_1 , $R_2 = -(CH_2)_4-$	145-147	366	47.7

The structure of Va was assumed by the satisfactory elemental analysis, spectral data and comparison with X-ray analysis of a similar compound.[6] Other compounds (Vb, VIa and VIb) were prepared in a similar manner and their melting points and yields are shown in Table 1.[6]

A solution of Va (3.0g) in dry DMSO (70ml) was refluxed for 1 h under nitrogen to give an almost single product on TLC. Extraction of the reaction product with ethyl acetate followed by evaporation of the solvent provided a brownish crystalline solid (1.75g, 63.9%) which was recrystallized from CH_2Cl_2-MeOH to afford yellow needles; dimethyl 5,6-dihydro-6,10-dioxo-10H-pyrido[1,2-a]-quinoxaline-7,8-dicarboxylate [VIIa, mp 282-284°, $C_{16}H_{12}N_2O_6$, m/e 328(M^+); ν_{max}^{KBr} (cm^{-1}) 1735, 1710, 1650, 1585; ^{1}H-nmr (DMSO-d_6) δ(ppm) 3.76, 3.85 (each s, 3H, OMe X 2), 7.27 (s, 1H, vinylic), 7.05-7.50 (m, 3H, aromatic), 9.11 (d, J = 8Hz, 1H, aromatic), 12.02 (broad, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ(ppm) 52.14, 53.12, 95.46, 116.02, 120.90, 122.26, 122.85, 125.77, 128.11, 128.31, 133.42, 136.78, 154.45, 160.51, 163.34 and 165.49]. This product was also prepared by treatment with Et_3N of Va in EtOH as shown in Table 2. Furthermore, we could obtain VIIa by photolysis

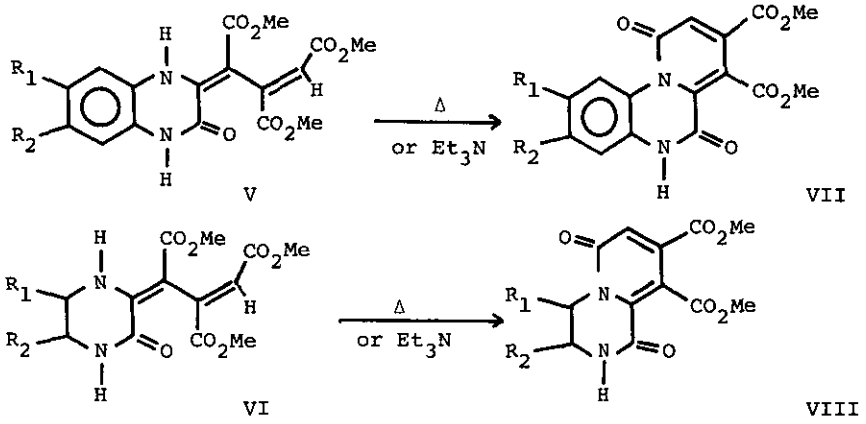

VIIa


VIIa'


VIIa"

scheme 2

of Va in acetone in low yield.[7] Similar thermal reactions of V and VI afforded VII and dimethyl 1,6-dioxo-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrazine-8,9-dicarboxylates (VIII), respectively, in each yields shown in Table 2.[8]
The spectral data described above suggest that this pyrolysis resulted in the elimination of MeOH from Va and hence an intramolecular cyclization was caused to form VIIa or VIIa'. In ^{1}H-nmr spectrum of VIIa, one of the aromatic protons (δ 9.11) is observed at a very low magnetic field. The low field resonances of aromatic protons (δ 8.58, 8.73 and 8.80) in the same solvent have been reported in analogous tricyclic compounds (VIIa").[9] The extent of down field shift in VIIa" is a little smaller than that in our compound. Studies with molecular models show that this paramagnetic shift is due to the close proximity between C_{10}(or C_9) carbonyl group and C_1 aromatic proton and that more downfield shift is expected for VIIa in contrast with VIIa' because the C_1 proton of VIIa lies in closer to the carbonyl group compared with that of VIIa'. Thus, the structure of this cyclized compound is assigned as dimethyl 5,6-dihydro-6,10-dioxo-10H-pyrido[1,2-a]quinoxaline-7,8-dicarboxylate (VIIa).


V VII VI VIII

scheme 3

Table 2 The cyclization products

Compound			mp(°C)	MS m/e(M^+)	yield(%)
VII	a	$R_1 = R_2 = H$	282-284	328	63.9(22.0*)
	b	$R_1 = H$, $R_2 = Cl$	295-296	362,364	51.7
VIII	a	$R_1 = Me$, $R_2 = H$	202.5-203.5	294	79.7
	b	R_1 , $R_2 = -(CH_2)_4-$	243-245	334	66.2(50.3*)

* treatment with Et_3N

In conclusion, pyrido[1,2-a]quinoxalines and pyrido[1,2-a]pyrazines were easily synthesized by the pyrolysis of the aconitate derivatives V and VI, respectively.

REFERENCES AND NOTES

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   IIIb : mp = 238-241°; MS m/e : 252, 254 (M^+); $\nu_{max}^{KBr}(cm^{-1})$: 3000, 1680, 1620; ^{1}H-nmr(DMSO-d_6): 3.82(s, 3H), 5.52(s, 1H), 7.03-7.53(m, 3H), 11.00(br, 1H).
   IVa : mp = 214-216.5°; MS m/e : 184 (M^+); $\nu_{max}^{KBr}(cm^{-1})$: 3200, 1680, 1620; ^{1}H-nmr($CDCl_3$) δ: 1.28(d, 3H, J=6.2), 3.00-3.60(m, 2H), 3.69(s, 3H),3.69-4.00 (m, 1H), 5.61(s, 1H), 7.20-7.26(br, 1H), 8.27(br, 1H).
   IVb : mp = 196-199°; MS m/e : 224 (M^+); $\nu_{max}^{KBr}(cm^{-1})$: 2930, 1680, 1610; ^{1}H-nmr ($CDCl_3$) δ: 1.70(m, 8H), 3.68(s, 3H), 3.72(s, 2H), 5.60(s, 1H), 7.50(br, 1H), 8.20(br, 1H).
6. Va : yellow leaflets, $C_{17}H_{16}N_2O_7$, MS m/e : 360 (M^+); $\nu_{max}^{KBr}(cm^{-1})$: 3100, 1720, 1650, 1595; ^{1}H-nmr($CDCl_3$) δ: 3.68, 3.71 and 3.76(each s, 3H, O-CH_3x3), 6.90 (s, 1H, vinylic), 7.00-7.06(m, 4H, aromatic), 10.56(br, 1H, NH), 12.23(br, 1H, NH). The structure of similar compound, trimethyl 2,3-dihydro-2-oxo-4H-[1,4]-benzoxazine-$\Delta^{3,Y}$-aconitate synthesized from o-aminophenol with DMAD in refluxing dioxane, have been determined by X-ray analysis, and the results will be reported in the near future.

Trimethyl 6-chloro-3-oxo-1,2,3,4-tetrahydroquinoxaline-$\Delta^{2,\gamma}$-aconitate (Vb) : ^{1}H-nmr($CDCl_3$) δ: 3.72(s, 6H), 3.84(s, 3H), 6.92(s, 1H), 6.90-7.08(m, 3H), 11.22 (br, 1H), 12.15(br, 1H); ν_{max}^{KBr}(cm^{-1}): 3400, 1690, 1620.

Trimethyl 5-methyl-3-oxo-pyperazine-$\Delta^{2,\gamma}$-aconitate (VIa) : ^{1}H-nmr($CDCl_3$) δ: 1.24 (d, 3H, J=6.3Hz), 3.61, 3.67 and 3.74(each s, 3Hx3), 3.00-4.00(m, 3H), 6.74(s, 1H), 7.20-7.28(br, 1H), 9.30(br, 1H); ν_{max}^{KBr}(cm^{-1}): 3300, 1710, 1640, 1570.

Trimethyl 3-oxo-decahydroquinoxaline-$\Delta^{2,\gamma}$-aconitate (VIb) : ^{1}H-nmr($CDCl_3$) δ: 1.73(m, 8H), 3.60(s, 3H), 3.66(s, 3H), 3.60-3.70(m, 2H), 3.70(s, 3H), 6.70(s, 1H), 8.22(br, 1H), 9.29(br, 1H); ν_{max}^{KBr}(cm^{-1}): 3280, 1710, 1640, 1575.

7. Photolysis were carried out in a flask fitted with a 300W high pressure mercury lamp covered with a quartz filter for 9-15 h under nitrogen. A part of the reaction mixture was purified by repeated preparative TLC on silica gel and the main product was recrystallized *from* CH_2Cl_2-MeOH to afford VIIa.

8. Dimethyl 3-chloro-5,6-dihydro-6,10-dioxo-10H-pyrido[1,2-a]quinoxaline-7,8-dicarboxylate (VIIb) : ^{1}H-nmr($CDCl_3$) δ: 3.76(s, 3H), 3.84(s, 3H), 7.20-7.30(m, 2H), 7.28(s, 1H), 9.16(d, 1H, J=9Hz), 12.09(br, 1H); ν_{max}^{KBr}(cm^{-1}): 1725, 1665, 1590.

Dimethyl 3-methyl-1,6-dioxo-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrazine-8,9-dicarboxylate (VIIIa) : ^{1}H-nmr($CDCl_3$) δ: 1.40(d, 3H, J=6.2Hz), 3.33-3.90(m, 2H), 3.88(s, 3H), 3.90(s, 3H), 4.70(m, 1H), 7.35(s, 1H), 8.14(br, 1H); ν_{max}^{KBr}(cm^{-1}): 3200, 1740, 1660.

Dimethyl decahydro-6,10-dioxo-10H-pyrido[1,2-a]quinoxaline-7,8-dicarboxylate (VIIIb) : ^{1}H-nmr($CDCl_3$) δ: 1.20-1.80(m, 8H), 3.87(s, 3H), 3.90(s, 3H), 3.90(m, 1H), 4.90(m,, 1H), 7.32(s, 1H), 8.55(br, 1H); ν_{max}^{KBr}(cm^{-1}): 2950, 1740, 1700, 1660.

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