THERMAL REACTIONS OF *o*-AMINOPHENOLS AND DIMETHYL ACETYLENEDICARBOXYLATE

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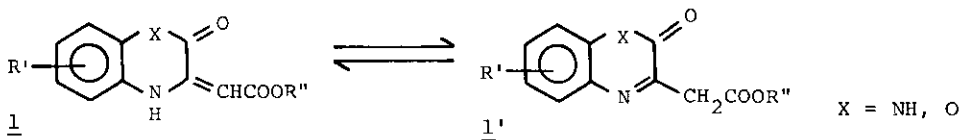
Abstract ——— *o*-Aminophenols reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing dioxane to give 1,4-benzoxazine derivatives and their isomers. Further, novel tricyclic compounds and benzoxazole derivative were prepared in this reaction.

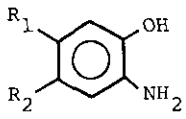
Acetylenic esters are useful reagents for the synthesis of heterocyclic compounds.[1] Thermal addition reactions of DMAD with phenylenediamines[2] or aminophenols[3] have been reported. The tautomeric behaviors of 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (1, X = NH) and other similar systems (1, X = O) have been studied by IR, UV and NMR spectroscopies.[4] Kurasawa *et al.*[5] have also reported the presence of the tautomeric equilibria of many similar quinoxaline derivatives

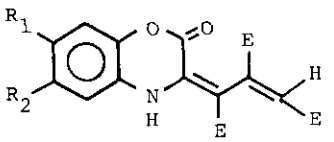


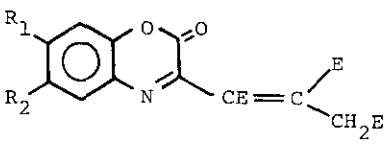
1 1'

as the results of studies by the ^{1}H-NMR and ^{13}C-NMR spectra. But there is no report that a compound of 1' type was isolated in a crystalline form. In this paper, we wish to describe that by the reaction of aminophenols with DMAD in refluxing dioxane, trimethyl aconitate derivative and its isomer corresponded to 1' were obtained in a crystalline form, and further, novel tricyclic intramolecular cyclization product and benzoxazole derivative were obtained in this reaction.

DMAD (35 ml) was added to a dioxane (300 ml) solution of 4-methyl-2-aminophenol (2, 0.1 mol) and the mixture was refluxed for 2 days. The solvent was removed *in vacuo* to leave an oily residue which was subjected to silica gel column chromatography (110 g) with benzene-ether as an eluent. Three crystalline compounds (3, 4 and 5) could be isolated from the reaction mixture. All of products have the same





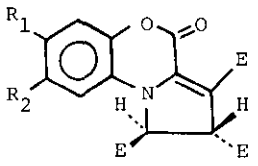


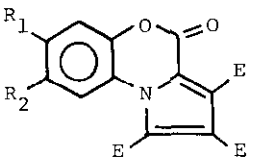
2 R_1=H, R_2=CH_3
6 R_1=R_2=H
9 R_1=H, R_2=Cl
12 R_1=CH_3, R_2=H

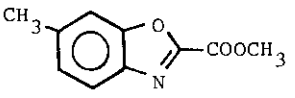
3 R_1=H, R_2=CH_3
7 R_1=R_2=H
10 R_1=H, R_2=Cl
13 R_1=CH_3, R_2=H

4 R_1=H, R_2=CH_3
14 R_1=CH_3, R_2=H

E = $COOCH_3$







5 R_1=H, R_2=CH_3 8 R_1=R_2=H

11

15

Chart 1

empirical formula $C_{18}H_{17}O_8N$ which was derived from elemental and mass spectral analyses. The structure of the first product (3, 28.2%) was confirmed by direct comparison with an authentic sample reported in the previous paper.[3] The second product (4, 5.1%) was recrystallized from CH_2Cl_2-MeOH to give yellow prisms [mp 153-154°C, MS m/z 375 (M^+)]. ^{1}H-NMR spectrum of 4 showed methyl protons at δ 2.45 (s), three methyl esters at δ 3.72 (s), 3.81 (s) and 3.87 (s), and three aromatic protons at δ 7.18-7.52 (m). A vinyl proton and an amino proton signals observed in 3 were not detected and instead a signal at δ 3.65 (2H, s) appeared. ^{13}C-NMR spectrum had a signal at δ 36.94 which became triplet by single frequency off-resonance mode. These signals (3.65 and 36.94) were assignable to the protons on the methylene carbon between two quaternary carbons. On the basis of these data, the structure of 4 was assigned to be a double bond isomer of 3 ; methyl 3,4-di(methoxycarbonyl)-4-(6-methyl-2-oxo-2H-1,4-benzoxazin-3-yl)-3-butenoate. The stereochemistry of around C_3 and C_4 is not obvious. A interconversion of enamine (3) and imine (4) was observed in boiling dioxane and enamine form (3) was predominant (approximately

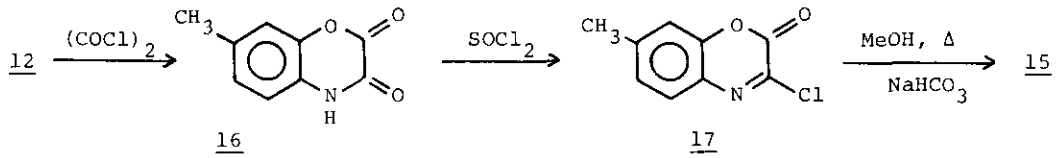
>10 : 1) in this tautomerism. The study of this enamine-imine tautomerism is now in progress. The third product (5, 8.4%) was recrystallized from ether to give white needles [mp 174-175°C, MS m/z 375 (M^+)]. ^{1}H-NMR spectrum of 5 indicated aromatic methyl protons at δ 2.31 (s), three methyl esters at δ 3.73 (s), 3.80 (s) and 3.90 (s), and three aromatic protons at δ 6.90-7.10 (m). Moreover, two protons appeared as an AB quartet (J = 5.4Hz) at δ 4.67 and 4.82, and signals due to a vinyl proton and an amino proton observed in 3 were not detected. In the ^{13}C-NMR spectrum of 5, both signals at δ 48.54 and 62.96 became doublet by single frequency off-resonance mode, respectively. These data suggested that this compound (5) is an intramolecular cyclization product which the side chain of 3 cyclyzed to nitrogen atom. Thus, the structure of this compound (5) was assigned as trimethyl 8-methyl-4-oxo-2-pyrrolino[2,1-c]-1,4-benzoxazine-1,2,3-tricarboxylate. It seemed reasonable to assume that the configuration between 1-H and 2-H in 5 is trans by the coupling constant (J = 5.4Hz). Furthermore, studies with molecular model showed that trans form of 5 may be a more sterically favorable configuration.

2-Aminophenol (6) was refluxed with DMAD in dioxane for 5 days and two crystalline compounds could be isolated from the reaction mixture. Trimethyl aconitate derivative (7)[3] was obtained in 45.4% yield and another product (8, 1.5%) was assigned to be the 2-pyrrolino compound.[6]

When 4-chloro-2-aminophenol (9) was heated with DMAD in refluxing dioxane for 4 days, two crystalline compounds were obtained. Together with trimethyl aconitate derivative (10,[3] 68.5%), a small amount (11, 0.7%) of the second product which was recrystallized from ether was obtained as white needles [mp 192-193.5°C, MS m/z 393, 395 (M^+), $C_{17}H_{12}O_8NCl$]. ^{1}H-NMR spectrum of this compound showed only three methyl esters at δ 3.89 (s), 4.02 (s) and 4.14 (s), and aromatic protons at δ 7.36-7.47 (3H, m). The signals of methyl esters were observed at slightly lower magnetic field (ca 0.2 ppm) compared with those of other compound described above. It was assumed that this down field shift is due to the magnetic anisotropic effect of the aromatic ring. Thus, the structure of this compound (11) was estimated as a dehydrocyclization product of 10 ;trimethyl 8-chloro-4-oxo-pyrrolo[2,1-c]-1,4-benzoxazine-1,2,3-tricarboxylate. A possible pathway accounting for the formation of 5, 8 and 11 is now under investigation.

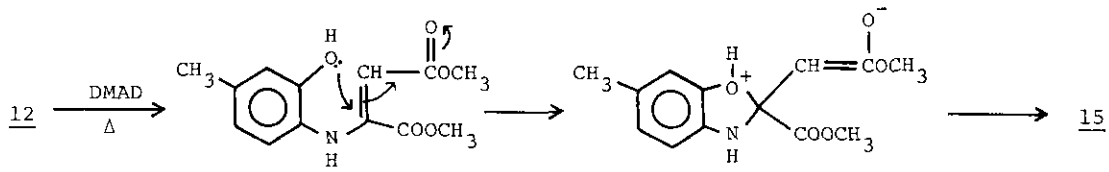
2-Amino-5-methylphenol (12) was treated in the same manner for 1 day and by the silica gel column chromatography of the reaction mixture, three crystalline products were isolated. The structures of 13 (12.9%)[3] and 14 (0.4%)[7] were elucidated by

comparison of their spectral data to those of similar compounds. Compound (15, 6.0%) was recrystallized from ether to give white needles [mp 111-112°C, MS m/z 191 (M^+), $C_{10}H_9O_3N$]. The ^{1}H-NMR spectrum of this product showed methyl protons at δ 2.53 (s), one methyl ester at δ 4.09 (s) and three aromatic protons at δ 7.22-7.79 (m). The empirical formula and ^{1}H-NMR spectral data suggested that 16 is a condensed-ring compound of a half molecule of DMAD to 13. We estimated that the structure of 15 is methyl 6-methylbenzoxazole-2-carboxylate and attempted the preparation of 15



16 17

by an alternate route. According to the literature,[8] 12 was treated with oxalyl chloride to give 16 (mp 255°C) in good yield. Compound (16) was readily converted to the imino chloride (17, mp 157-158°C) by treatment with thionyl chloride which was heated with MeOH and $NaHCO_3$ overnight to afford a coloured solid. The crude product was purified by recrystallization from ether to give white needles (mp 112-113°C). This synthetic compound was perfectly in accordance with 15 by direct compariсon. Bisi Castellani *et al.* have reported[9] that the copper (II) complex of *o*-quinone monooxime reacted with DMAD in anhydrous MeOH to give methyl 1,3-benzoxazole-2-carboxylate. A plausible reaction sequence for the synthesis of 15 from 12 with DMAD is outlined below.



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6) 8, mp 153-154°C ; MS m/z 361 (M^+) ; ^{1}H-NMR ($CDCl_3$) δ 3.74, 3.81 and 3.89 (each 3H,s,OCH_3x3), 4.69(1H,d,J=5.6Hz,=CH-), 4.85(1H,d,J=5.6Hz,=CH-), 7.10-7.29(4H, m,aromatic) ; ^{13}C-NMR ($CDCl_3$) δ 48.58(d), 51.75(q), 53.12(q), 53.51(q), 62.91 (d), 104.04(s), 117.97(d), 119.83(d), 124.95(s), 125.48(d), 126.41(d), 143.75 (s), 147.56(s), 161.25(s), 163.24(s), 163.68(s), 171.19(s).

7) 14, mp 178-180°C ; MS m/z 375 (M^+) ; ^{1}H-NMR ($CDCl_3$) δ 2.48(3H,s,C-CH_3), 3.64, 3.74 and 3.78(each 3H,s,OCH_3x3), 4.03(2H,s,-CH_2-), 7.14-7.26(2H,m,aromatic), 7.56-7.68(1H,m,aromatic) ; ^{13}C-NMR ($CDCl_3$) δ 21.69(q), 35.57(t), 52.34(q), 52.92(q), 116.66(d), 126.70(d), 128.89(d,s), 135.47(s), 140.09(s), 143.17(s), 146.48(s), 150.87(s), 151.98(s), 164.41(s), 166.46(s), 169.39(s).

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10) Satisfactory elemental analyses were obtained for all compounds reported herein.

11) NMR spectra were measured on a JNM-FX 100 spectrometer (JEOL) and MS spectra were taken by direct insertion method with 9000B (Shimadzu).

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