

Isolation of Stable Diels-Alder Adducts

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Room temperature reaction of 2-aminooxazole **1** and its 4- and 4,5-substituted derivatives, with dimethyl acetylenedicarboxylate gave good yields of Diels-Alder adducts **2**, isolated as stable crystalline compounds. A competing process produced oxazolo[3,2-*a*]pyrimidines **3**, also in good yield. Minor products were also identified. 2-Amino-4-methylthiazole (**6**) reacted in a similar manner and gave the Diels-Alder adduct **7** and a thiazolo[3,2-*a*]pyrimidine **8** as main products with a lesser amount of a thiazole [3,2-*d*][1:3]diazepine (**9**). The aminooxazoles reacted with olefinic dienophiles to give pyridine derivative, formed by breakdown of the original unstable adducts.

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Diels-Alder reactions of oxazoles were discovered by Kondrat'eva [1] and have received considerable attention as synthetic routes to Vitamin B₁ analogues. Olefinic dienophiles were mostly used and gave unstable Diels-Alder adducts, which were not isolated, but decomposed to give pyridine derivatives [2]. Acetylenic dienophiles have not been so well studied but are reported to form unstable adducts which eliminate a nitrile and form furan derivatives [3]. To our knowledge there are no reports in the literature on the use of 2-aminooxazoles in Diels-Alder reactions. In the present paper we report our observation that 2-aminooxazoles readily react with dienophiles and give stable crystalline adducts with dimethyl acetylenedicarboxylate.

Results and Discussion.

The reaction of 2-aminooxazole (**1a**) with dimethyl acetylenedicarboxylate (DMAD) in toluene was exothermic and was completed within a few minutes. After removal of solvent the reaction mixture was separated by column chromatography on silica gel. The first product eluted from the column was identified as the Diels-Alder adduct 1-amino-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[3.2.1]hepta-2,5-diene (**2a**) and its yield was 35%. This structure was supported by the spectral data, particularly

the pmr which showed two singlet methyl groups, two doublets and an exchangeable broad peak.

The second product obtained from the column (21% yield) was identified as 5-methoxycarbonyloxazolo[3,2-*a*]pyrimidine-7-one (**3a**). Its pmr showed a methyl singlet at δ 3.9, a singlet (1H) at 6.64 and two doublets (each 1H) at 7.97 and 8.19.

The reaction was repeated with various 4- and 4,5-substituted-2-aminooxazoles and the main products were the Diels-Alder adduct **2** and the oxazolo[3,2-*a*]pyrimidine (**3**). Table 1 lists the experimental results.

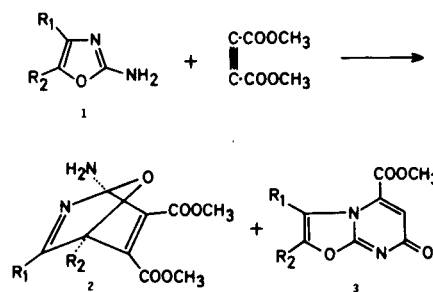


Figure 1

Results indicate that 4-alkyl-2-aminooxazoles react in a similar manner with roughly the same proportion of pro-

Table 1
Products of Reactions of 2-Aminooxazoles with DMAD

	Substituents on Oxazole 1		Product 2 % Yield	Product 3 % Yield	Others % Yield
	R ₁	R ₂			
a	H	H	44	16	—
b	CH ₃	H	41	14	—
c	C ₂ H ₅	H	41	16	—
d	C ₃ H ₇	H	48	23	—
e	<i>t</i> -C ₄ H ₉	H	50	—	4 14
f	C ₆ H ₅	H	37	—	4 19
g	CH ₃	CH ₃	22	21	5 0.5
h	CH ₃	C ₂ H ₅	21	42	—
i	C ₆ H ₅	C ₆ H ₅	5	54	—

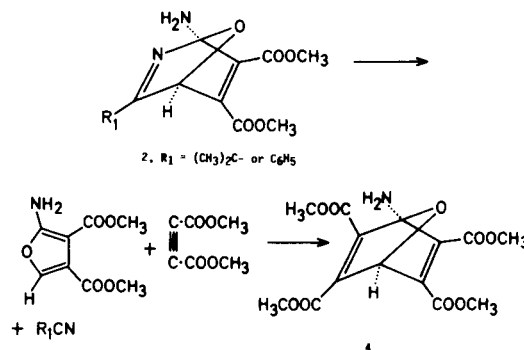


Figure 2

ducts **2** and **3** being formed. Exceptions were found with the *t*-butyl derivative **1e** and phenyl derivative **1f** which gave the bicyclic products **2e** and **2f** but did not form type **3** products. Instead 1-amino-2,3,5,6-tetra(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (**4**) was formed in both cases. The formation of **4** may be envisaged as a retro Diels-Alder reaction from the original adduct, with the elimination of a nitrile, followed by a second Diels-Alder addition of DMAD to the intermediate furan.

From the reaction of 2-amino-4,5-dimethyloxazole (**1g**) a small amount of another side product was isolated. It was identified as 2,3-dimethyl-5,6,7,8-tetra(methoxycarbonyl)-5,6-dihydrooxazolo[3,2-*d*][1,3]diazepine (**5**) on the basis of spectral data and the structure was confirmed by an x-ray crystallographic analysis.

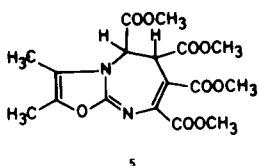


Figure 3

The formation of **5** involves the condensation of 2 molecules of DMAD with **1g**.

The isolation of the bicyclic adducts **2** is unusual since previous work on the oxazoles [4] indicated that the adducts were too unstable to be isolated, however 2-aminooxazoles were not included in these studies.

Our experiments were extended to the corresponding thiazole system by use of 2-amino-4-methylthiazole (**6**) which was treated with DMAD under the same conditions. The major products isolated were the Diels-Alder adduct 1-amino-3-methyl-5,6-bis(methoxycarbonyl)-2-aza-7-thiabicyclo[2.2.1]hepta-2,5-diene (**7**) and 3-methyl-5-methoxycarbonylthiazolo[3,2-*a*]pyrimidine-7-one (**8**) showing that this reaction proceeded in the same manner as for the cor-

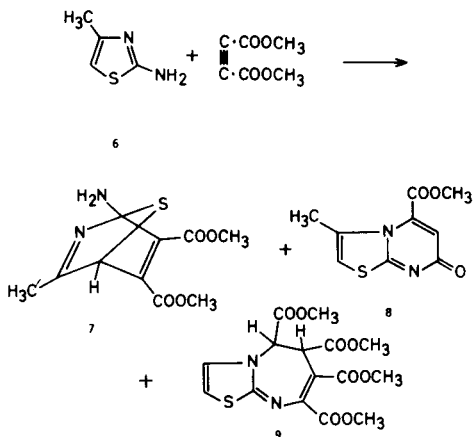


Figure 4

responding oxazole **1b**. A small amount of a minor product 3-methyl-5,6,7,8-tetra(methoxycarbonyl)-5,6-dihydrothiazolo[3,2-*d*][1,3]diazepine (**9**) was also isolated.

In contrast the reaction of 2-aminooxazoles with olefinic dienophiles proceeded in the expected manner [2]. Diethyl maleate reacted with **1b** to give the pyridine derivatives **10** and **11**. This reaction agrees with the established pattern of reactivity of oxazoles with olefinic dienophiles, where an unstable adduct is formed which can undergo a variety of breakdown reactions. Ring opening followed by dehydration gives **10** whilst **11** involves oxidation with loss of two hydrogen atoms.

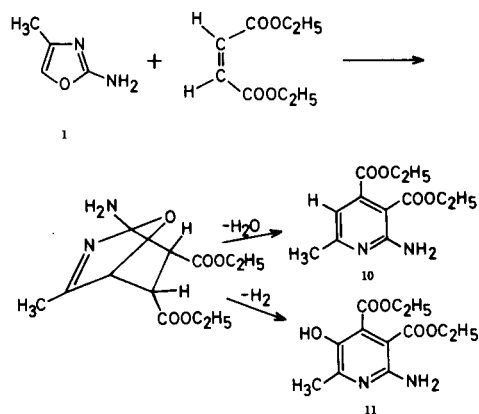


Figure 5

Similarly the *N*-acetyl derivative of **1b** reacted with maleic anhydride to form the pyridine derivative **12**. In this case the postulated intermediate must lose two hydrogen atoms and also decarboxylate.

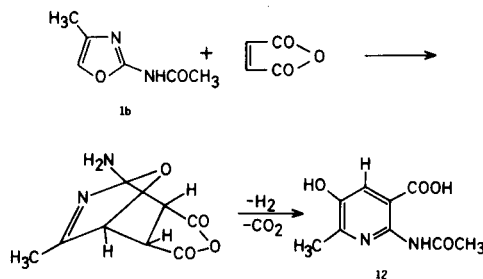


Figure 6

EXPERIMENTAL

Melting points were obtained on a Leitz hot stage microscope and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, University of New South Wales. Infrared spectra were taken on a Unicam SP-100 spectrophotometer and pmr spectra on a Jeol FX-100 spectrometer. Mass spectra were obtained from an AEI-MS12 spectrometer (70 eV). Chromatographic separations were carried out in columns using Merck silica gel G (type 60) eluted with varying proportions of light petroleum (60-80°) and ethyl acetate. 2-Amino-oxazoles were prepared by condensation of cyanamide with the appropriate α -hydroxyaldehyde or α -hydroxyketone [5].

Reaction of 2-Aminooxazole with DMAD.

2-Aminooxazole (**1a**) (2.0 g, 0.023 mole) and DMAD (3.4 g, 0.023 mole) were mixed in toluene (20 ml). An exothermic reaction took place and the solution became dark red. After standing for 0.5 hour solvent was removed by evaporation leaving a dark oil (**5g**) which was separated by column chromatography.

(i) 1-Amino-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[3.2.1]hepta-2,5-diene (**2a**) was eluted with petrol/ethyl acetate (7:3) and formed colourless crystals (2.27 g, 44%) mp 180-181°; ms: m/e 226 (M⁺); pmr (deuteriochloroform): δ 3.72 (s, 3H, -OCH₃), 3.96 (s, 3H, OCH₃), 5.96 (d, 1H, J 1.5 Hz, H3), 6.35 (d, 1H, J 1.5 Hz, H4), 9.5 (broad, 2H, exchanged with deuterium oxide, NH₂); ir (potassium bromide): 1600, 1680, 1720, 3050, 3150, 3400 cm⁻¹.

Anal. Calcd. for C₉H₁₀N₂O₅: C, 47.8; H, 4.4; N, 12.4. Found: C, 47.9; H, 4.3; N, 12.0.

(ii) 5-Methoxycarbonyloxazol[3,2-*a*]pyrimidine-7-one (**3a**) was eluted with petrol/ethyl acetate (1:1) and formed colourless crystals (0.82 g, 16%) mp 192-193°; ms: m/e 194 (M⁺); pmr (deuteriochloroform): δ 3.90 (s, 3H, -OCH₃), 6.64 (s, 1H, H6), 7.97 (d, 1H, J 2 Hz, H3), 8.19 (d, 1H, J 2 Hz, H2); ir (potassium bromide): 1460, 1540, 1645, 1745 cm⁻¹.

Anal. Calcd. for C₈H₈N₂O₄: C, 49.5; H, 3.1; N, 14.4. Found: C, 49.6; H, 2.9; N, 14.4.

Reaction of 2-Amino-4-methyloxazole with DMAD.

In the same way 2-amino-4-methyloxazole (**1b**) (3.0 g, 0.031 mole) and DMAD (4.35 g, 0.031 mole) in toluene at room temperature gave an oil separated chromatographically.

(i) 1-Amino-3-methyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2b**) was eluted with petrol/ethyl acetate (3:1) and formed colourless crystals (2.982 g, 41%) mp 133-135°; ms: m/e 240 (M⁺); pmr (deuteriochloroform): δ 1.83 (s, 3H, -CCH₃), 3.69 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 6.35 (s, 1H, H4), 7.0 (broad s, exchanged with deuterium oxide, NH₂); ir (potassium bromide): 1605, 1690, 1720, 1740, 3050, 3400 cm⁻¹.

Anal. Calcd. for C₁₀H₁₂N₂O₅: C, 50.0; H, 5.0; N, 11.7. Found: C, 49.7; H, 4.9; N, 11.4.

(ii) 3-Methyl-5-methoxycarbonyloxazol[3,2-*a*]pyrimidine-7-one (**3b**) was eluted with petrol/ethyl acetate (3:7) and formed colourless crystals (0.89 g, 14%) mp 118°; ms: m/e 208 (M⁺); pmr (deuteriochloroform): δ 1.89 (s, 3H, C-CH₃), 3.97 (s, 3H, OCH₃), 6.72 (s, 1H, H6), 7.20 (s, 1H, H2); ir (potassium bromide): 1440, 1540, 1570, 1640, 1740 cm⁻¹.

Anal. Calcd. for C₉H₈N₂O₄: C, 51.9; H, 3.3; N, 13.5. Found: C, 51.8; H, 3.9; N, 13.3.

Reaction of 2-Amino-4-ethyloxazole with DMAD.

As described above 2-amino-4-ethyloxazole (**1c**) (3.5 g, 0.031 mole) and DMAD (4.4 g, 0.031 mole) in toluene gave a mixture separated chromatographically.

(i) 1-Amino-3-ethyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2c**) was eluted with petrol/ethyl acetate (3:1) and formed colourless crystals (3.21 g, 41%) mp 161-162°; ms: m/e 254 (M⁺); pmr (deuteriochloroform): δ 1.00 (t, 3H, CH₂CH₃), 2.15 (q, 2H, CH₂CH₃), 3.69 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 6.35 (s, 1H, H4), 7.3 (broad s, 2H, exchanged with deuterium oxide, NH₂); ir (potassium bromide): 1605, 1695, 1720, 1740, 3100, 3400 cm⁻¹.

Anal. Calcd. for C₁₁H₁₄N₂O₅: C, 52.0; H, 5.6; N, 11.0. Found: C, 51.7; H, 5.3; N, 10.9.

(ii) 3-Ethyl-5-methoxycarbonyloxazol[3,2-*a*]pyrimidine-7-one (**3c**) was eluted with petrol/ethyl acetate (3:2) and formed colourless crystals (1.26 g, 16%) mp 135-136°; ms: m/e 222 (M⁺); pmr (deuteriochloroform): δ 1.1 (t, 3H, CH₂CH₃), 2.25 (q, 2H, CH₂CH₃), 3.95 (s, 3H, OCH₃), 6.71 (s, 1H, H6), 7.15 (s, 1H, H2); ir (potassium bromide): 1460, 1540, 1640, 1730, 3040 cm⁻¹.

Anal. Calcd. for C₁₀H₁₀N₂O₄: C, 54.0; H, 4.5; N, 12.6. Found: C, 54.4; H, 4.4; N, 12.4.

Reaction of 2-Amino-4-propyloxazole with DMAD.

In the same way 2-amino-4-propyloxazole (**1d**) (3.6 g, 0.029 mole) and DMAD (4.1 g, 0.028 mole) gave a mixture resolved chromatographically.

(i) 1-Amino-3-propyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2d**) was eluted with petrol/ethyl acetate (3:1) and formed colourless crystals (3.6 g, 48%) mp 183-185°; ms: m/e 268 (M⁺); pmr (deuteriochloroform): δ 0.90 (t, 3H, CH₂CH₃), 1.48 (m, 2H, CH₂CH₂CH₃), 2.15 (t, 2H, CH₂CH₂), 3.65 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 6.3 (s, 1H, H4), 6.95 (broad s, 2H, exchanged with deuterium oxide, NH₂); ir (potassium bromide): 1460, 1590, 1610, 1720, 1740, 3150, 3350 cm⁻¹.

Anal. Calcd. for C₁₂H₁₆N₂O₅: C, 53.7; H, 6.0; N, 10.5. Found: C, 53.6; H, 6.1; N, 10.6.

(ii) 3-Propyl-5-methoxycarbonyloxazol[3,2-*a*]pyrimidine-7-one (**3d**) was eluted with petrol/ethyl acetate (3:2) and formed colourless crystals (1.52 g, 23%) mp 162-164°; ms: m/e 236 (M⁺); pmr (deuteriochloroform): δ 0.90 (s, 3H, CH₂CH₃), 1.52 (m, 2H, CH₂CH₂CH₃), 2.21 (t, 2H, CH₂CH₂), 3.75 (s, 3H, OCH₃), 6.70 (s, 1H, H6), 7.10 (s, 1H, H2); ir (potassium bromide): 1460, 1530, 1640, 1720, 3050 cm⁻¹.

Anal. Calcd. for C₁₁H₁₂N₂O₄: C, 55.9; H, 5.1; N, 11.9. Found: C, 55.8; H, 5.2; N, 11.5.

Reaction of 2-Amino-4-*t*-butyloxazole with DMAD.

In the same way 2-amino-4-*t*-butyloxazole (**1e**) (5.0 g, 0.036 mole) and DMAD (5.1 g, 0.036 mole) gave a mixture separated chromatographically.

(i) 1-Amino-2,3,5,6-tetra(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (**4**) was eluted with petrol/ethyl acetate (6:1) and formed colourless crystals (1.7 g, 14%) mp 94-95°; ms: m/e 341 (M⁺); pmr (deuteriochloroform): δ 3.84 (s, 6H, -OCH₃), 3.87 (s, 6H, -OCH₃), 5.95 (s, 1H, H4), 9.4 (broad s, 2H, exchanged with deuterium oxide, NH₂); ir (potassium bromide): 1465, 1620, 1690, 1710, 1730, 3300, 3420 cm⁻¹.

Anal. Calcd. for C₁₄H₁₅NO₆: C, 49.3; H, 4.4; N, 4.1. Found: C, 49.3; H, 4.7; N, 4.6.

(ii) 1-Amino-3-*t*-butyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2e**) was eluted with petrol/ethyl acetate (6:4) and formed colourless crystals (5.1 g, 50%) mp 136-139°; ms: m/e 282 (M⁺); pmr (deuteriochloroform): δ 1.15 (s, 9H, (CH₃)₃C), 3.72 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 5.1 (broad s, 2H, exchanged with deuterium oxide NH₂); ir (potassium bromide): 1460, 1590, 1670, 1730, 3120 3430 cm⁻¹.

Anal. Calcd. for C₁₃H₁₈N₂O₅: C, 55.3; H, 6.4; N, 9.9. Found: C, 55.0; H, 6.6; N, 9.7.

Reaction of 2-Amino-4-phenyloxazole with DMAD.

In the same way 2-amino-4-phenyloxazole (**1f**) (3.5 g, 0.022 mole) and DMAD (3.1 g, 0.022 mole) gave a mixture separated chromatographically.

(i) 1-Amino-2,3,5,6-tetra(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (**4**) (1.36 g, 19%) was identified as above.

(ii) 1-Amino-3-phenyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2f**) was eluted with petrol/ethyl acetate (4:1) and formed pale yellow crystals (2.4 g, 37%) mp 136-137°; ms: m/e 302 (M⁺); pmr (deuteriochloroform): δ 3.50 (s, 3H, OCH₃), 3.64 (s, 3H, OCH₃), 5.8 (broad, 2H, exchanged with deuterium oxide, NH₂), 6.73 (s, 1H, H4), 7.3-7.5 (m, 5H, aromatic H); ir (potassium bromide): 1470, 1590, 1690, 1720, 3120, 3450 cm⁻¹.

Anal. Calcd. for C₁₅H₁₄N₂O₅: C, 59.6; H, 4.6; N, 9.3. Found: C, 59.6; H, 4.9; N, 9.3.

Reaction of 2-Amino-4,5-dimethyloxazole with DMAD.

In the same way 2-amino-4,5-dimethyloxazole (**1g**) (3.5 g, 0.031 mole) and DMAD (4.5 g, 0.031 mole) gave a mixture separated chromatographically.

(i) 2,3-Dimethyl-5,6,7,8-tetra(methoxycarbonyl)-5,6-dihydrooxazol[3,2-*a*][1,3]diazepine (**5**) was eluted with petrol/ethyl acetate (4:1). It formed colourless needles (50 mg) mp 203-204°; ms: m/e 396 (M⁺); pmr (deuteriochloroform): δ 2.05 (s, 3H, CH₃-C), 2.12 (s, 3H, CH₃-C), 3.05 (s, 3H, OCH₃), 3.75 (s, 6H, OCH₃), 3.85 (s, 6H, -OCH₃), 5.01 (d, 1H, H5 or H6), 5.55 (d, 1H, H5 or H6); ir (potassium bromide): 1470, 1570, 1600, 1690,

1730, 1740, 1760 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$: C, 51.5; H, 5.1; N, 7.1. Found: C, 51.6; H, 5.3; N, 7.4.

(ii) 1-Amino-3,4-dimethyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2g**) was eluted with petrol/ethyl acetate (3:1) and formed colourless crystals (1.75 g, 22%) mp 195°; ms: *m/e* 254 (M^+); pmr (deuteriochloroform): δ 2.03 (s, 3H, CH_3C), 2.11 (s, 3H, CH_3C), 3.65 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.7 (broad s, 2H, exchanged with deuterium oxide, NH_2); ir (potassium bromide): 1460, 1570, 1590, 1690, 1750, 3130, 3370, 3470 cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5$: C, 52.0; H, 5.5; N, 11.0. Found: C, 51.8; H, 5.4; N, 11.0.

(iii) 2,3-Dimethyl-5-methoxycarbonyloxazolo[3,2-*a*]pyrimidine-7-one (**3g**) was eluted with petrol/ethyl acetate (2:1) and formed colourless crystals (1.47 g, 21%) mp 125-127°; ms: *m/e* 222 (M^+); pmr (deuteriochloroform): δ 2.09 (s, 3H, CH_3C), 2.25 (s, 3H, CH_3C), 3.90 (s, 3H, OCH_3), 6.51 (s, 1H, H6); ir (potassium bromide): 1460, 1540, 1550, 1620, 1750 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_4$: C, 54.1; H, 4.5; N, 12.6. Found: C, 54.3; H, 4.8; N, 12.9.

Reaction of 2-Amino-5-ethyl-4-methyloxazole with DMAD.

In the same way 2-amino-5-ethyl-4-methyloxazole (**1h**) (2.5 g, 0.02 mole) and DMAD (2.8 g, 0.02 mole) gave a mixture resolved chromatographically.

(i) 1-Amino-4-ethyl-3-methyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2h**) was eluted with petrol/ethyl acetate (3:1) and formed colourless crystals (1.1 g, 21%) mp 152-154°; ms: *m/e* 268 (M^+); pmr (deuteriochloroform): δ 1.72 (t, 3H, CH_2CH_3), 2.03 (s, 3H, CH_3C), 2.31 (q, 2H, CH_2CH_3), 3.65 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.5 (broad s, 2H, exchanged with deuterium oxide, NH_2); ir (potassium bromide): 1455, 1570, 1590, 1690, 1750, 3130, 3370, 3460 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5$: C, 53.7; H, 6.0; N, 10.5. Found: C, 53.5; H, 6.1; N, 10.7.

(ii) 2-Ethyl-3-methyl-5-methoxycarbonyloxazolo[3,2-*a*]pyrimidine-7-one (**3h**) was eluted with petrol/ethyl acetate (1:1) and formed colourless crystals (2.0 g, 42%) mp 132-134°; ms: *m/e* 236 (M^+); pmr (deuteriochloroform): δ 1.27 (t, 3H, CH_2CH_3), 2.15 (s, 3H, CH_3C), 2.65 (q, 2H, CH_2CH_3), 3.98 (s, 3H, OCH_3), 6.63 (s, 1H, H6); ir (potassium bromide): 1455, 1540, 1640, 1745 cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4$: C, 55.9; H, 5.1; N, 11.9. Found: C, 55.7; H, 5.3; N, 11.8.

Reaction of 2-Amino-4,5-diphenyloxazole with DMAD.

In the same way 2-amino-4,5-diphenyloxazole (**1i**) (5.0 g, 0.021 mole) and DMAD (3.0 g, 0.021 mole) gave a mixture resolved chromatographically.

(i) 1-Amino-3,4-diphenyl-5,6-bis(methoxycarbonyl)-2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene (**2i**) was eluted with petrol/ethyl acetate (3:1). Colourless crystals (0.4 g, 5%) mp 210-212° were collected; ms: *m/e* 378 (M^+); pmr (deuteriochloroform): δ 3.15 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 6.97 (broad s, 2H, exchanged with deuterium oxide, NH_2), 7.35 (broad s, 5H, ArH's), 7.60 (broad s, 5H, ArH's).

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_5$: C, 66.7; H, 4.8; N, 7.4. Found: C, 66.5; H, 4.5; N, 7.0.

(ii) 2,3-Diphenyl-5-methoxycarbonyloxazolo[3,2-*a*]pyrimidine-7-one (**3i**) was eluted with petrol/ethyl acetate (3:2). It formed pale yellow crystals (4.1 g, 54%) mp 224-225°; ms: *m/e* 346 (M^+); pmr (deuteriochloroform): δ 3.25 (s, 3H, OCH_3), 6.5 (s, 1H, H6), 7.2-7.6 (m, 10H, ArH's); ir (potassium bromide): 1460, 1635, 1740 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_4$: C, 65.9; H, 4.1; N, 8.1. Found: C, 66.0; H, 4.2; N, 8.3.

Reaction of 2-Amino-4-methylthiazole with DMAD.

In the same way 2-amino-4-methylthiazole (**6**) (3.5 g, 0.031 mole) with DMAD (4.4 g, 0.031 mole) in acetonitrile (50 ml) reacted at room temperature in 1 hour. Evaporation of the solvent gave a sticky residue resolved chromatographically.

(i) 3-Methyl-5,6,7,8-tetra(methoxycarbonyl)-5,6-dihydrothiazolo[3,2-*d*][1,3]diazepine (**9**) was eluted with petrol/ethyl acetate (5:1). It formed pale

yellow needles (0.1 g, 0.8%) mp 164-165°; ms: *m/e* 398 (M^+); pmr (deuteriochloroform): δ 2.22 (d, 3H, CH_3C), 3.64 (s, 3H, OCH_3), 3.75 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 5.2 (d, 1H, H5 or H6), 5.51 (d, 1H, H5 or H6), 6.05 (d, 1H, H2); ir (potassium bromide): 1260, 1370, 1460, 1535, 1610, 1680, 1730, 1750 cm^{-1} .

(ii) 1-Amino-3-methyl-5,6-bis(methoxycarbonyl)-2-aza-7-thiabicyclo[2.2.1]hepta-2,5-diene (**7**) was eluted with petrol/ethyl acetate (3:2) and formed pale yellow crystals (3.3 g, 42%) mp 145-146°; ms: *m/e* 256 (M^+); pmr (deuteriochloroform): δ 1.75 (s, 3H, C-CH_3), 3.60 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.25 (s, 1H, H4), 7.2 (s, 2H, exchanged with deuterium oxide, NH_2); ir (potassium bromide): 1300, 1350, 1375, 1415, 1440, 1570, 1660, 1680, 1720, 1740, 3050, 3400 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$: C, 46.9; H, 4.7; N, 10.9. Found: C, 46.6; H, 5.0; N, 10.5.

(iii) 3-Methyl-5-methoxycarbonylthiazolo[3,2-*a*]pyrimidin-7-one (**8**) was eluted with petrol/ethyl acetate (1:1) and formed pale yellow crystals (2.1 g, 30%) mp 155-157°; ms: *m/e* 224 (M^+); pmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3C), 3.99 (s, 3H, OCH_3), 6.52 (s, 1H, H6), 6.58 (s, 1H, H2); ir (potassium bromide): 1380, 1455, 1490, 1600, 1635, 1755, 3080 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_3\text{S}$: C, 48.2; H, 3.6; N, 12.5. Found: C, 47.9; H, 3.9; N, 12.3.

Reaction of 2-Amino-4-methyloxazole with Diethyl Maleate.

2-Amino-4-methyloxazole (3.0 g, 0.03 mole) in 50 ml of ethanol was mixed with diethyl maleate (5.2 g, 0.03 mole) in 20 ml of ether. The reaction was mildly exothermic and the mixture was allowed to stand for 30 minutes. Solvent was removed by evaporation leaving an oil which was separated by column chromatography.

(i) 2-Amino-3,4-bis(ethoxycarbonyl)-6-methylpyridine (**10**) was eluted with petrol/ethyl acetate (9:1). Colourless needles (2.64 g, 35%) mp 100-101° were collected; ms: *m/e* 252 (M^+); pmr (deuteriochloroform): δ 1.30 (m, 6H, $\text{O-CH}_2\text{CH}_3$), 2.31 (s, 3H, CH_3C), 4.20 (m, 4H, OCH_2CH_3), 6.48 (s, 1H, H5), 7.0 (s, 2H, exchanged with deuterium oxide, NH_2); ir (potassium bromide): 1450, 1475, 1590, 1630, 1700, 1745, 2800, 3075, 3300, 3450 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4$: C, 57.1; H, 6.4; N, 11.1. Found: C, 57.0; H, 6.4; N, 11.0.

(ii) 2-Amino-3,4-bis(ethoxycarbonyl)-5-hydroxy-6-methylpyridine (**11**) was eluted with petrol/ethyl acetate (3:1) and formed colourless crystals (0.89 g, 11%) mp 102-104°; ms: *m/e* 268 (M^+); pmr (deuteriochloroform): δ 1.2 (m, 6H, OCH_2CH_3), 2.28 (s, 3H, CH_3C), 4.2 (m, 4H, $\text{-OCH}_2\text{CH}_3$), 6.7 (s, 2H, exchanged with deuterium oxide, NH_2), 8.4 (s, 1H, exchanged with deuterium oxide, OH); ir (potassium bromide): 1400, 1450, 1470, 1570, 1595, 1625, 1690, 1755, 2800, 3000-3500 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5$: C, 53.7; H, 6.0; N, 10.5. Found: C, 53.7; H, 6.0; N, 10.4.

Reaction of 2-Acetamido-4-methyloxazole with Maleic Anhydride.

2-Acetamido-4-methyloxazole (3.5 g, 0.025 mole) and maleic anhydride (2.45 g, 0.025 mole) in toluene (100 ml) were warmed to 50° for 1 hour. Evaporation of solvent gave a residue from which was crystallized 2-acetamido-5-hydroxy-6-methylpyridine-3-carboxylic acid (**12**) (2.9 g, 55%) mp 238-240°; ms: *m/e* 210 (M^+); pmr (deuteriochloroform): δ 2.06 (s, 3H, NHC(O)CH_3), 2.28 (s, 3H, C-CH_3), 7.46 (s, 1H, H4), 7.8 (s, 1H, exchanged with deuterium oxide, NH_2), 9.9 (s, 1H, exchanged with deuterium oxide, OH), 10.3 (s, 1H, exchanged with deuterium oxide, COOH); ir (potassium bromide): 1380, 1420, 1460, 1565, 1635, 1665, 2000-3500 (broad) cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_4$: C, 47.8; H, 4.4; N, 12.4. Found: C, 47.9; H, 4.3; N, 12.0.

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