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2-Amino-4-methyloxazole reacts with aldehydes to give products having a hydroxymethyl function at C-5. No Schiff's bases were formed. Reactions seem to be confined to 4-alkyl substituted-2-aminooxazoles as 2-aminooxazole and its 4-phenyl and 2-acetamido derivatives fail to react with aldehydes. The nature of the aldehyde affects the amount of the product formed.

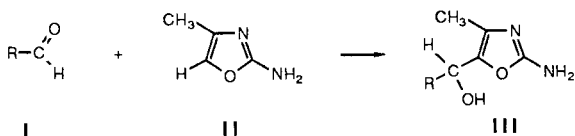
J. Heterocyclic Chem., **25**, 815 (1988).

Reactions of aldehydes and amines, including heterocyclic amines [1-3] are straightforward and give imines or Schiff's bases. However, when 2-amino-4-methyloxazole was reacted with aldehydes, no Schiff's bases were formed. Instead, products having free amino groups were obtained and were identified as oxazole-5-hydroxymethyl derivatives [4].

Results and Discussion.

2-Amino-4-methyloxazole **II** when heated with an equimolar ratio of anisaldehyde in toluene gave as the sole product, a colourless crystalline solid formed in 77% yield. Elemental analysis and mass spectral analysis established that the product had a molecular composition $C_{12}H_{14}N_2O_2$ ($M^+ = 234$). The nmr spectrum had signals at δ 5.59 (s, 1H, CH-OH), 6.30 (s, 2H, exchanged with deuterium oxide, NH_2) and 7.26 (m, 3H, aromatic protons + OH, 1H exchanged with deuterium oxide), beside usual peaks for other groups. On this basis it was concluded that the product was 2-amino-4-methyl-5-(α -hydroxy-4'-methoxybenzyl)oxazole. The general nature of the reaction is shown in Scheme 1 and Table 1.

Scheme 1



Although there are not enough examples to accurately determine the trend, it appears that *para*-substituted aldehydes react in higher yield than their *ortho* counterparts. It is noteworthy that aliphatic aldehydes gave similar types of products but in lower yield. Reactions seem to be exclusive for 4-alkyl substituted 2-aminooxazoles since unsubstituted 2-aminooxazoles and the corresponding

Table 1

Products of the Reaction of 2-Amino-4-methyloxazole and Aldehydes

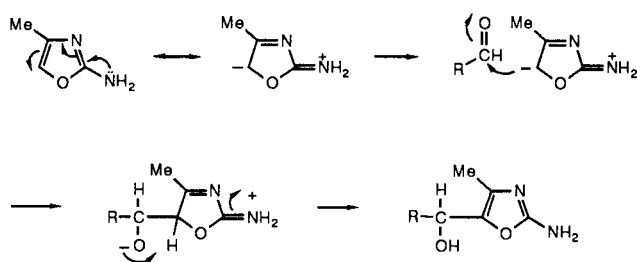
Aldehydes	Product	Yield %
(a) Anisaldehyde	III R(P-CH ₃ OC ₆ H ₄)	77
(b) Benzaldehyde	IV R(Ph)	69
(c) Toluylaldehyde	V R(CH ₃ C ₆ H ₄)	60
(d) <i>p</i> -Nitrobenzaldehyde	VI R(<i>p</i> -NO ₂ C ₆ H ₄)	87
(e) <i>o</i> -Nitrobenzaldehyde	VII R(<i>o</i> -NO ₂ C ₆ H ₄)	40
(f) <i>o</i> -Chlorobenzaldehyde	VIII R(<i>o</i> -ClC ₆ H ₄)	20
(g) Salicylaldehyde	IX R(<i>o</i> -HOC ₆ H ₄)	16.4
(h) Phthaldehyde	X R(<i>o</i> -CHOC ₆ H ₄)	20
(i) Choral Hydrate	XI R(Cl ₃ C)	45
(j) Propionaldehyde	XII R(C ₂ H ₅)	62

4-phenyl and 2-*N*-acetyl derivatives fail to give any products. However, it should be noted that even in these cases no Schiff's bases were formed.

The failure of 2-aminooxazole to react with aldehydes indicates that despite the electron releasing nature of the 2-amino group, it is insufficient on its own for electrophilic substitution to occur at C-5. The presence of a methyl group at C-4 is a further requirement for activation of C-5. However, such activation does not confer general reactivity at C-5 for other electrophiles since acetophenone fails to react with 2-amino-4-methyloxazole under identical conditions. Similarly, when transfer of electron density from the 2-amino group to C-5 is hindered, as in 2-acetamido-4-methyloxazole, no reaction occurred.

On the other hand, the reaction proceeds more smoothly with *p*-substituted aldehydes (in particular with an electron withdrawing group) but less smoothly with their *ortho* counterparts. This is probably due to the steric crowding of the transition state. Consistent with this view are the yields with alkyl aldehydes. A plausible mechanism for the reactions is represented in Scheme 2.

Scheme 2



EXPERIMENTAL

Melting points were recorded 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 recorded on a Pye Unicams SP-100 spectrophotometer and pmr spectra on a Joel FX-100 spectrometer. Mass spectra were obtained from an AEI-MS12 spectrometer (70eV). 2-Amino-4-methyloxazole was prepared by condensation of cyanamide with acetol [5].

Reaction of 2-Amino-4-methyloxazole (I) with Anisaldehyde.

2-Amino-4-methyloxazole (1 g, 0.01 mole) and anisaldehyde (1.36 g, 0.01 mole) were dissolved in dry toluene and the mixture was refluxed and left at room temperature for one hour. The colourless solid on recrystallisation from chloroform/ethyl acetate gave the colourless product III (2-amino-4-methyl-5-(α -hydroxy-4'-methoxybenzyl)oxazole) (1.8 g, 77%) mp 150-151°; ms: m/e 234 (M^+); pmr (deuteriochloroform): δ 1.8 (s, 3H, CH_3 -C), 3.7 (s, 3H, OCH_3), 5.6 (s, 1H, $CHOH$), 6.4 (s, 2H, exchanged with deuterium oxide, NH_2), 6.9-7.3 (m, 5H, aromatic protons + OH, 1H exchanged with deuterium oxide); ir (potassium bromide): 730, 750, 1002, 1180, 1248, 1310, 1520, 1590, 1620, 3260, 3310, 3465 cm^{-1} .

Anal. Calcd. for $C_{12}H_{11}N_2O_3$: C, 61.52; H, 6.02; N, 11.95. Found: C, 61.28, H, 6.21, N, 11.93.

Reaction of 2-Amino-4-methyloxazole (I) with Benzaldehyde.

2-Amino-4-methyloxazole (1 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole) were mixed together and the mixture was left at room temperature for 0.5 hour. The colourless product IV (2-amino-4-methyl-5-(α -hydroxybenzyl)oxazole) (1.4 g, 69%) was recrystallised from ethyl acetate mp 144-145°; ms: m/e 204 (M^+); pmr (deuteriochloroform): δ 1.85 (s, 3H, CH_3 -C), 5.6 (s, 1H, $H-COH$), 6.3 (s, 2H, exchanged with deuterium oxide, NH_2), 7.1-7.4 (m, 6H, aromatic protons + OH, 1H exchanged with deuterium oxide); ir (potassium bromide): 705, 755, 1380, 1440, 1600, 1660, 3000-3480 (broad), 3580 cm^{-1} .

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.88; N, 13.71. Found: C, 64.43; H, 5.74; N, 13.70.

Reaction of 2-Amino-4-methyloxazole with *p*-Tolylaldehyde.

2-Amino-4-methyloxazole and *p*-tolylaldehyde were mixed together and the mixture was left at room temperature for two hours. The yellow solid on recrystallisation from ethyl acetate gave the colourless product V (2-amino-4-methyl-5-(α -hydroxy-4'-methylbenzyl)oxazole) in 60% yield (1.3 g) mp 139-141°; ms: m/e 218 (M^+); pmr (deuteriochloroform): δ 1.8 (s, 3H, CH_3 -C), 2.3 (s, 3H, *p*- CH_3 -C), 5.6 (s, 1H, $H-COH$), 6.4 (s, 2H, exchanged with deuterium oxide, NH_2), 7.2-7.4 (m, 5H, aromatic protons + OH, 1H exchanged with deuterium oxide); ir (potassium bromide): 725, 780, 1410, 1593, 1651, 3210, 3340, 3380 cm^{-1} .

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 65.91; H, 6.38; N, 12.78.

Reaction of 2-Amino-4-methyloxazole with *p*-Nitrobenzaldehyde.

2-Amino-4-methyloxazole (1 g, 0.01 mole) and *p*-nitrobenzaldehyde (1.6 g, 0.01 mole) were refluxed for two hours in dry toluene. The solvent was

evaporated and the yellow crystalline solid VI (2-amino-4-methyl-5-(α -hydroxy-4'-*p*-nitrobenzyl)oxazole) was obtained. (2.16 g, 87%) mp 352-354°; ms: m/e 249 (M^+); pmr (deuteriochloroform): δ 1.95 (s, 3H, CH_3 -C), 5.82 (s, 1H, $CHOH$), 6.4 (s, 2H, exchanged with deuterium oxide, NH_2), 7.5-7.7 (d, 2H, aromatic protons), 8.15-8.25 (m, 3H, aromatic protons + OH, 1H, exchanged with deuterium oxide); ir (potassium bromide): 750, 850, 1010, 1075, 1110, 1235, 1450, 1585, 1650, 3350, 3480 cm^{-1} .

Anal. Calcd. for $C_{11}N_1N_3O_4$: C, 52.96; H, 4.44; N, 16.93. Found: C, 52.69; H, 4.44; N, 16.90.

Reaction of 2-Amino-4-methyloxazole with *o*-Nitrobenzaldehyde.

2-Amino-4-methyloxazole (1 g, 0.01 mole) and *o*-nitrobenzaldehyde (1.5 g, 0.01 mole) were mixed together in a small beaker and the mixture was left at room temperature for 0.5 hour. The yellow product VII (2-amino-4-methyl-5-(α -hydroxy-2'-nitrobenzyl)oxazole) was recrystallised from ethylacetate (1.4 g, 40%) mp 156-157°; ms: m/e 231 ($M^+ - H_2O$); pmr (deuteriochloroform): δ 1.8 (s, 3H, CH_3 -C), 6.1 (d, 1H, $H-COH$ exchanged with deuterium oxide), 6.2 (d, 1H, $H-COH$), 6.4 (s, 2H, exchanged with deuterium oxide, NH_2), 7.8-7.98 (m, 4H, aromatic protons).

Anal. Calcd. for $C_{11}H_{11}N_3O_4$: C, 52.96; H, 4.44; N, 16.93. Found: C, 52.69; H, 4.45; N, 16.69.

Reaction of 2-Amino-4-methyloxazole with *o*-Chlorobenzaldehyde.

2-Amino-4-methyloxazole (1 g, 0.01 mole) and *o*-chlorobenzaldehyde (1.41 g, 0.01 mole), were mixed well together and the mixture was left at room temperature for 0.5 hour. The solid obtained on recrystallisation from ethyl acetate gave the colourless product VIII (2-amino-4-methyl-5-(α -hydroxy-2'-chlorobenzyl)oxazole) (0.48 g, 20%) mp 130-134°; ms: m/e 240:238 (3:1) (M^+); pmr (deuteriochloroform): δ 1.9 (s, 3H, CH_3 -C), 5.8 (s, 1H, $H-COH$), 6.4 (s, 2H, exchanged with deuterium oxide, NH_2), 7.3 (m, 3H, aromatic H's), 7.8 (m, 2H, aromatic protons + OH, 1H, exchanged with deuterium oxide); ir (potassium bromide): 698, 748, 1580, 1650, 3200, 3250, 3320 cm^{-1} .

Anal. Calcd. for $C_{11}H_{11}N_2O_2Cl$: C, 55.34; H, 4.64; N, 11.78. Found: C, 54.94; H, 4.91; N, 11.53.

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

Salicylaldehyde (1.22 g, 0.01 mole) and 2-amino-4-methyloxazole (1 g, 0.01 mole) were well mixed together and the mixture was left at room temperature for 0.5 hour. The solid was recrystallised from chloroform/ethyl acetate to give the colourless product IX (2-amino-4-methyl-5-(α -2'-dihydroxybenzyl)oxazole) (0.36 g, 16%) mp 119-121°; ms: m/e 202 ($M - H_2O$); pmr (deuteriochloroform): δ 1.8 (s, 3H, CH_3 -C), 5.5 (s, 1H, $H-COH$), 6.3 (s, 2H, exchanged with deuterium oxide, NH_2), 6.9-7.4 (m, 5H, aromatic protons + OH, 1H exchanged with deuterium oxide); ir (potassium bromide): 765, 930, 1100, 1245, 1610, 1671, 3170-3340 (broad), 3442 cm^{-1} .

Anal. Calcd. for $C_{11}H_{11}N_2O_3$: C, 60.00; H, 5.45; N, 12.73. Found: C, 60.15; H, 5.23; N, 12.82.

Reaction of 2-Amino-4-methyloxazole with *o*-Phthalaldehyde.

2-Amino-4-methyloxazole (1.92 g, 0.02 mole) and *o*-phthalaldehyde (1.34 g, 0.01 mole) were mixed together in chloroform. The mixture was refluxed for 10 minutes. The solid which formed was recrystallised from methanol to give the colourless product X (2-amino-4-methyl-5-(α -hydroxy-2'-formylbenzyl)oxazole) (0.46 g, 20%) mp 146-148°; ms: m/e 232 (M^+); pmr: δ 1.95 (s, CH_3 , CH_3 -C) 3.4 (s, 2H, exchanged with deuterium oxide, NH_2), 6.2 (d, 1H, exchanged with deuterium oxide $H-C-OH$) 6.3 (m, 1H, $HCOH$), 7.4 (m, 4H, aromatic protons), 10.5 (s, 1H, $H-C=O$); ir (potassium bromide): 730, 860, 978, 1040, 1182, 1260, 1420, 1628, 3250-3350 cm^{-1} .

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.02; H, 5.20; N, 12.11. Found: C, 62.21; H, 5.00; N, 12.53.

Reaction of 2-Amino-4-methyloxazole with Chloral Hydrate.

Chloral hydrate (1.66 g, 0.01 mole) and 2-amino-4-methyloxazole (1 g, 0.01 mole) were mixed well by stirring and the mixture was left at room

temperature for 1.5 hours. The yellow solid on crystallisation gave the colourless product **XI** (2-amino-4-methyl-5-(α -hydroxy-2'2'2'-trichloroethyl)oxazole (1.1 g, 45%) mp 145-148°; ms: m/e 250:248:246:244 (1:10:35:35) (M^+); pmr (deuteriochloroform): δ 1.8 (s, 3H, CH_3-C), 4.9 (s, 1H, H-COH), 6.5 (s, 2H, exchanged with deuterium oxide, NH_2), 7.3 (s, 1H, exchanged with deuterium oxide, $H-O-CH$); ir (potassium bromide): 640, 750, 802, 982, 1016, 1078, 1310, 1565, 1670, 3040-3300 (broad), 3380, 3478 cm^{-1} .

Anal. Calcd. for $C_6H_7Cl_3N_2O_2$: C, 29.33, H, 2.85; N, 11.40. Found: C, 29.20; H, 2.76; N, 11.15.

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

2-Amino-4-methyloxazole (5 g, 0.05 mole) and propionaldehyde (3.1 g, 0.053 mole) were refluxed in toluene for 0.25 hour. The colourless crystalline product **XII** (2-amino-4-methyl-5-(α -hydroxy propyl)oxazole (4.9 g, 62%) was recrystallised from ethyl acetate/methanol mp 113-115°; ms: m/e 156 (M^+); pmr (deuteriochloroform): δ 0.78 (t, 3H, CH_2CH_3), 1.64 (q, 2H, CH_2CH_3), 1.8 (s, 3H, CH_3C), 4.3 (t, 1H, $CHCH_2$), 4.76 (s, broad), 1H, exchanged with deuterium oxide OH), 6.32 (s, 2H, exchanged with deuterium oxide, NH_2); ir (potassium bromide): 695, 750, 900, 990, 1030, 1220, 1335, 1590, 1640, 1680, 3000-3450 (broad) cm^{-1} .

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.84; H, 7.74; N, 17.94. Found: C, 53.81; H, 8.03; N, 17.84.

Reaction of 2-Amino-4-methyloxazole with Acetic Anhydride.

The mixture of 2-amino-4-methyloxazole (5 g, 0.05 mole) and acetic anhydride (5 g, 5 ml, 0.058 mole) was refluxed for six hours at 140°. The unreacted acetic anhydride was removed under reduced pressure (rotary, vacuum pump was used). The colourless product (2-acetamido-4-methyloxazole) (5.78 g, 81%) was recrystallised from ethyl acetate mp 91-93°; ms: m/e 140 (M^+); pmr (deuteriochloroform): δ 2.07 (s, 3H, CH_3C) 2.25 (s, 3H, $COCH_3$) 7.1 (s, 1H, H5), 11.82 (s, 1H, exchanged with deuterium oxide NH); ir (potassium bromide): 745, 1220, 1420, 1550, 1600, 1665,

3260-3300 cm^{-1} .

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.25; H, 5.82; N, 19.98. Found: C, 51.42; H, 5.75; N, 20.12.

Attempted Reaction of 2-Acetamido-4-methyloxazole with Benzaldehyde.

The mixture of benzaldehyde (0.45 g, 0.0043 mole) and 2-acetamido-4-methyloxazole (0.42 g, 0.0043 mole) was refluxed for 8 hours at 120°; tlc showed only starting materials.

Attempted Reaction of 2-Aminooxazole and Benzaldehyde.

Benzaldehyde (2.2 g, 0.02 mole) and 2-aminooxazole (2 g, 0.02 mole) were refluxed in toluene for 21 hours but tlc analysis showed that no new product was formed.

Attempted Reaction of 2-Amino-4-phenyloxazole and Benzaldehyde.

2-Amino-4-phenyloxazole (5.0 g, 0.03 mole) and benzaldehyde (3.26 g, 0.031 mole) were dissolved in a mixture of toluene and pyridene (2:1) and refluxed for 48 hours. However, no reaction was observed.

Attempted Reaction of 2-Amino-4-phenyloxazole and Anisaldehyde.

2-Amino-4-phenyloxazole (5 g, 0.03 mole) and anisaldehyde (4.26 g, 0.031 mole) were reacted in a similar fashion, but no reaction was observed.

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