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3-Methyl (3a) and 3-t-butyl-1,4-2H-benzoxazine (3b) were synthesized by cyclization of the appropriate acetamidoketone (Scheme 1). The former is a highly unstable molecule which rapidly converts in an intractable mixture, while the latter slowly undergoes aerial oxidation affording the hemiacetal 4. The 4H-forms of the same 3-methyl (6a) and of the parent 1,4-benzoxazine (9) could be obtained as 4-acetyl derivatives. This latter, by hydrolysis, gave the cyclic trimer 10.

Various substituted 1,4-benzoxazines [2a-b], including some from natural sources [3], are known but 3-alkyl derivatives have not been described in the literature. The same parent compound is a very unstable molecule, which was only evidenced [4], in the immonium salt form, in strongly acidic medium by ¹H nmr spectroscopy. In slightly acidic or neutral solutions it readily undergoes aldolization [5] to give mainly the trimer 10.

We now wish to report the synthesis and chemical behaviour of 3-methyl (3a) and 3-t-butyl-2H-1,4-benzoxazine (3b) which were obtained by a general route involving cyclization of the corresponding aminoketones 2a,b, generated *in situ* by treatment of the acetamides 1a and 1b respectively, with 6M hydrochloric acid (Scheme 1).

Scheme 1

a R = CH₃   b R = C(CH₃)₃
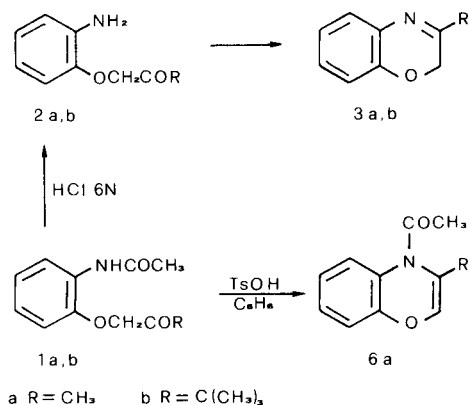
Hydrolysis of acetaminoketone 1a afforded a pale yellow oil which resulted homogenous on immediate tlc analysis. Examination of the crude oil by ¹H nmr spectroscopy revealed, in addition to the aromatic protons, two singlets (2H and 3H respectively) at δ 4.52 and 2.12, according to the immine structure 3a of 3-methyl-1,4-benzoxazine. Unfortunately, further characterization of the compound was precluded because it is rapidly converted, even under a nitrogen atmosphere, into an intractable mixture. Probably 3-methylbenzoxazine (3a) behaves somewhat similarly to the parent compound [5] and to other enamines

[6] in giving polymeric aldolization products.

On the other hand, 3-t-butyl-2H-1,4-benzoxazine (3b) was found to be rather stable, although in solution undergoes aerial oxidation, catalyzed by acids. Thus, when oxygen was bubbled into a solution of 3b in benzene, containing a catalytic amount of trifluoroacetic acid, oxidation rapidly takes place, affording mainly the cyclic hemiacetal 4. This assignment, deriving from straightforward spectral analysis, was further supported by the reaction of 4 with methanol saturated with hydrochloric acid which gave the corresponding methyl acetal 5.
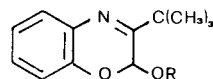
4 R = H
5 R = CH₃

The 2H-1,4-benzoxazine and 4H-1,4-benzoxazine systems are tautomeric and the 2H-form is normally prefered, unless tautomerism is precluded. Thus, heating of the same acetamidoketone 1a in benzene solution, containing a catalytic amount of toluene-4-sulfonic acid, afforded 4-acetyl-3-methyl-1,4-benzoxazine 6a in the enamine form. Unfortunately the corresponding 3-t-butyl-derivative could not be obtained in similar manner because cyclization of acetamidoketone 1b failed to take place, even in boiling xylene. On the other hand, analogous reaction of the acetamidoacetal 7 in refluxing benzene, in the presence of toluene-4-sulfonic acid, gave 4-acetyl-4H-1,4-benzoxazine 9, *via* 4-acetyl-2-ethoxyphenomorpholine 8. This latter could actually be isolated in high yield carrying out the cyclization at room temperature.

As expected, hydrolysis of 4-acetylbenzoxazine 9 with 0.5 M hydrochloric acid in sealed tube at 110° afforded the cyclic trimer 10, by us previously obtained [5] in an attempt to synthesize 1,4-benzoxazine.

This result suggests that the high instability of 1,4-benzoxazine is due to the concomitant presence of imine and

Scheme 2
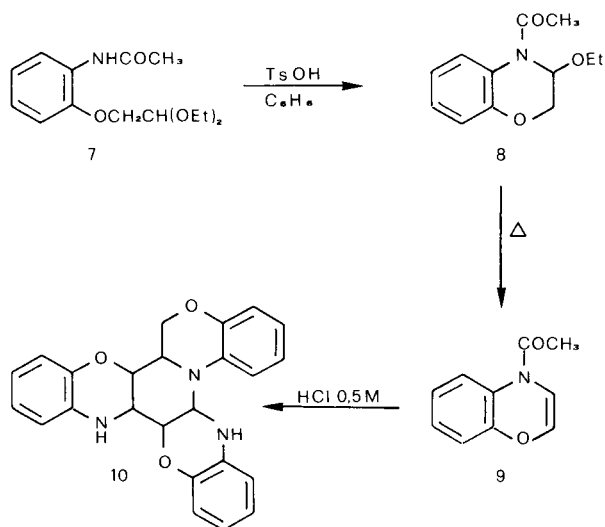
enamine forms which rapidly undergo aldolic polymerization.

EXPERIMENTAL

1-(2-Acetamidophenoxy)propan-2-one (1a).

To a solution of 2-acetamidophenol (1.51 g) in anhydrous dimethyl sulfoxide (6 ml) sodium (230 mg) was added. When this latter was completely dissolved, to the mixture bromoacetone (0.84 ml) in anhydrous dimethyl sulfoxide (2 ml) was added dropwise, with stirring, at room temperature. After 30 minutes the reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organic extracts were washed with 2N sodium hydroxide and with water, dried over anhydrous sodium sulfate and evaporated. The residue, crystallized from ethyl acetate, gave 1a (1.00 g, 49% yield) as colourless needles, mp 105-106°; ir (chloroform): ν max 3440 and 3340 (NH), 1740 (C=O, ketone) and 1680 cm^{-1} (C=O, amide); ^{1}H nmr (deuteriochloroform): δ 8.4 (1H, br, NH, removed by D-exchange), 8.2 and 6.9 (4H, m, ArH), 4.68 (2H, s, CH$_2$), 2.22 and 2.18 (3H each, 2s, 2CH$_3$); ms: m/e 207 (M$^+$).

Anal. Calcd. for C$_{11}$H$_{13}$NO$_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.30; N, 6.73.

1-(2-Acetamidophenoxy)-3,3-dimethylbutan-2-one (1b).

Condensation of 2-acetamidophenol (1.51 g) with 1-bromo-3,3-dimethylbutanone as above gave 1b (2.2 g, 90% yield) as colourless prisms, mp 71-72° (from *n*-hexane); ^{1}H nmr (deuteriochloroform): δ 8.7 (1H, br, NH, removed by D-exchange), 8.4 and 6.8 (4H, m, ArH), 4.78 (2H, s, CH$_2$), 2.10 (3H, s, COCH$_3$) and 1.14 (9H, s, C(CH$_3$)$_3$); ms: m/e 249 (M$^+$).

Anal. Calcd. for C$_{14}$H$_{19}$NO$_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.41; H, 7.73; N, 5.49.

3-Methyl-2H-1,4-benzoxazine (3a).

A solution of 1a in aqueous 6N hydrochloric acid was refluxed for 13 minutes under nitrogen. The reaction mixture was then basified with saturated aqueous sodium bicarbonate and extracted three times with diethyl ether. The combined organic extracts, dried over anhydrous sodium sulfate and evaporated, left a pale yellow oil, homogenous on tlc, which analyzed by ^{1}H nmr (deuteriochloroform) showed the previously described spectral features.

3-t-Butyl-2H-1,4-benzoxazine (3b).

Cyclisation of 1b (1.24 g) with aqueous 6N hydrochloric acid as above gave 3b (800 mg, 84% yield) as a pale yellow oil, homogeneous on tlc, that failed to crystallize; ir (carbon tetrachloride): λ max 1630 cm^{-1} (C=N); ^{1}H nmr (carbon tetrachloride): δ 7.3-6.5 (4H, m, ArH), 4.38 (2H, s,

CH$_2$) and 1.14 (9H, s, C(CH$_3$)$_3$); ms: m/e 189 (M$^+$).

Anal. Calcd. for C$_{12}$H$_{15}$NO: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.01; H, 8.02; N, 7.51.

Reaction of 3-t-Butyl-2H-1,4-benzoxazine (3b) with Oxygen.

A stream of oxygen was bubbled through a solution of 3b (756 mg) in benzene (20 ml) containing trifluoroacetic acid (0.3 ml) at room temperature for three hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate and evaporated. The residue, purified by plc on silica gel in benzene-diethyl ether (9:1) and crystallized from carbon tetrachloride, gave 250 mg (30% yield) of 4, as colourless needles, mp 148-149°; ir (chloroform): ν max 3580 cm^{-1} (OH); ^{1}H nmr (deuteriochloroform): δ 7.6-6.6 (4H, m, ArH), 5.78 (1H, s, hemiacetal proton), 3.5 (1H, br, OH, removed by D-exchange) and 1.28 (9H, s, C(CH$_3$)$_3$); ms: m/e 205 (M$^+$).

Anal. Calcd. for C$_{12}$H$_{15}$NO$_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.03; H, 7.34; N, 6.77.

2-Methoxy-3-t-butyl-2H-1,4-benzoxazine (5).

A solution of 4 (70 mg) in anhydrous methanol saturated with dry hydrochloric acid was left at room temperature for 12 hours. The reaction mixture was then concentrated *in vacuo*, diluted with chloroform, washed with saturated aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate and evaporated. The residue, purified by plc on silica gel in benzene afforded, besides some unchanged starting material, the methyl acetal 5 (25 mg, 33% yield) as pale yellow oil; ^{1}H nmr (carbon tetrachloride): δ 7.5-6.8 (4H, m, ArH), 5.26 (1H, s, acetal proton), 3.34 (3H, s, OCH$_3$) and 1.24 (9H, s, C(CH$_3$)$_3$); ms: m/e 219 (M$^+$).

Anal. Calcd. for C$_{13}$H$_{17}$NO$_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.48; H, 7.79; N, 6.39.

4-Acetyl-3-methyl-4H-1,4-benzoxazine (6a).

A solution of 1a (517 mg) in anhydrous benzene (40 ml), in the presence of 4-toluenesulfonic acid (20 mg), was refluxed for 6 hours with continuous removal of the water formed. The reaction mixture was then diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate and evaporated. The brown oil residue, purified by plc on silica gel in benzene-diethyl ether (6:4) and crystallized from ethanol afforded 273 mg (58% yield) of 6a, as colourless prisms, mp 78-79°; ir (chloroform): ν max 1665 (C=O); ^{1}H nmr (deuteriochloroform): δ 7.55-6.75 (4H, m, ArH), 6.38 (1H, q, J = 1 Hz, vinyl proton), 2.18 (3H, s, COCH$_3$) and 2.08 (3H, d, J = 1 Hz, =C-CH$_3$); ms: m/e 189 (M$^+$, 47), 147 (100) and 146 (97%).

Anal. Calcd. for C$_{11}$H$_{11}$NO$_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.91; N, 7.35.

1-(2-Aminophenoxy)-2,2-diethoxyethane (7).

This compound was prepared, as previously described [4], by reduction of the corresponding nitroacetal, which was obtained by condensation of sodium 2-nitrophenoxide with bromoacetaldehyde diethyl acetal.

4-Acetyl-4H-1,4-benzoxazine (9).

To a solution of 7 (200 mg) in benzene (40 ml), 4-toluenesulfonic acid (30 mg) was added and the suspension was refluxed for 18 hours. After cooling, the reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate and evaporated. The solid residue, purified by plc on silica gel in benzene-diethyl ether (7:3) and crystallized from carbon tetrachloride, gave 100 mg (66% yield) of 9, as colourless prisms, mp 98-100°; ir (carbon tetrachloride): ν max 1675 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 8.0-6.6 (4H, m, ArH), 6.0 (2H, br, vinyl protons) and 2.18 (3H, s, COCH$_3$); ms: m/e 175 (M$^+$).

Anal. Calcd. for C$_{10}$H$_9$NO$_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.66; H, 5.15; N, 8.05.

4-Acetyl-2-ethoxyphenomorpholine (8).

To a solution of 7 (200 mg) in anhydrous benzene (25 ml) 4-toluenesulfonic acid (40 mg) was added and the suspension was vigorously stirred at room temperature for 24 hours. The reaction mixture was then di-

luted with diethyl ester and washed with saturated sodium bicarbonate and water.

The organic layer, dried over anhydrous sodium sulfate and evaporated, afforded 153 mg (93% yield) of **8**, as white solid, homogeneous on tlc. The phenomorpholine crystallized from ethanol-water (2:1) as large colourless prisms, mp 80-81°; ir (carbon tetrachloride): ν max 1670 cm^{-1} (C=O); ^{1}H nmr (carbon tetrachloride): δ 7.0 (4H, m, ArH), 5.95 (1H, q, J = 2 and 3 Hz, CH), 4.38 and 4.06 (1H each, 2q, J = 2 and 10 Hz respectively, cyclic CH$_2$), 3.46 (2H, q, J = 7 Hz, exocyclic CH$_2$), 2.20 (3H, s, COCH$_3$), 1.08 (3H, t, J = 7 Hz, remaining CH$_3$); ms: m/e 221 (M$^+$).

Refluxing of **8** with 4-toluenesulfonic acid in benzene for 12 hours gave, after the usual work up, **9** in 70% yield.

Anal. Calcd. for C$_{12}$H$_{15}$NO$_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.23; H, 6.75; N, 6.39.

Conversion of **9** to the Trimer **10** by Acid Hydrolysis.

A suspension of 4-acetyl-4H-1,4-benzoxazine (**9**, 40 mg) in aqueous 0.5 M hydrochloric acid (6 ml) was heated in a sealed tube at 110° for 6 hours. After cooling, the reaction mixture was extracted three times with chloroform and combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated. The oily residue, fractionated on silica gel in benzene, gave 14 mg (46% yield) of the trimer **10**, identical in all respects to an authentic sample, obtained by the reported procedure [5].

REFERENCES AND NOTES

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