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New Synthesis of 3-Chloroisoxazoles

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A new synthesis of 3-chloroisoxazoles, based on treatment of 2-methyl-4-isoxazolin-3-ones with phosphorus oxychloride, is described. The use of mixtures of phosphorus pentachloride and phosphorus oxychloride instead of the latter reagent alone gave lower yields and more contaminated products. The 2-methyl-4-isoxazolin-3-ones were obtained together with the isomeric 3-methoxyisoxazoles by treatment of 3-isoxazolols with diazomethane or methyl iodide and base. The ratios between *N*- and *O*-methylated products proved strongly dependent on the type of methylating reagent and the structure of the 3-isoxazolols.

Muscimol and ibotenic acid (Fig. 1), which are constituents of *Amanita muscaria*,[1] interact with the central receptors for 4-aminobutyric acid (GABA) and glutamic acid (GLU), respectively,[2,3] with higher efficacy than the endogenous neurotransmitters, indicating that the 3-isoxazolol unit can substitute for carboxyl groups in these biological systems. This bioisosteric relationship (Fig. 1) has been utilized for the design of drugs with potent and specific effects on the GABA [4] and GLU [5] systems. It has recently been shown that 3-methoxyisoxazoles and other 3-alkoxyisoxazoles can be utilized as bioisosteres of esters.[6] These aspects have focused our interest on the development of versatile intermediates, such as 3-halogenoisoxazoles, for the preparation of 3-alkoxyisoxazoles and other 3-substituted isoxazoles.

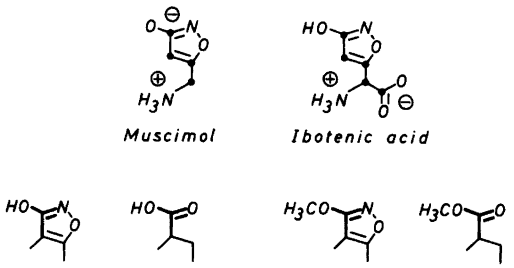

Fig. 1. The structures of muscimol and ibotenic acid. The structural similarity of these compounds to 4-aminobutyric acid and glutamic acid, respectively, is emphasized. The isosteric relationships between 3-isoxazolols and carboxyl groups and between 3-methoxyisoxazoles and methoxycarbonyl groups are indicated.

Mixtures of 3-methoxyisoxazoles and 2-methyl-4-isoxazolin-3-ones can be prepared from 3-isoxazolols, using different reagents (Scheme 1).[7–11] The *N*-methylated compounds, which frequently are the dominating reaction products, have hitherto been considered "useless by-products", and this situation has prompted us to develop a procedure for the conversion of these compounds into 3-chloroisoxazoles, which have proved convertible into 3-alkoxyisoxazoles.[6,11–14] The very few 3-chloroisoxazoles so far described have been synthesized *via* cycloaddition reactions, using the very toxic dichloroformoxime [11,15] or by cyclization of β-nitroketones under drastic acid conditions.[13,16,17]

We here report the synthesis of 3-chloroisoxazoles (*4*) by treatment of 2-methyl-4-isoxazolin-3-ones (*3*) with neat phosphorus oxychloride under mild conditions. In preparation for this work a number of 3-isoxazolols (*1*) were con-

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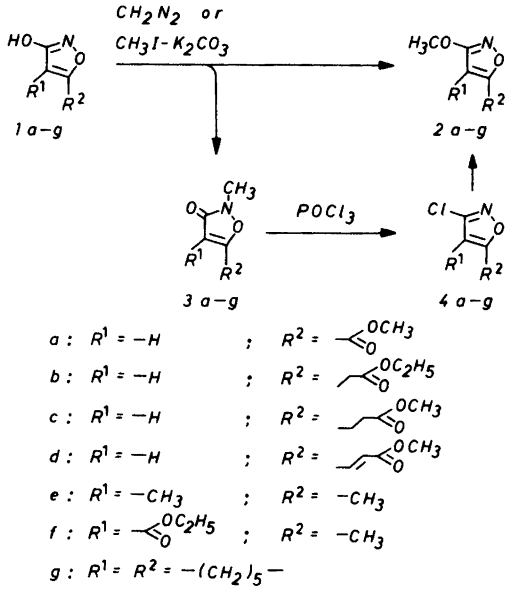

verted into separable mixtures of *O*-(*2*) and *N*-methylated (*3*) products (Scheme 1).

RESULTS AND DISCUSSION

Conversion of 3-isoxazolols into 3-methoxyisoxazoles and 2-methyl-4-isoxazolin-3-ones. Treatment of the 3-isoxazolols *1b,f* with diazomethane gave mixtures of the *N*- and *O*-methylated products the latter being the predominant components (Table 1). Treatment of different 3-isoxazolols (*1*) with methyl iodide and base gave varying amounts of *2* and *3* (Table 1). The 5-monosubstituted 3-isoxazolols *1a,c,d* gave *2* and *3* in comparable amounts, although the *O*-methylated products were slightly dominating in the case of *1a,d*. The prevailing *O*-methylation of these 3-isoxazolols may reflect that the negative charge at the nitrogen atom of the compounds is reduced as a result of the conjugation with the side chain carbonyl groups. It is, however, difficult to rationalize the pronounced differences between the relative amounts of *N*- and *O*-methylated products obtained from *1e,g*, using diazomethane or methyl iodide and base. The structures of the new compounds were established on the basis of elemental analyses and ^{1}H NMR and IR spectroscopic data.

Conversion of 2-methyl-4-isoxazolin-3-ones into 3-chloroisoxazoles. Treatment of 1-methyl-5-phenyl-2(1*H*)-pyrimidones with a mixture of phosphorus pentachloride and phosphorus oxychloride has been shown to provide 2-chloro-5-phenylpyrimidines.[18] This report prompted us to subject at first the 2-methyl-4-isoxazolin-3-ones *3a,e* to the same reaction conditions, and the reaction mixtures actually proved to contain the respective 3-chloroisoxazoles *4a,e* as the major components. Attempts to find the optimal conditions for these reactions led to the observation that the heating of *3a–g* with neat phosphorous oxychloride gave almost completely pure *4a–g*. With the notable exceptions of *4b* (yield 5 %) and *4g* (yield 18 %) moderate to good yields (54–86 %) were obtained. The structure determinations of *4a–g* were based on elemental analyses, IR and ^{1}H NMR spectroscopy, and mass spectrometry. Although the mechanism for the conversion of *3* into *4* is unknown, it is

Table 1. Methylation of 3-isoxazolols.

Compound	Reagent	Yield (%)	Relative amounts (%) 2	3
1b	CH_2N_2	63	65	35
1f	–	78	65	35
1e[a]	–	70	58	42
1g[b]	–	100	47	53
1e	CH_3I,K_2CO_3	89	0	100
1g	–	100	20	80
1c	–	98	48	52
1a	–	98	58	42
1d	–	94	58	42

[a] Ref. 10; [b] Ref. 9.

tempting to relate the very low yield of *4b* to the particular position of the carbonyl group of this compound. Thus, it might be assumed that this group could impair the rearrangement process *via* formation of a conjugated exocyclic double bond at an intermediate step. Accordingly, the yields of the higher homologue *4c* (54 %) and in particular of *4d* (71 %) are much higher than the one of *4b*. Studies on the mechanism of the transformation of *3* into *4* is in progress and, furthermore, the synthetic and medicinal chemical scope of the conversion of a series of 3-chloroisoxazoles into 3-alkoxyisoxazoles and other 3-substituted isoxazoles are under investigation.

EXPERIMENTAL

Melting points determined in capillary tubes are corrected. Elemental analyses were made by Mr. G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark. A Perkin-Elmer grating infrared spectrophotometer model 247, a Varian EM-360A (60 MHz) ^{1}H NMR instrument, and a Finnigan 3100D mass spectrometer were used. ^{1}H NMR spectra were recorded using TMS as an internal standard. Thin-layer chromatography (TLC) and column chromatography (CC) were accomplished using silica gel F_{254} plates (Merck) and silica gel (Woelm 0.063–1.00 mm), respectively.

*Methyl 3-methoxyisoxazole-5-carboxylate (*2a*) and methyl 2-methyl-3-oxo-4-isoxazoline-5-carboxylate (*3a*).* A mixture of *1a*[19] (286 mg; 2.0 mmol), potassium carbonate (0.7 g), methyl iodide (2 ml), and dry acetone (10 ml) was stirred magnetically at 25 °C for 16 h. Upon filtration and evaporation *in vacuo* the crude product was subjected to CC [eluents: light petroleum to which ethyl acetate (30–100 %) was gradually added] to give *2a* and *3a*. The IR spectrum of *2a* was identical with that of an authentic sample.[11] *3a*: m.p. 120.0–121.0 °C (ethyl acetate). Anal. $C_6H_7NO_4$: C, H, N. IR ($CHCl_3$): 3130 (m), 2980–2840 (s, several bands), 1725 (s), 1690 (s), 1620 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.40 (1 H, s), 3.95 (3 H, s), 3.62 (3 H, s).

Methyl 3-chloroisoxazole-5-carboxylate (4a). A solution of *3a* (942 mg; 5 mmol) in phosphorus oxychloride (10 ml) was heated at 90 °C for 6 h. The solution was evaporated *in vacuo*, and upon addition of water (15 ml) the mixture was extracted with chloroform (3×25 ml). The organic phase was dried ($MgSO_4$) and evaporated and the residue subjected to CC [eluent: light petroleum-ethyl acetate (9:1)] to give *4a* (836 mg; 86 %), m.p. 56.0–57.0 °C (light petroleum). Anal. $C_5H_4NO_3Cl$: C, H, N, Cl. IR ($CHCl_3$): 3125 (w), 2950 (m), 1720 (s), 1570 (s), 1420 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.95 (1 H, s), 4.00 (3 H, s). MS [70 eV; *m/z* (% rel. int.)]: 163, 161 (11, 32, M), 132, 130 (14, 44), 126 (2), 104, 102 (5, 15), 76, 74 (15, 47), 67 (45), 59 (100).

*Ethyl 3-methoxyisoxazol-5-ylacetate (*2b*) and ethyl 2-methyl-3-oxo-4-isoxazolin-5-ylacetate (*3b*).* To a solution of *1b*[20] (30.9 g; 180 mmol) in dry ether (600 ml) an ether solution (600 ml) of diazomethane (*ca.* 9 g) was added, prepared from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (MNTS) (64.5 g; 300 mmol). The solution was left at 25 °C for 2 h, evaporated *in vacuo*, and the residue subjected to CC [eluents: benzene–ethyl acetate–formic acid (90:9:1) to which ethyl acetate was gradually added] to give *2b* and *3b* as oils, which were purified by ball-tube distillation at 0.3 mmHg (oven temperature 130 °C). *2b*: Anal. $C_8H_{11}NO_4$: C, H, N. IR (film): 3135 (w), 2980 (s), 2930 (m), 1740 (s), 1625 (s), 1530 (s), 1460 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.83 (1 H, s), 4.1 (2 H, q, *J* 7 Hz), 3.91 (3 H, s), 3.65 (2 H, s), 1.3 (3 H, t, *J* 7 Hz). *3b*: Anal. $C_8H_{11}NO_4$: C, H, N. IR (film): 3140 (w), 2990 (m), 2890 (m), 1745 (s), 1690 (s), 1645 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.77 (1 H, s), 4.2 (2 H, q, *J* 7 Hz), 3.6–3.5 (5 H, two s), 1.3 (3 H, t, *J* 7 Hz).

*Ethyl 3-chloroisoxazol-5-ylacetate (*4b*).* *4b* was synthesized from *3b* (925 mg; 5 mmol) and purified as described for *4a*. Obtained was *4b* (48 mg; 5 %) as an oil purified by ball-tube distillation at 1 mmHg (oven temperature 150 °C). Anal. $C_7H_8NO_3Cl$: C, H, N, Cl. IR ($CHCl_3$): 3150 (w), 2950 (w), 1740 (s), 1600 (m), 1440 (m), 1385 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.30 (1 H, s), 4.38 (0.4 H, q, *J* 6 Hz), 4.18 (1.6 H, q, *J* 6 Hz), 3.75 (2 H, s), 1.35 (0.6 H, t, *J* 6 Hz, 1.28 (2.4 H, t, *J* 6 Hz). Very similar ^{1}H NMR spectra were obtained using CCl_4 or DMSO-d_6 as solvents at *ca.* 25 °C and at *ca.* 50 °C. MS [70 eV; *m/z* (% rel. int.)]: 191, 189 (0.3, 1, M), 146, 144 (0.6, 2), 119, 117 (5, 14), 118, 116 (4, 12), 29 (100).

*Methyl 3-hydroxyisoxazol-5-ylpropionate (*1c*).* A solution of *2c*[13] (2.3 g; 12 mmol) in a solution of hydrogen bromide in glacial acetic acid (33 %; 20 ml) was kept at 25 °C for 16 h and then evaporated *in vacuo*. CC [eluent: dichloromethane-ethyl acetate (7:3)] of the residue gave *1c* (1.6 g; 75 %), m.p. 98.0–100.5 °C (ethyl acetate–light petroleum). Anal. $C_7H_9NO_4$: C, H, N. IR ($CHCl_3$): 3300–2600 (m–s, broad signal), 3080 (m), 3000 (s), 1730 (s), 1620 (s), 1530 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 12.0 (1 H, s), 5.72 (1 H, s), 3.70 (3 H, s), 3.2–2.7 (4 H, m).

*Methyl 3-methoxyisoxazol-5-ylpropionate (*2c*)*

and methyl 2-methyl-3-oxo-4-isoxazolin-5-ylpropionate (3c). *2c* and *3c* were synthesized from *1c* (342 mg; 2 mmol) and purified as described for *2a* and *3a*. The IR spectrum of *2c* was identical with that of an authentic sample.[13] *3c*: m.p. 51.0–53.0 °C (ethyl acetate–light petroleum). Anal. $C_8H_{11}NO_4$: C, H, N. IR ($CHCl_3$); 3140 (w), 2980–2870 (s, several bands), 1725 (s), 1675 (s), 1630 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.53 (1 H, s), 3.70 (3 H, s), 3.45 (3 H, s), 3.1–2.6 (4 H, m).

Methyl 3-chloroisoxazol-5-ylpropionate (4c). *4c* was synthesized from *3c* (925 mg; 5 mmol) and purified as described for *4a*. Obtained was *4c* (513 mg; 54 %), m.p. 43.0–44.0 °C (light petroleum). Anal. $C_7H_8NO_3Cl$: C, H, N, Cl. IR ($CHCl_3$): 3140 (w), 2980 (m), 2860 (m), 1725 (s), 1600 (s), 1360 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.05 (1 H, s), 3.67 (3 H, s), 3.4–2.5 (4 H, m). MS [70 eV; *m/z* (% rel. int.)]: 191, 189 (3, 8, M), 160, 158 (5, 14), 132, 130 (35, 100), 131, 129 (18, 37), 67 (26), 59 (46), 55 (85).

Methyl (E)-3-hydroxyisoxazol-5-ylpropenoate (1d). *1d* was synthesized from *2d*[10] (641 mg; 3.5 mmol) and purified as described for *1c*. Obtained was *1d* (550 mg; 93 %), m.p. 150–154 °C (ethyl acetate–light petroleum). Anal. $C_7H_7NO_4$: C, H, N. IR ($CHCl_3$): 3350–2700 (m–s, broad signal), 3100 (m), 2980 (s), 1710 (s), 1645 (s), 1605 (m), 1520 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.0 (1 H, s), 7.25 (1 H, d, *J* 16 Hz), 6.45 (1 H, d, *J* 16 Hz), 6.00 (1 H, s), 3.75 (3 H, s).

Methyl (E)-3-methoxyisoxazol-5-ylpropenoate (2d) *and methyl (E)-2-methyl-3-oxo-4-isoxazolin-5-ylpropenoate* (3d). *2d* and *3d* were synthesized from *1d* (338 mg; 2 mmol) and purified as described for *2a* and *3a*. The IR spectrum of *2d* was identical with that of an authentic sample.[10] *3d:* oil purified by ball-tube distillation at 0.2 mmHg (oven temperature 140 °C). Anal. $C_8H_9NO_4$: C, H, N. IR ($CHCl_3$): 3140 (w), 2980 (m), 1720 (s), 1670 (s), 1600 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30 (1 H, d, *J* 16 Hz), 6.52 (1 H, d, *J* 16 Hz), 6.02 (1 H, s), 3.82 (3 H, s), 3.56 (3 H, s).

Methyl (E)-3-chloroisoxazol-5-ylpropenoate (4d). *4d* was synthesized from *3d* (915 mg; 5 mmol) and purified as described for *4a*. Obtained was *4d* (667 mg; 71 %), m.p. 98.0–99.0 °C (light petroleum). Anal. $C_7H_6NO_3Cl$: C, H, N, Cl. IR ($CHCl_3$): 3145 (w), 2990 (m), 2860 (m), 1720 (s), 1600 (w), 1375 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.37 (1 H, d, *J* 15 Hz), 6.61 (1 H, d, *J* 15 Hz), 6.43 (1 H, s), 3.80 (3 H, s). MS [70 eV; *m/z* (% rel. int.)]: 189, 187 (6, 21, M), 158, 156 (21, 56), 152 (66), 121 (100), 93 (44), 67 (38).

2,4,5-Trimethyl-4-isoxazolin-3-one (3e). *3e* was synthesized from *1e*[21] (226 mg; 2 mmol) and purified as described for *2a* and *3a*. The IR spectrum of *3e* was identical with that of an authentic sample.[10] *2e* could not be detected in the reaction product [^1H NMR; TLC (eluent: toluene)].

3-Chloro-4,5-dimethylisoxazole (4e). *4e* was synthesized from *3e* (635 mg; 5 mmol) and purified as described for *4a*. Obtained was *4e* (403 mg; 61 %), b.p. 66 °C/20 mmHg. Anal. C_5H_6NOCl: C, H, N, Cl. IR ($CHCl_3$): 2880 (m), 1640 (s), 1450 (s), 1400 (s), 1375 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.32 (3 H, s), 1.91 (3 H, s). MS [70 eV; *m/z* (% rel. int.)]: 133, 131 (6, 19, M), 118, 116 (0.3, 1), 96 (9), 90, 88 (6, 19), 64, 62 (2, 6), 43 (100).

Ethyl 3-methoxy-5-methylisoxazole-4-carboxylate (2f) *and ethyl 2,5-dimethyl-3-oxo-4-isoxazoline-4-carboxylate* (3f). *2f* and *3f* were synthesized from *1f*[11] (30.9 g; 180 mmol) and purified as described for *2b* and *3b*. The IR spectrum of *2f* was identical with that of an authentic sample.[11] *3d*: m.p. 46.0–47.0 °C (ethyl acetate–light petroleum). Anal. $C_8H_{11}NO_4$: C, H, N. IR ($CHCl_3$): 2980 (s), 2880 (m), 1730 (s), 1690 (s), 1620 (s), 1530 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.24 (2 H, q, *J* 7 Hz), 3.40 (3 H, s), 2.50 (3 H, s), 1.36 (3 H, t, *J* 7 Hz).

Ethyl 3-chloro-5-methylisoxazole-4-carboxylate (4f). *4f* was synthesized from *3f* (925 mg; 5 mmol) and purified as described for *4a*. Obtained was *4f* (713 mg; 75 %). The IR spectrum of *4f* was identical with that of an authentic sample.[11] MS [70 eV; *m/z* (% rel. int.)]: 191, 189 (1.5, 5, M), 176, 174 (0.1, 0.3), 163, 161 (6, 18), 146, 144 (9, 29), 43 (100).

3-Methoxycyclohepteno[1,2-d]isoxazole (2g) *and 2-methylcyclohepteno[1,2-d]isoxazolin-3-one* (3g). *2g* and *3g* were synthesized from *1g*[9] (306 mg; 2 mmol) and purified as described for *2a* and *3a*. The IR spectra of *2g* and *3g* were identical with those of authentic samples.[9]

3-Chlorocyclohepteno[1,2-d]isoxazole (4g). *4g* was synthesized from *3g* (835 mg; 5 mmol) and purified as described for *4a*. Obtained was *4g* (155 mg; 18 %) as an oil purified by ball-tube distillation. Anal. $C_8H_{10}NOCl$: C, H, N, Cl. IR ($CHCl_3$): 2900 (s), 1625 (s), 1440 (s), 1390 (s), 1320 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.90 (2 H, m), 2.40 (2 H, m), 2.0–1.5 (6 H, m). MS [70 eV; *m/z* (% rel. int.)]: 173, 171 (16, 42, M), 136 (16), 131, 129 (8, 22), 108 (31), 81 (100), 80 (63).

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