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SYNTHESIS OF 3-HALOISOXAZOLES BY NOVEL OXIDATIVE DEGRADATION OF THE SIDE-CHAIN OF 3-(3-HALO-ISOXAZOL-5-YL) PROPIONIC ACIDS

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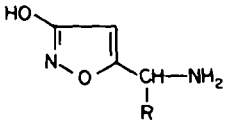
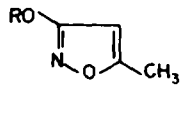
Abstract—A novel method for the oxidative degradation of the side-chain of 3-(3-haloisoxazol-5-yl) propionic acids has been developed. The *E*-3-(3-chloroisoxazol-5-yl) propenoic acid **13a** obtained by treatment of the *s*-triazolo[2,3-*c*] quinazolin-4-ium iodide **11a** with $PhI(OAc)_2$ and Bz_2O_2, respectively, and subsequent hydroxysis, has been used for the synthesis of numerous 3-haloisoxazole derivatives.

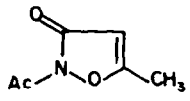
Ibotenic acid, (RS) - α - amino - 3 - hydroxyisoxazole - 5 - acetic acid **1a** and muscimol, 5 - aminomethyl - 3 - hydroxyisoxazole **1b**, isolated from *Amanita muscaria*, are of remarkable pharmacological interest.[1] Because of their neurochemical importance and limited availability from natural sources, their syntheses have been carried out by a number of investigators.[2] Most of the existing methods follow lengthy procedures and involve low yields. Our recent interest in isoxazoles[3] prompted us to study the synthetic possibilities of isoxazole derivatives being suitable for the preparation of these natural products. We wish to report here the synthesis of *E* - 3 - (3 - chloroisoxazol - 5 - yl) propenoic acid **13a**, a useful intermediate for the synthesis of **1a** and **1b**.



1a: R = COOH
1b: R = H



2a: R = H
2b: R = Ac



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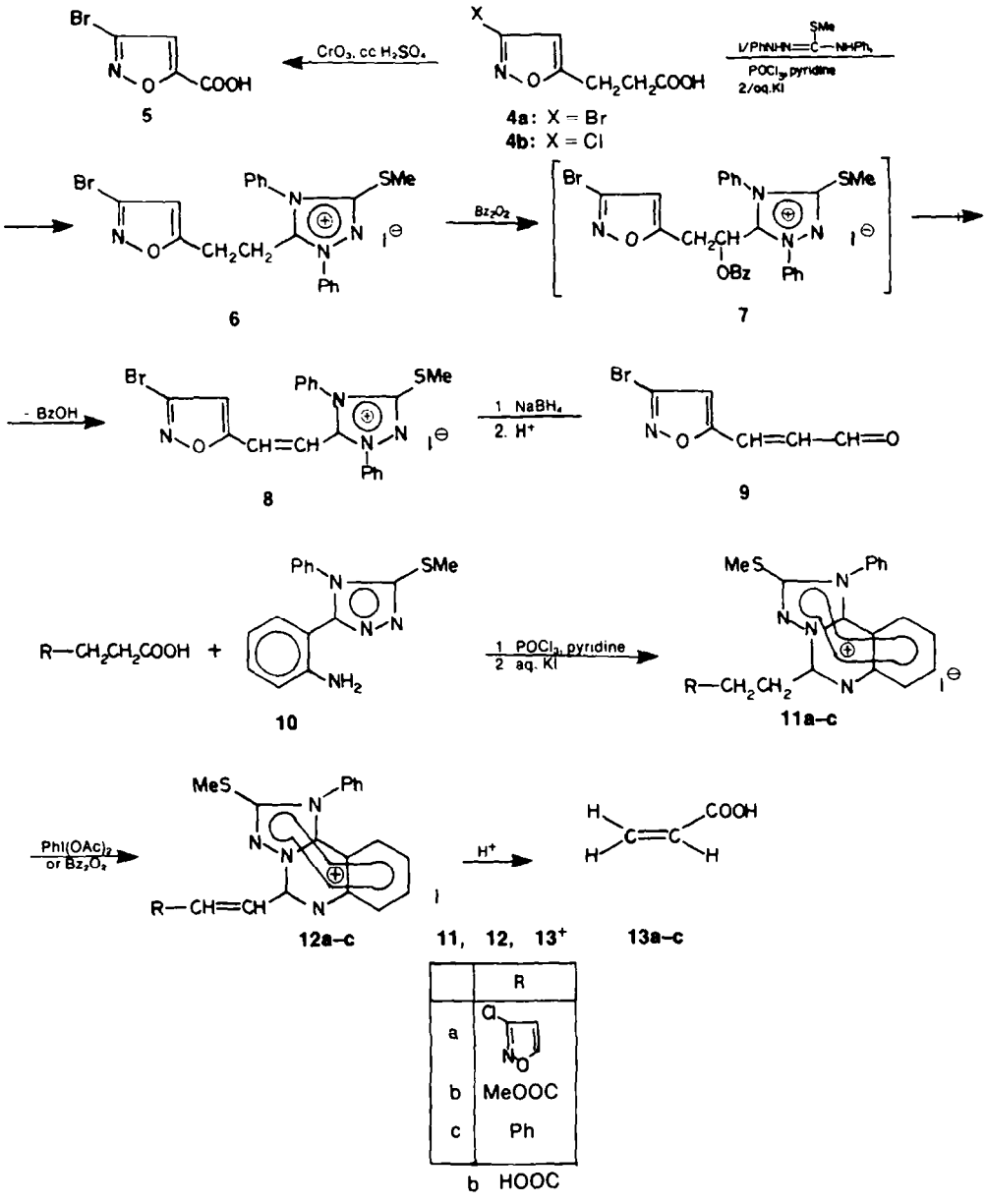
The rather stable 3-haloisoxazole derivatives may be converted into the 3-hydroxy compounds.[4] Unfortunately there is no convenient method for the preparation of 3 - halo - 4 - unsubstituted isoxazoles containing a 5-substituent suitable for further reactions.[5] Moreover, according to our earlier investigations,[6] the readily accessible 3 - hydroxy - 5 - methyl - isoxazole **2a**, a known fungicide,[7] and its *O*- and *N*-acylated derivatives **2b** and **3** respectively, proved not to be suitable for the synthesis of **1a** and **1b**, because both electrophiles and radicals attack the 4-position of the isoxazole nucleus.[4]

Finally, 3 - (3 - bromoisoxazol - 5 - yl) - and 3 - (3 - chloroisoxazol - 5 - yl) propionic acids **4** prepared according to a simplified and improved procedure described by Thiele and Landers,[8] have been utilized as starting materials. To our knowledge only one method has been published for the oxidation of **4a**, treatment of which with chromic acid in sulphuric acid furnished the 3 - bromo - 5 - isoxazolecarboxylic acid **5**.[9]

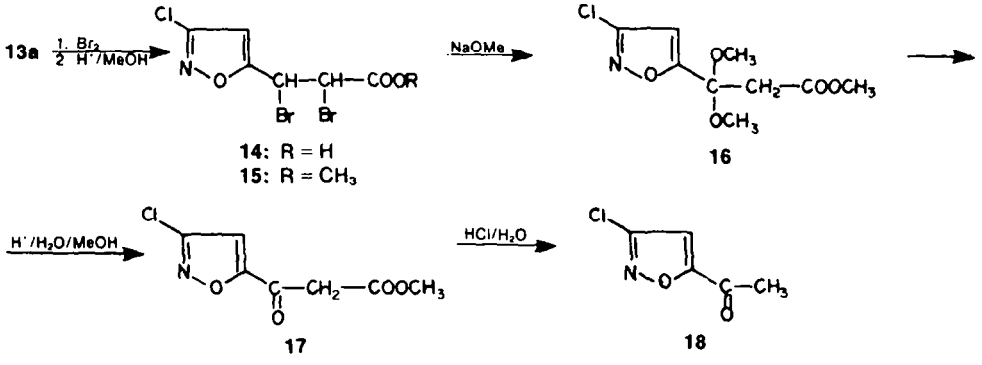
Our first aim was to convert the propionic acid side-chain into a carboxaldehyde with one less carbon atom using the method developed by one of us.[10] Masking the carboxylic group with *S* - methyl - 1, 4 - diphenyl - isothiosemicarbazide and phosphorus oxychloride in pyridine and adding aqueous potassium iodide to the reaction mixture afforded the *s*-triazolium iodide **6**, but treatment of the latter with benzoyl peroxide furnished **8** instead of the desired product **7**. This result can be rationalized by postulating that benzoic acid is eliminating rapidly from **7** because of the strong electron-withdrawing effect of the 3-haloisoxazole ring.[4] Since the aldehyde **9** obtained after the sodium borohydride reduction and hydrolysis of **8** could be isolated only in poor yield, attempts were made to prepare the corresponding carboxylic acid.

Previously we found that carboxylic acids and the *s*-triazole **10** in the presence of phosphorus oxychloride and pyridine followed by treatment with aqueous alkali iodide furnished the *s*-triazolo [2,3-c] quinazolin - 4 - ium iodides of type **11**, and could be reconverted by acidic hydrolysis into compound **10** and the appropriate carboxylic acid.[11] Thus, **11a** was prepared from **4b** and **10** in this manner, which was treated with iodosobenzene diacetate to give **12a**, and acidic hydrolisis of **12a** furnished the α, β-unsaturated carboxylic acid **13a** in 44% overall yield, based on the carboxylic acid **4b**. Intermediates need not be isolated in pure form. This oxidation method could be generalized in the case of propionic acids having an electron withdrawing group in the β-position, thus methyl hydrogen succinate and 3-phenylpropionic acid were transformed into **12b** and **12c**, respectively, the acidic hydrolysis of which afforded *trans*-cinnamic acid and fumaric acid, respectively. Benzoyl peroxide could be used instead of iodosobenzene diacetate, but the yields were somewhat decreased.

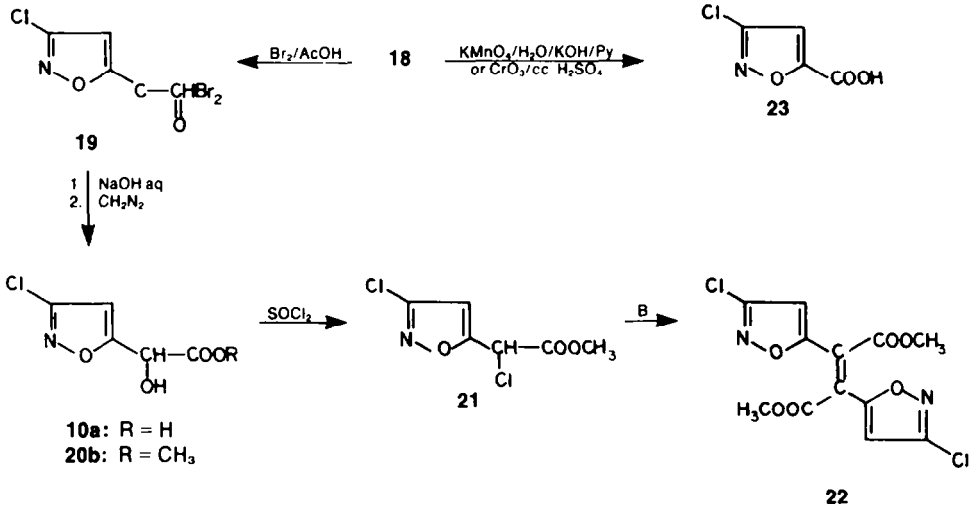
The reaction of **13a** with bromine in boiling acetic acid



followed by esterification furnished **15**, which was treated with two equivalent of sodium methoxide in methanol to give **16**. The ketal **16** was converted smoothly to **17** upon treatment with aqueous-methanolic HCl at 60°. The structure proof of the products **16** and **17** rests on their spectral data as well as on hydrolysis of **17**; treatment with 20% aqueous HCl 2 hr on the steambath **17** afforded **18**, already prepared in a different and complicated way.[12] **18** could be obtained directly from **15** in 80% yield.



Oxidation of **18** with selenium dioxide was unsuccessful, however, with potassium permanganate in water in the presence of KOH and pyridine,[12] or with chromic acid in conc sulphuric acid led to the known **23**. Treatment of **18** with bromine in acetic acid at 65–70° furnished **19**, the structure of which was proved by its ^{1}H NMR spectrum. The crude **19** was submitted to the treatment with aqueous NaOH at 0° to yield the glycolic acid **20a**, transformed immediately into its methyl ester **20b** by usind diazomethane in ethereal solution (overall yield 40%, based on **13a**). The structure of the crude **20a** and **20b** was confirmed by their IR and ^{1}H NMR spectra as well as the reaction of **20b** with thionyl chloride at 0° to give **21**, which could be purified by distillation *in vacuo*. Attempt to displace the α-chloro- substituent in **21** with potassium phtalimide was not successful due to the rapid α-elimination and a dimerized product **22** was formed, the structure of which was based on its IR, ^{1}H NMR and mass spectra the geometrical configuration was not determined.



However, it is described in the literature,[9] that **1a** and/or **1b** can be prepared from 3 - benzyloxy - 5 - isoxazole glycolic acid derivatives. Since in general the 3 - haloisoxazoles could be easily converted into 3-benzyloxy derivatives,[4,9] **20b** also might be a suitable intermediate for **1a** and **1b**.

EXPERIMENTAL

All the m.ps are uncorrected. IR spectra were measured using a Spectromom 2000 spectrometer. ^{1}H NMR spectra were obtained at 60 MHz on a Perkin–Elmer R12 and at 80 MHz on a Bruker WP 80 spectrometer, using TMS as an internal standard. Mass spectrum was obtained using a JEOL JNS-OI SG-2 mass spectrometer.

3-(3-Chloroisoxazol-5-yl)propionic acid **4b**

The following procedure is an improved version of that reported in the literature.[8] Nitromethane (246 g; 4.03 mole) was added, with stirring and ice-cooling, to the mixture of cold 25% aq KOH (900 ml; 4 mole) and crushed ice (1800 ml) in 5 min, followed by dropping of freshly distilled furfural (348 g; 3.62 mole) in 10 min. The resulting solution was poured into the mixture of ice (1500 g) and conc HCl (1750 ml) under stirring. The yellow precipitate was filtered off at once, washed with water (2 × 500 ml) and dissolved in CH_2Cl_2 (200 ml). The water was separated and the organic layer was evaporated to dryness *in vacuo*. The residue was dissolved in conc HCl (2000 ml), 1-octanol (40 ml) was added to it and the mixture was heated on the steambath for 1 hr and at 140° for 9 hr. After cooling to 80°, tar was filtered off and washed with hot water (2 × 500 ml). The filtrate was treated twice with charcoal and extracted with ether (2000 ml + 2 × 1000 ml). The combined ethereal solutions were washed with water (500 ml), dried ($CaCl_2$) and evaporated to yield 119–143 g (20–24%) of **4b**, m.p. 82–83° (lit[8] m.p. 84°).

5 - [2 - (3 - *Bromoisoxazol* - 5 - *yl*]*ethyl* - 3 - *methylthio* - 1,4 - *diphenyl* - s - *triazolium iodide* **6**

$POCl_3$ (10 g; 65 mmole) was added under vigorous stirring to the mixture of *S* - *methyl* - 1,4 - diphenylisothiosemicarbazide[10] (12.9 g; 50 mmole) **4a**[8] (11 g; 50 mmole) and dry pyridine (45 ml) at such a rate that the mixture started and was kept boiling (2–3 min). The hot mixture was stirred for another 1 min. Dry MeOH (30 ml) was added dropwise. The warm solution was treated with 20% aq KI (60 ml) and chilled (0°), affording a white precipitate which was filtered off and washed with water (2 × 50 ml), i-ProH (2 × 200 ml), and ether (2 × 50 ml) to yield 20.3 g (72%) of **6**, m.p. 174–175° dec (MeOH). Found: C, 42.32; H, 3.14; N, 9.93; S, 5.41. Calc. for $C_{20}H_{18}N_4BrIOS$ (569.28): C, 42.19; H, 3.19; N, 9.84; S, 5.63%. ^{1}H NMR ($CDCl_3$): δ8.45–8.25, m, 4H, *N*-Ph, *o* – H'S; 7.8–7.4, m, 6H, *N*-Ph, *m*- and *p*-H's; 6.0, s, 1H, C*4*-H; 3.45, tr, 2H, CH_2; 3.0, tr, 2H, CH_2; 2.6, s, 3H, *S*-CH_3.

5 - [2 - (3 - *Bromoisoxazol* - 5 - *yl*)]*vinyl* - 3 - *methylthio* - 1,4 - *diphenyl* - s - *triazolium iodide* **8**

A mixture of **6** (2.84 g, 5 mmole), Bz_2O_2 (1.4 g; 5.8 mmole) and $CHCl_3$ (30 ml) was refluxed for 1 hr and washed with an aq solution (50 ml) of $NaHSO_3$ (3 g) and KI (15 g) and then with water (2 × 15 ml), dried ($MgSO_4$) and evaporated. The residue was dissolved in a warm mixture of methanol (80 ml) and water (20 ml) and 20% aq KI (50 ml) was added. The precipitation was filtered off, washed with water, cold EtOH and ether to yield 2.4 g (85%) of **8**, m.p. 202° dec (EtOH-H_2O). Found: C, 42.07; H, 2.71; N, 9.31; S, 5.70. Calc. for $C_{20}H_{16}N_4BrIOS$ (567.26): C, 42.34; H, 2.84; N, 9.88; S, 5.65%. ^{1}H NMR (DMSO-d_6): δ7.8, s, 10H, ArH's; 7.35, d, 1H, =Cl-H; 6.95, dd, 1H, =C2-H; 6.8, s, 1H, C4-H.

E - 3 - (3 - *Bromoisoxazol* - 5 - *yl*)*propenal* **9**

8 (28.4 g; 50 mmole) was dissolved in the mixture of dry DMF (150 ml) and MeOH (150 ml). Aq solution (50 ml) of $NaBH_4$ (2.27 g; 60 mmole), made alkaline by addition of a few drops of 10% aq NaOH, was added under cooling and stirring at such a rate that the temp did not exceed 8°. The excess of the $NaBH_4$ was decomposed by adding AcOH (10 ml); water (50 ml) was added and the mixture was extracted with ether (3 × 150 ml). The combined ethereal solutions were washed with water (2 × 150 ml) and evaporated. The residue was treated with 40% aq HCHO (30 ml) and conc HCl (30 ml) and stirred for 10 min at r.t. and

extracted with ether (3 × 50 ml). The combined ethereal solutions were washed with 20% aq HCl (2 × 40 ml) and water (20 ml), dried ($MgSO_4$), evaporated and the residue was triturated with *n*-pentane (10 ml) to yield 2.6 g (28%) of **9**, m.p. 136–137° (*n*-PrOH). Found: C, 35.65; H, 1.73; N, 6.80; Br, 39.04. Calc. for $C_6H_4BrNO_2$ (202.02): C, 35.67; H, 1.98; N, 6.93; Br, 39.56%. ^1H NMR (DMSO-d_6): δ9.7, d, 1H, CH=O, J = 9; 7.65, d, 1H, =CH, J = 18; 7.25, s, 1H, C4-H; 6.82, dd, 1H, =CH–CHO, J = 18, J = 9 Hz.

E - 3 - (3 - *Chloroisoxazol* - 5 - *yl*)*propenoic acid* **13a**

$POCl_3$ (106 g; 0.69 mole) was added, with stirring, to a mixture of **10**[11] (141.2 g; 0.5 mole), **4b** (87.75 g; 0.5 mole), dry pyridine (450 ml) dropwise at such a rate that the mixture came to boiling (2–3 min). The excess $POCl_3$ was decomposed with dry MeOH (430 ml), and 20% aq KI (1000 ml) was added to the warm solution. The mixture was filtered off washed with water (2 × 400 ml), cold *i*-PrOH (2 × 250 ml) and ether (2 × 450 ml) to give 250 g (91%) of **11a**, m.p. 280° dec. The crude product was too insoluble for recrystallization and analyzed as such.

A mixture of crude **11a** (250 g; 0.455 mole), $PhI(OAc)_2$ (160 g; 0.5 mole) and dry DMF (430 ml) was stirred. The temp rose to 40°. Stirring was continued for 3 hr at r.t. Treatment of the mixture with a mixture of KI (270 g), $NaHSO_3$ (21.5 g), H_2O (1000 ml) and conc HCl (55 ml) gave the product, which was filtered off, washed with water (2 × 400 ml), acetone (2 × 400 ml) and ether (2 × 400 ml) to give 175 g (70%) of **12a**, m.p. 240° dec. The crude product was too insoluble for recrystallization and analyzed as such.

Sodium methoxide (25.1 g; 0.47 mole) in dry MeOH (400 ml) was added to a mixture of crude **12a** (175 g; 0.32 mole) resulting a clear solution, which was poured into ice-water (3500 ml), the precipitation was filtered off and washed with water and refluxed in a mixture of AcOH (400 ml), cm^3. H_2SO_4 (200 ml) and water (2000 ml) for 10 hr. The mixture was poured into water (2000 ml) and extracted with ether (3 × 800 ml). The aqueous and organic layers were worked up separately. The aqueous layer was neutralized with 40% aq. NaOH and extracted with $CHCl_3$ (3 × 350 ml). The combined chloroformic solutions were washed with water (2 × 250 ml), dried ($MgSO_4$) and evaporated to give 79 g (56%) of **10**, m.p. 141–142° (EtOH). The organic layer was washed with water (2 × 600 ml) and evaporated. The residue was triturated with warm water (180 ml), chilled (0°) to yield 38.5 g (69%); 44% based on **4b**) **13a**, m.p. 190° dec (H_2O-AcOH). Found: C, 41.39; H, 2.40; Cl, 20.56; N, 8.01. Calc. for $C_6H_4ClNO_3$ (173.56): C, 41.52; H, 2.32; Cl, 20.43; N, 8.07%. ^1H NMR (DMSO-d_6): δ7.25, d, 1H, =CH, J = 18; 7.0, s, 1H, C4-H; 6.35, d, 1H, =CH, J = 18 Hz.

Oxidation of **11a** *with* Bz_2O_2

Bz_2O_2 (27 g; 0.11 mole) was added under stirring to a mixture of crude **11a** (55 g; 0.1 mole) and dry $CHCl_3$ (250 ml) in 30 min at such a rate that the temperature did not exceed 40°. The mixture was stirred for another 30 min at r.t., treated with ether (500 ml) and chilled (0°). The precipitate was filtered off, slurried with a mixture of MeOH (100 ml), DMF (200 ml) and conc HCl (20 ml), treated with 20% aq KI (250 ml) to yield 30 g (54%) **12a**, m.p. 240° dec.

5 - (2 - *Methoxycarbonyl vinyl*) - 2 - *methylthio* - 1 - *phenyl* - s - *triazolo*[2,3-*c*]*quinazolin* - **4** - *ium iodide* **12b**

11b[11] was treated with $PhI(OAc)_2$ or Bz_2O_2, as described for **11a** to yield 65% or 48% of **12b**, m.p. 275–276° dec (MeOH). Found: C, 47.85; H, 3.63; N, 11.03; I, 24.91; S, 6.73. Calc. for $C_{20}H_{17}N_4IO_2S$ (504.35): C, 47.62; H, 3.40; N, 11.11; I, 25.16; S, 6.36%. ^1H NMR (DMSO-d_6): δ8.6–7.7, m, 9H, ArH's; 7.45, d, 1H, =CH, J = 18; 3.87, d, 1H, =CH, J = 18; 3.0, s, 3H, OCH_3; 2.45, s, 3H, SCH_3.

2 - *Methylthio* - 1 - *phenyl* - 5 - (2 - *phenylethyl* - s - *triazolo*[2,3-*c*]*quinazolin* - **4** - *ium*) *iodide* **11c**

11c was prepared according to the method described for **11a** and **11b**. Yield: 85.5%. M.p. 220–222° dec (MeOH). Found: C, 54.97; H, 4.10; N, 10.67; I, 24.80; S, 6.18. Calc. for $C_{24}H_{21}IN_4S$ (524.42): C, 54.96; H, 4.04; N, 10.68; I, 24.20; S, 6.11%. ^1H NMR ($CDCl_3$): δ8.4–7.9, m, 4H, o-H's; 7.9–7.05, m, 10 H, other ArH's; 3.85, tr, 2 H, CH_2; 3.45, tr, 2 H, CH_2; 2.95; 2.95, s, 3H, SCH_3.

2 - *Methylthio* - 1 - *phenyl* - 5 - (2 - *phenylethenyl*) - s - *triazolo*[2,3-*c*]*quinazolin* - **4** - *ium iodide* **12c**

11c was treated with $PhI(OAc)_2$ or Bz_2O_2, as described for **11a** to yield 68% or 50% of **12c**, m.p. 266–268° dec (EtOH). Found: C, 55.41; H, 3.89; N, 10.43; S, 6.16; I, 24.17. Calc. for $C_{24}H_{19}IN_4S$ (522.40): C, 55.18; H, 3.66; N, 10.72; S, 6.14; I, 24.29%. ^1H NMR (DMSO-d_6): δ8.7-7.45, m, 14H, ArH's; 8.3, d, 1H, =CH, J = 8; 7.2, d, 1H, =CH, J = 8 Hz; 3.1, s, CH_3.

2,3 - *Dibromo* - 3 - (3 - *chloroisoxazol* - 5 - *yl*) *propionic acid* **14**

A mixture of **13a** (35 g; 0.2 mole), Br_2 (35.2 g; 0.22 mole) and AcOH (150 ml) was refluxed for 30 min, poured into the mixture of $NaHSO_3$ (20 g), ice (300 g) and water (300 ml), and extracted with CH_2Cl_2 (3 × 300 ml). The combined organic solutions were washed with water (2 × 200 ml) and evaporated. The residue was triturated with *n*-pentane (80 ml) to yield 60 g (89%) of **14**, m.p. 162–163° (H_2O). Found: C, 21.90; H, 1.41; N, 4.37. Calc. for $C_6H_4Br_2ClNO_3$ (321.34): C, 21.61; H, 1.20; N, 4.20% IR (KBr): 1730 cm^{-1} ($\nu_{C=O}$). ^1H NMR (DMSO-d_6): δ7.95, broad s, 1H, CH; 7.2, s, 1H, C/4/-H; 5.93, d, 1H, CH; 5.18, d, 1H, CH.

Methyl 2,3 - *dibromo* - 3 - (3 - *chloroisoxazol* - 5 - *yl*) *propionate* **15**

A mixture of **14** (60 g; 0.187 mole), conc H_2SO_4 (30 ml) and dry MeOH (500 ml) was refluxed for 10 hr poured into ice-water (2000 ml) and extracted with ether (3 × 600 ml). The combined ethereal solutions were washed with water (2 × 600 ml), 5% aq $NaHCO_3$ (2 × 300 ml) and water (300 ml), dried ($CaCl_2$) and evaporated. The residue was dissolved in hot CCl_4 (75 ml), treated with *n*-pentane (150 ml), chilled (0°) to precipitate 55 g (78%) of **15**, m.p. 90–91° (CCl_4-*n*-pentane). Found: C, 23.90; H, 1.70; N, 4.31. Calc. for $C_7H_6Br_2ClNO_3$ (347.42): C, 24.19; H, 1.72; N, 4.03%. IR (KBr): 1740 cm^{-1} ($\nu_{C=O}$). ^1H NMR /$CDCl_3$/: δ6.6, s, 1H, C(4)-H; 5.55, dd, 1H, C/3/-H, J = 12, J = 1.3 Hz; 4.95, d, 1H, C(2)-H; 3.95, s, 3H, CH_3.

Methyl 3,3 - *dimethoxy* - 3 - (3 - *chloroisoxazol* - 5 - *yl*) *propionate* **16**

A mixture of **15** (12.5 g; 36 mmole), NaOMe (4.34 g; 80 mmole) and dry MeOH (100 ml) was refluxed for 2 hr, poured into ice-water (400 ml) and extracted with ether (3 × 125 ml). The combined ethereal solutions were washed with water (2 × 100 ml), dried ($MgSO_4$) and evaporated. The residue was dissolved in hot *n*-pentane (80 ml) and filtered off. The filtrate was evaporated to one quarter of its volume, chilled (0°) affording a light precipitation, which was filtered off and washed with cold *n*-pentane (5 ml) to yield 5.8 g (65%) of **16**, m.p. 64–65° (*n*-pentane). Found: C, 41.31; H, 4.93, Cl, 14.02; N, 5.72. Calc. for $C_9H_{12}ClNO_5$ (249.66): C, 43.29; H, 4.84; Cl, 14.20; N, 5.61%. IR (KBr): 1745 cm^{-1} ($\nu_{C=O}$). ^1H NMR ($CDCl_3$): δ6.45, s, 1H, C(4)-H; 3.6, s, 3H, $COOCH_3$; 3.25, s, 6H, 2 CH_3; 3.15, s, 2H, CH_2.

Methyl 3 - *oxo* - 3 - (3 - *chloroisoxazol* - 5 - *yl*) *propionate* **17**

A mixture of **15** (10.4 g; 30 mmole), NaOMe (4.16 g; 77 mmole) and dry MeOH (100 ml) was refluxed for 2 hr, evaporated *in vacuo* to one fifth of its volume, treated with 20% HCl (40 ml) at 70° with stirring for 15 min and chilled (0°) to precipitate 4.7 g (77%) of **17**, m.p. 116–117° (benzene). Found: C, 41.40; H, 3.01; Cl, 17.24; N, 6.86. Calc. for $C_7H_6ClNO_4$ (203.59): C, 41.29; H, 2.96; Cl, 17.42; N, 6.88%. IR (KBr): 3150 (w, ν_{OH}), 1680 ($\nu_{C=O}$), 1570 cm^{-1}. ^1H NMR spectrum in $CDCl_3$ shows the mixture of keto and enol form in a ratio of 7:3 at 32°: δ11.5, broad s, 1H, OH; 6.95, s, 1H, C(4)-H in the keto form; 6.7, s, 1H, C(4)-H in the enol form; 5.85, s, 1H, =CH; 3.95, s, 3H, CH_3 in the keto form; 3.8, s, 3H, CH_3 in the enol form; 3.75, s, 2H, CH_2.

5 - *Acetyl* - 3 - *chloroisoxazole* **18**

A mixture of **15** (65 g; 0.187 mole), NaOMe (25.8 g; 0.48 mole) and dry MeOH (400 ml) was refluxed for 2 hr and evaporated. The residue was dissolved in 20% HCl (300 ml), kept with stirring

at the steambath for 2 hr and extracted with ether (4 × 250 ml). The combined ethereal solutions were washed with water (2 × 150 ml), dried ($CaCl_2$) and evaporated. The residue was triturated with *n*-pentane (25 ml) to yield 21.5 g (80%) of **18**, m.p. 63–64° (*n*-hexane). Found: C, 41.44; H, 2.70; Cl, 24.20; N, 9.46. Calc. for $C_5H_4ClNO_2$ (145.55): C, 41.26; H, 2.75; Cl, 24.36; N, 9.62%. IR (KBr): 1700, 1575 cm^{-1}. ^1H NMR ($CDCl_3$): δ6.9, s, 1H, C(4)-H; 2.6, s, 3H, CH_3.

Methyl hydroxy - (3 - chloroisoxazol - 5 - yl)acetate **20b**

A mixture of Br_2 (18.4 g; 0.115 mole) and acetic acid (50 ml) was added dropwise to a mixture of **18** (7.25 g; 50 mmole) and AcOH (25 ml) at 65–70°. The resulting mixture was evaporated. *n*-Heptane (100 ml) was added to the residue and evaporated. The oily residue was added dropwise with stirring and ice-cooling, to a mixture of NaOH (10 g; 250 mmole) and water (100 ml) in 5 min. The mixture was stirred for 1 hr at 0° and for 2 hr at r.t., acidified with AcOH and extracted with ether (3 × 125 ml). The inorganic layer was acidified with conc. HCl and extracted with ether (3 × 150 ml). The latter combined ethereal solutions were washed with water and evaporated to yield 6.2 g (70%) **20a** as a yellow oil, which was dried over P_2O_5 *in vacuo*. ^1H NMR ($CDCl_3$): δ8.6, s, 2H, OH's; 6.2, s, 1H, C(4)-H; 5.25, s, 1H, CH.

An excess of ethereal diazomethane was added to a mixture of crude **20a** (6.2 g; 35 mmole) and ether (25 ml), and the resulting mixture was evaporated. The residue was dissolved in ether (25 ml), washed with water (2 × 20 ml), dried ($MgSO_4$) and evaporated to yield 5.26 g (80%); 56% based on **18**) of **20b**, as a colourless oil, which proved to be unstable at distillation *in vacuo* therefore it was identified as **21**. Spectral data of crude **20b**: IR (liquid film): 3400, 1755, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ6.6, s, 1H, C(4)-H; 5.6, s, 1H, CH; 5.0, broad s, 1H, OH; 3.85, s, 3H, CH_2.

Methyl chloro - (3 - chloroisoxazol - 5 - yl) acetate **21**

20b (5.75 g; 30 mmole) was added dropwise to $SOCl_2$ (20.23 g; 170 mmole) with stirring and ice-cooling. The resulting mixture was stirred for 30 min at 0°, kept overnight at r.t. and evaporated to dryness *in vacuo*. The residue was submitted to fractional distillation *in vacuo* to yield 3.78 g (65%) of **21**, b.p. 83–84°/3 torr; 98–99°/5 torr. Found: C, 34.07; H, 2.56; N, 6.68; Cl, 33.29. Calc. for $C_6H_5Cl_2NO_3$ (210.03): C, 34.31; H, 2.39; N, 6.67; Cl, 33.77%. IR (liquid film): 1750, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ6.65, s, 1H, C(4)-H; 5.6, s, 1H, CH; 3.9, s, 3H, CH_3.

Dimethyl 2,3 - bis(3 - chloroisoxazol - 5 - yl) butendioate **22**

A mixture of **21** (2.63 g; 10 mmole), potassium phtalimide (1.6 g; 11 mmole) and dry DMF (10 ml) was stirred for 1 hr at r.t. Water (30 ml) was added and the resulting mixture was chilled (0°) to precipitate 0.8 g (23%) of **22**, m.p. 215–217° (DMF). Found: C, 41.27; H, 2.50; Cl, 20.80; N, 7.80. Calc. for $C_{12}H_8Cl_2N_2O_6$ (347.11): C, 41.52; H, 2.32; Cl, 20.43; N, 8.07%. ^1H NMR (DMSO-d_6): δ7.3, s, 1H, C(4)-H; 4.0, s, 3H, CH_3. MS *m/e* 346 (10%) $2(C_6H_4ClNO_3)$; 315 (15.8) (M^+ –OCH_3); 311 (100) (M^+ –HCl); 287 (8.3) (M^+ –$COOCH_3$); 59 (47.1) ($^+O{=}C{-}OCH_3$).

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