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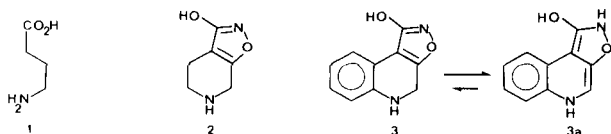
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The synthesis of a new heterocyclic compound, **3a**, combining a quinoline and an isoxazolol ring is described. The preparation involves cyclisation of the carbamate **14**, followed by concomitant deprotection of the acidic and amino functions to give compound **3a**, the stable tautomeric form of **3**.

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In our studies of new heterocyclic analogues [2] of GABA (*gamma*-aminobutyric acid) **1**, a major neurotransmitter in the central nervous system [3], we were interested in preparing derivatives of a potent GABA<sub>A</sub> receptor agonist, THIP **2** (4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol) [4], in which the crucial carboxylic function has been replaced by the isosteric 3-hydroxyisoxazole.

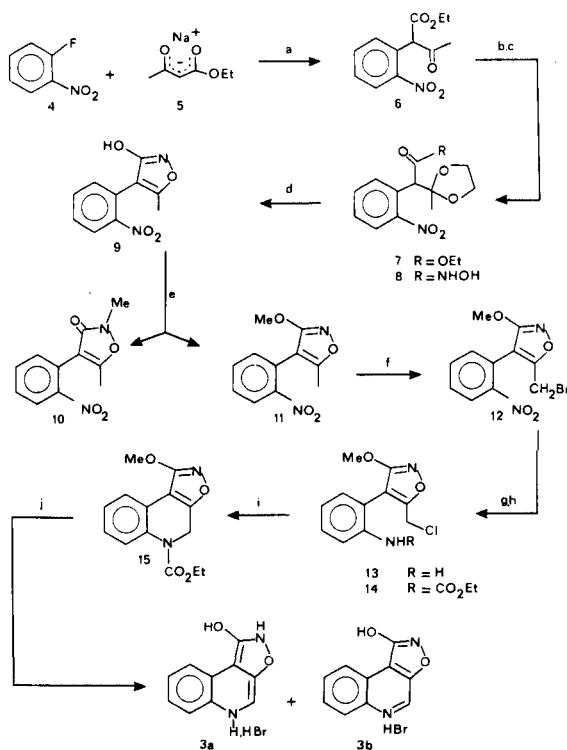
In order to study the influence of a benzene nucleus on the gabaergic activity, we chose as a model compound "benzo-THIP" **3** (1-hydroxy-4,5-dihydroisoxazolo[5,4-*c*]quinoline).



As far as we know, this type of heterocycle combining a quinoline and an isoxazolole ring has not yet been described. Only two examples of related compounds, isoxazolo[4,5-*c*]quinoline derivatives, have been reported [5,6], however, their synthetic pathways cannot be adapted to the preparation of our target compound.

In this paper, we report the first synthesis of this new heterocycle, outlined in Scheme 1.

The key step in our synthesis is the formation of isoxazolole **9** via the ethylene ketal **7** of the *beta*-ketoester **6**, the analogy with a reported sequence [7]. Compound **6** was prepared by reacting sodium enolate **5** with *o*-nitrofluorobenzene **4**. We observed that the nucleophilic displacement of aromatic fluoride was affected by the solvent. Satisfactory yields (55%) were obtained using 1-methyl-2-pyrrolidinone instead of hexamethyl phosphorous triamide (35%) according to an already reported procedure [8]. Protecting the ketone with ethylene glycol gave ketal **7** which was converted, with good yields (70%), into the corresponding hydroxamic acid **8** by treatment with hydroxylamine hydrochloride in basic medium, at 4° for 64 hours. Heating **8** in concentrated hydrochloric acid gave **9** which, treated with a solution of diazomethane, gave a separable 1:2 mixture of *N*- and *O*-methylate products **10** and **11**, which tallies with general findings [7]. Bromination of **11**



Scheme 1. a: 1-methyl-2-pyrrolidinone; b: ethylene glycol/*p*-TsOH/toluene/110°; c: KOH/MeOH/NH<sub>2</sub>OH, HCl/+4°; d: HCl/MeOH/70°; e: CH<sub>2</sub>N<sub>2</sub>/Et<sub>2</sub>O/25°; f: NBS/AIBN/CCl<sub>4</sub>/80°; g: SnCl<sub>2</sub>/HCl/MeOH/80°; h: K<sub>2</sub>CO<sub>3</sub>/ClCO<sub>2</sub>Et/acetone/25°; i: K<sub>2</sub>CO<sub>3</sub>/acetone/65°; j: HBr/AcOH/70°.

with *N*-bromosuccinimide in presence of 2,2'-azobisisobutyronitrile, gave **12**. The nitro group was reduced with tin chloride in hydrochloric acid giving the chloro compound **13** (90%), characterized mainly by its mass spectrum (*m/z* 238/240 (3/1) M<sup>+</sup>). Cyclisation with potassium carbonate in acetone to obtain **15**, required prior protection of the amino group with ethylchloroformate. The structure of compound **15** was confirmed by its <sup>1</sup>H-nmr and mass spectra, and by elemental analysis. Concomitant deprotection of the methoxy and carbamate groups in hydrobromic acid: acetic acid at 70° gave a 2:1 mixture (determined by hplc) of two hydrobromide salts **3a** and **3b**, separable by recrystallization (ethyl acetate: methanol). The proposed

structure was confirmed for **3a**, isolated at a 40% yield, on the basis of its 200 MHz  $^1\text{H}$  nmr,  $^{13}\text{C}$  nmr, mass spectra and elemental analysis. Under these conditions, the expected "benzo-THIP" **3** apparently exists only in the tautomeric form **3a** stabilized by virtue of an extended conjugated system. This was confirmed in two ways: 1) in  $^1\text{H}$ -nmr, by the absence of the methylene singlet at  $\delta = 4.95$  (N-CH<sub>2</sub>-), by the presence of a vinylic proton singlet at  $\delta = 8.81$  (N-CH=C-) and three deuterium oxide exchangeable protons; and 2) in the DEPT 90  $^{13}\text{C}$  nmr, by the presence of five tertiary and five quaternary carbons and the absence of any secondary carbons.

The biological evaluation of this new heterocycle **3a** is under way and should prove useful in structure-activity analysis of conformation restricted GABA analogues.

## EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. Elemental analyses were performed by the Service Central de Microanalyses du CNRS. Infrared spectra were run on a Philips PU 9716 spectrophotometer. The main bands are described by their frequency ( $\nu$ , cm<sup>-1</sup>) and their relative intensity (weak, medium, strong). The proton nmr spectra were obtained on a Perkin-Elmer R24B spectrometer (60 MHz) or a Bruker WP 200 SY spectrometer (200 MHz). The peaks are described in ppm downfield from tetramethylsilane (internal standard). The carbon nmr spectra were obtained with a Bruker WP 200 SY spectrometer. The Mass spectra were recorded on a LKB 2091.

### Ethyl 2-(2-Nitrophenyl)-3-oxobutyrat 6.

To a suspension of sodium hydride (21.6 g, 0.9 mole) in 1-methyl-2-pyrrolidinone (200 ml), a solution of ethyl acetoacetate (78 g, 0.6 mole) in the same solvent (200 ml) was added at 0° over 2 hours. Then a solution of 1-fluoro-2-nitrobenzene (84.6 g, 0.6 mole) in the same solvent (200 ml) was added. The reaction mixture was stirred at room temperature for 48 hours. It was then poured into ice cold water (200 ml), neutralized by the addition of dilute hydrochloric acid, and extracted with ether (3 x 200 ml). The combined organic layers were dried (magnesium sulfate), filtered and evaporated to dryness to give crude **6**. Following purification by distillation, the title compound was obtained (82.8 g, 55%), bp 130-135° (0.2 Torr), (lit [8] bp 110° 0.02 Torr); ir (carbon tetrachloride):  $\nu$  OH 3200-2700 (w),  $\nu$  CO<sub>2</sub> Et 1720 (m),  $\nu$  CO 1640 (s),  $\nu$  C=C 1600 (s),  $\nu$  NO<sub>2</sub> 1340 (s);  $^1\text{H}$ -nmr (deuteriochloroform): 1.12 (2.6 H, t, J = 7.5 Hz, OCH<sub>2</sub>CH<sub>3</sub>, enol), 1.28 (0.4 H, t, J = 7.5 Hz, OCH<sub>2</sub>CH<sub>3</sub>, ketone), 1.87 (2.6 H, s, CH<sub>3</sub>, enol), 2.39 (0.4 H, s, CH<sub>3</sub>, ketone), 3.98-4.28 (2, 15H, m, OCH<sub>2</sub>CH<sub>3</sub> + PhCH), 7.26-7.64 (3 H, m, Ph), 7.98-8.03 (1 H, m, Ph), 13.62 (0.85 H, s, OH, exchangeable deuterium oxide, enol); ms: m/z 251 (M<sup>+</sup>), 234, 209, 191, 163, 147.

### Ethyl 2-(2-Nitrophenyl)-3-(1,2-ethylenedioxy)butyrat 7.

A mixture of  $\beta$ -ketoester **6** (27.9 g, 0.108 mole), ethylene glycol (33.0 g, 0.542 mole), 4-toluenesulfonic acid (1.5 g, 0.008 mole) was refluxed in toluene (550 ml) for 48 hours, using a Dean-Stark water separator. The cold solution was neutralized by adding aqueous potassium carbonate. The organic layer was separated, washed with water then brine, and finally dried (magnesium sulfate). Removal of the solvent afforded crude **7** which was purified by chromatography (silica gel, hexane:ether, 6:4) to give pure **7** (25.1 g, 78%) as yellow crystals, mp 86-88° (from hexane); ir (carbon tetrachloride):  $\nu$  CO<sub>2</sub>Et 1725 (s),  $\nu$  NO<sub>2</sub> 1340 (s);  $^1\text{H}$ -nmr (deuteriochloroform): 1.25 (3 H, t, J = 8 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.35 (3 H, s, CH<sub>3</sub>), 3.6-4 (4 H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 4.2 (2 H, q, J = 8 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.95 (1 H, s, PhCH), 7.3-8 (4 H, m, Ph).

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>5</sub>: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.92; H, 6.06; N, 4.79.

### 2-(2-Nitrophenyl)-3-(1,2-ethylenedioxy)butyrohydroxamic Acid 8.

To a well stirred and ice cold solution of potassium hydroxide (28.5 g, 0.5 mole) in methanol (75 ml), a suspension of hydroxylamine hydrochloride (28 g, 0.8 mole) in the same solvent (100 ml) was added. The mixture was stirred at 0° for 0.5 hour. Then a solution of ester **7** (30.0 g, 0.1 mole) in the same solvent (75 ml) was added. The mixture was left at 4° for 64 hours. After the addition of glacial acetic acid (38 ml), the suspension was filtered. The filtrate was evaporated to give a solid residue which was purified by chromatography (silica gel, dichloromethane:ethyl acetate: methanol, 50:47:3) to afford pure **8** (37.0 g, 66%) as yellow crystals, mp 160-162° (from ethyl acetate:isopropyl ether); ir (chloroform):  $\nu$  NH 3450 (m),  $\nu$  OH 3400-2800 (large),  $\nu$  CO 1650 (s),  $\nu$  NO<sub>2</sub> 1340 (s);  $^1\text{H}$ -nmr (methanol-d<sub>4</sub>): 1 (3 H, s, CH<sub>3</sub>), 3.2-3.6 (4 H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 4.1 (1 H, s, PhCH), 4.4 (2 H, s, NHOH, exchangeable deuterium oxide), 7-7.8 (4 H, m, Ph).

*Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>: C, 51.07; H, 5.00; N, 9.83. Found: C, 50.82; H, 5.00; N, 9.89.

### 3-Hydroxy-4-(2-nitrophenyl)-5-methylisoxazole 9.

A solution of hydroxamic acid **8** (37 g, 0.265 mole) in methanol (225 ml) was treated with concentrated hydrochloric acid (225 ml) at 70° for 4 hours. The solvent was evaporated *in vacuo*. The residue was dissolved in water (50 ml) and extracted with chloroform (3 x 200 ml). The organic layer was dried (magnesium sulfate), filtered and evaporated to give a white solid. Recrystallization (from ethyl acetate) yielded **9** (26 g, 90%), as white crystals, mp 196-198°; ir (chloroform):  $\nu$  OH 3500 (m) 3200-2900 (large),  $\nu$  isoxazole 1640 (s),  $\nu$  NO<sub>2</sub> 1340 (s);  $^1\text{H}$ -nmr (dimethyl sulfoxide-d<sub>6</sub>): 2.2 (3 H, s, CH<sub>3</sub>), 7-7.8 (4 H, m, Ph), 11.4 (1 H, broad s, OH, exchangeable deuterium oxide).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>4</sub>: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.78; H, 3.56; N, 12.79.

### 2,5-Dimethyl-4-(2-nitrophenyl)-3-oxo-isoxazoline 10 and 3-Methoxy-4-(2-nitrophenyl)-5-methylisoxazole 11.

To a suspension of isoxazole **9** (22.0 g, 0.1 mole) in ether (200 ml) was added dropwise an ethereal solution of diazomethane at 0°. Stirring was continued at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the residue purified by chromatography (silica gel; dichloromethane:ethyl acetate, 9:1) to afford isoxazolone **11** (13.5 g, 58%), mp 71-73° (from hexane) as white crystals, and isoxazoline **10** (7.0 g, 30%), mp 172-174° (from isopropyl ether), as yellow crystals.

Compound **11** had ir (carbon tetrachloride):  $\nu$  isoxazole 1635 (s),  $\nu$  NO<sub>2</sub> 1340 (s);  $^1\text{H}$ -nmr (deuteriochloroform): 2.35 (3 H, s, CH<sub>3</sub>), 3.9 (3 H, s, OCH<sub>3</sub>), 7.25-8.1 (4 H, m, Ph).

Compound **10** had ir (chloroform):  $\nu$  isoxazoline 1645 (s),  $\nu$  NO<sub>2</sub> 1340 (s);  $^1\text{H}$ -nmr (deuteriochloroform): 2.15 (3 H, s, CH<sub>3</sub>), 3.4 (3 H, s, NCH<sub>3</sub>), 7.25-8.1 (4 H, m, Ph).

*Anal.* Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.45; H, 4.23; N, 12.11.

### 3-Methoxy-4-(2-nitrophenyl)-5-bromomethylisoxazole 12.

A solution of isoxazole **11** (10.0 g, 0.042 mole) in carbon tetrachloride (200 ml) was treated with *N*-bromosuccinimide (12.0 g, 0.068 mole) in the presence of 2,2'-azobisisobutyronitrile (0.05 g) at 80° over 48 hours. The cold suspension was filtered and the filtrate evaporated. The residue was purified by chromatography (silica gel:dichloromethane) to afford pure **12** (9.4 g, 70%) as a yellow liquid;  $^1\text{H}$ -nmr (deuteriochloroform): 3.95 (3 H, s, OCH<sub>3</sub>), 4.35 (2 H, s, CH<sub>2</sub>Br), 7.40-8.30 (4 H, m, Ph); ms: m/z 313/315 (1/1) M<sup>+</sup>, 234 (M-Br), 173.

### 3-Methoxy-4-(2-aminophenyl)-5-chloromethylisoxazole 13.

Compound **12** (6 g, 0.018 mole) was dissolved in methanol (100 ml) and treated with a solution of tin chloride dihydrate (14.4 g, 0.064 mole) in concentrate hydrochloric acid (20 ml) at 80° over 2.5 hours. The solvents were evaporated *in vacuo*. The residue was dissolved in an ice cold solu-

tion of sodium hydroxide (100 ml, 10 *N*) and extracted with dichloromethane (3 x 100 ml). The organic layer was dried (magnesium sulfate), filtered and evaporated. The residue was purified by chromatography (silica gel:dichloromethane) to afford pure **13** (4 g, 95%) as a yellow liquid; <sup>1</sup>H-nmr (deuteriochloroform): 3.75 (2 H, s, NH<sub>2</sub>, exchangeable deuterium oxide), 3.95 (3 H, s, OCH<sub>3</sub>), 4.4 (2 H, s, CH<sub>2</sub>Cl), 6.6-7.3 (4 H, m, Ph); ms: m/z 238/240 (3/1) M<sup>+</sup>, 203 (M-Cl).

#### 3-Methoxy-4-(2-*N*-ethoxycarbonylamino)phenyl)-5-chloromethylisoxazole **14**.

To an ice cold solution of amine **13** (3.2 g, 0.013 mole) in acetone (20 ml), a solution of potassium carbonate (2.6 g, 0.018 mole) in water (10 ml) followed by ethyl chloroformate (3 ml, 0.028 mole) was added. The mixture was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuo*, the residue was dissolved in water (20 ml) and extracted with ether (3 x 50 ml). The combined extract was dried (magnesium sulfate) and evaporated. The residue was purified by chromatography (silica gel, dichloromethane:ethyl acetate, 98:2) to afford pure **14** (3.6 g, 90%), as yellow crystals, mp 73-75° (from petroleum ether); ir (carbon tetrachloride): ν NH 3400 (m), ν CO<sub>2</sub>Et 1725 (s); <sup>1</sup>H-nmr (deuteriochloroform): 1.25 (3 H, t, J = 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.05 (3 H, s, OCH<sub>3</sub>), 4.20 (2 H, q, J = 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 6.65 (1 H, broad s, NH), 7.10-8.05 (4 H, m, Ph); ms: m/z 310/312 (3/1) M<sup>+</sup>.

*Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 54.11; H, 4.87; N, 9.02. Found: C, 54.39; H, 4.95; N, 9.08.

#### *N*-Ethoxycarbonyl-1-methoxy-4,5-dihydroisoxazolo[5,4-*c*]quinoline **15**.

A solution of compound **14** (2.76 g, 8.9 mmoles) in acetone (50 ml) and potassium carbonate (1.23 g, 8.9 mmoles) was refluxed for 10 hours. The solvent was evaporated and the residue was dissolved in water (20 ml) and extracted with dichloromethane (3 x 200 ml). The organic layer was dried (magnesium sulfate) and evaporated. The residue was purified by chromatography (silica gel, hexane:ether, 6:4) to give pure **15** (2.25 g, 92%) as a white powder, mp 94-96° (from petroleum ether); ir (carbon tetrachloride): ν CO<sub>2</sub>Et 1700 (s), ν isoxazole 1645 (m); <sup>1</sup>H-nmr (deuteriochloroform): 1.30 (3 H, t, J = 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.05 (3 H, s, OCH<sub>3</sub>), 4.25 (2 H, q, J = 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.95 (2 H, s, NCH<sub>2</sub>), 7.1-7.7 (4 H, m, Ph); ms: m/z 274 (M<sup>+</sup>), 229 (M-OEt), 201 (M-CO<sub>2</sub>Et).

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 61.31; H, 5.15; N, 10.11. Found: C, 61.58; H, 5.30; N, 10.49.

#### Hydrobromide of 1-Hydroxy-2*H*,5*H*-dihydroisoxazolo[5,4-*c*]quinoline **3a**.

The carbamate **15** (450 mg, 1.6 mmoles) was treated at 70° with a solution of hydrobromide acid in glacial acetic acid (7 ml, 33%) over 6 hours. After evaporation to dryness *in vacuo*, the residue was treated with the same reagent (7 ml) for a further 5 hours. After cooling at room temperature, the salt formed was filtered and washed with acetic acid (5 ml) and ether (20 ml). After three recrystallizations (from ethyl acetate:methanol) **3a** was obtained pure (190 mg, 45%) as yellow crystals, mp 240-243°; ir (potassium bromide): ν NH 3300 (m) 3100 (m), ν OH 2900-2400 (broad), ν C=COH 1660 (s), ν C=C 1600 (w) 1550 (m); <sup>1</sup>H-nmr (dimethylsulfoxide-*d*<sub>6</sub>): 7.68-7.77 (2 H, m, Ph), 7.82-7.88 (1 H, m, Ph), 7.89-8.12 (3 H, m, Ph + 2 NH, 2 H exchangeable with deuterium oxide), 8.81 (1 H, s, PhNCH), 10.8 (1 H, broad s, OH, exchangeable with deuterium oxide); <sup>13</sup>C-nmr (methanol-*d*<sub>4</sub>): 122.75, 127.41, 129.17, 132.84, 133.82, 136.16, 137.66, 139.33, 150.18, 167.98.

*Anal.* Calcd. for C<sub>10</sub>H<sub>7</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.53; H, 3.27; N, 10.39.

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#### REFERENCES AND NOTES

- [1] This work was presented at the Second Belgian Organic Synthesis Symposium, Ghent, 16-20 May, 1988.
- [2] U. S. Patent Pending, G. Leclerc, B. Ruhland, G. Andermann, G. De Burlet, M. Dietz.
- [3] P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod, eds, "Gaba-Neurotransmitters Pharmacological, Biochemical and Pharmacological Aspects", Munksgaard, Copenhagen, 1979.
- [4] P. Krogsgaard-Larsen, G. A. R. Johnson, D. Lodge and D. R. Curtis, *Nature* (London) **268**, 53 (1977).
- [5] T. Moriwake and H. Namba, *J. Med. Chem.*, **11**, 636 (1968).
- [6] R. T. Coutts, J. G. Mukherjee, R. A. Abramovitch and M. A. Brewster, *J. Chem. Soc. (C)*, 2207 (1969).
- [7] R. Jacquier, C. Petrus, F. Petrus and J. Verducci, *Bull. Soc. Chim. France*, 1970 (1978).
- [8] M. H. Creuzet, C. Feniou, F. Guichard and G. Prat, *Brev. Fr.* 800,3774.