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POLYNUCLEAR ISOXAZOLE TYPES—IV

THE SYNTHESIS OF ISOXAZOLO[4.5-b]PYRAZINES[1]

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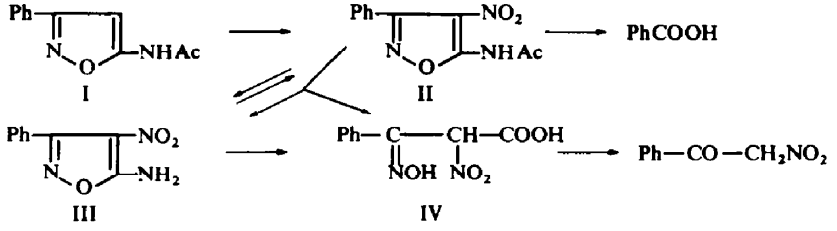
Abstract—The synthesis of 3-phenyl-4,5-diaminoisoxazole from 3-phenyl-5-acetylaminoisoxazole in a three-step sequence has been described. The reaction of the diaminoisoxazole with several α-diketones represents a convenient route to isoxazolo [4.5-b] pyrazine derivatives.

WHILE several examples of the isoxazolopyridazine and isoxazolopyrimidines ring systems have been described, very little is known about the structurally related isoxazolopyrazine system. Recently while the present work was in progress, two isoxazoloquinoxalines were prepared by oximation of 2-carboxy (or carbamide)3-acylquinoxalines.[2]

There are three possible synthetic routes to the isoxazolopyrazine ring system: cyclization of a suitable pyrazine derivative with formation of the isoxazole ring, synthesis of an isoxazolin-4,5-dione and subsequent condensation with 1,2-diamines, or synthesis of 4,5-diaminoisoxazoles and subsequent condensation with α-dicarbonyl compounds. As a convenient method for the introduction and subsequent reduction of a nitro group in the 4-position of the isoxazole ring[3] was available, the third route was chosen.

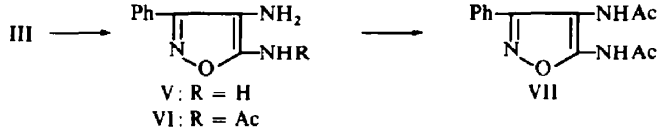
The most convenient intermediate, 3-phenyl-5-acetylaminoisoxazole (I),[4] was nitrated in good yield to the 4-nitroderivative (II), the structure of which was confirmed by oxidative degradation to benzoic acid without trace of nitrobenzoic acid.

Quantitative deacetylation of II was accomplished by heating the product with dil sulphuric acid. Treatment of the resulting 3-phenyl-4-nitro-5-aminoisoxazole (III) with acetic anhydride gave the starting material (II). Alkaline hydrolysis with hot 5% sodium hydroxide gave, besides a small amount of the nitroamino derivative (III), a product m.p. 117° dec and this same product was obtained from the alkaline treatment of III. IR data (ν_{OH} 3465, ν_{CO} 1725, ν_{NO_2} 1490, 1258 cm^{-1}), solubility in bicarbonate solution and hydrolysis with contemporary decarboxylation to ω-nitroacetophenone suggested the known oxime of α-nitrobenzoylacetic acid (IV)[5] as the

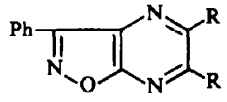


structure for this product. This was confirmed by direct comparison with an authentic sample.

Reduction of III with $NaBH_4$ in presence of Pd/C yielded the unstable 3-phenyl-4,5-diaminoisoxazole (V), which could be isolated as the monohydrochloride. Treatment of the base V with acetic anhydride gave the 4,5-diacetyl derivative (VII). Structure of the latter was confirmed by its preparation from 3-phenyl-4-nitro-5-acetylaminoisoxazole (II) by reduction to the monoacetyl derivative (VI) and subsequent acetylation.

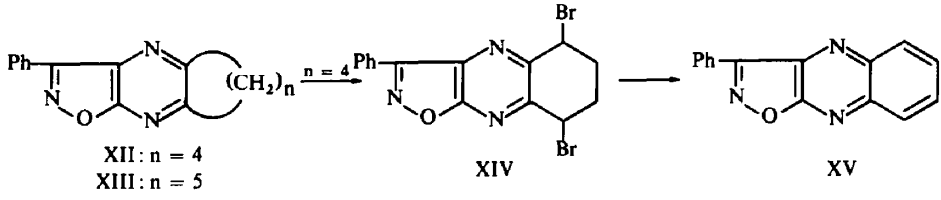


The reactivity of the diamine V toward several α-diketones resembles that of *o*-phenylenediamine. Very good yields of the isoxazolo[4.5-b]pyrazines (VIII–XIII) have been obtained by condensation with glyoxal, diacetyl, benzil, 1,4-dibromobutan-2,3-dione, cyclohexan-1,2-dione and cycloheptan-1,2-dione. Compound XI was also prepared *via* bromination of IX with N-bromosuccinimide.



VIII: R = H; X: R = Ph
IX: R = Me XI: R = CH_2Br

Bromination of 3-phenyl-4,5,6,7-tetrahydroisoxazolo[4.5-b]quinoxaline (XII) with N-bromosuccinimide yielded a dibromo derivative, for which structure XIV was considered. Treatment of this dibromo derivative with triethylamine finally afforded the known[2] 3-phenylisoxazolo[4.5-b]quinoxaline (XV).



XII: n = 4
XIII: n = 5
XIV
XV

EXPERIMENTAL

All m.ps are uncorrected. IR spectra: Nujol mulls, Perkin–Elmer 257 spectrophotometer. Microanalyses: by Dr. Lucia Maggi Dacrema; UV spectra: by Dr. Maria De Bernardi.

3-Phenyl-4-nitro-5-acetylaminoisoxazole (II)

(a) A soln of HNO_3 (*d* 1·52; 60 ml) in Ac_2O (600 ml) was added at −10° under vigorous stirring (1 hr) to a suspension of powdered I (239 g) in Ac_2O (3000 ml). After standing at room temp for 12 hr, the ppt was filtered off and dried (116·5 g). From the mother liquor diluted with water (20 l.) a second fraction of the same product (81·7 g) was collected (total, 197·2 g; 67·5%).* Crystallization from EtOH gave yellow needles, m.p. 165–166°. (Found: C, 53·17; H, 3·99; N, 16·97. Calc. for $C_{11}H_9N_3O_4$: C, 53·44; H, 3·67; N, 17·00%); IR: 3323 (NH); 1747 (CO).

* Possible unchanged starting material can be separated from II by treatment with Na_2CO_3 aq, in which it is insoluble.

(b) The same product was obtained by treatment of III (0·1 g) with Ac_2O (5 ml) and H_2SO_4 (traces) for 2 hr at 90°, followed by decomposition with ice.

Oxidation of 3-phenyl-4-nitro-5-acetylaminoisoxazole

A suspension of II (0·5 g) in water (70 ml) and powdered $KMnO_4$ (2 g) was heated for 6 hr over a steam bath. After standing overnight the excess oxidant was destroyed by addition of Na_2SO_3 and the filtered solution, concentrated to 10 ml, was acidified with conc HCl. The ppt (0·1 g) was filtered off dried and sublimed at 70°/14 mm, yielding a product m.p. 121–122°, identical in every respect with a sample of benzoic acid.

3-*Phenyl*-4-*nitro*-5-*aminoisoxazole* (III)

A mixture of II (20 g) and 20% H_2SO_4 aq (300 ml) was heated under reflux 4 hr until heavy brown oily drops covered the bottom of the flask. After cooling, soft cream-coloured needles separated from the soln and the oil solidified. The crude III was filtered off, washed with water, dried and recrystallized from diisopropyl ether as light yellow small prisms, m.p. 112–114° (14 g, 87%). (Found: C, 53·14; H, 3·53; N, 20·57. Calc. for $C_9H_7N_3O_3$: C, 52·68; H, 3·44; N, 20·48%); IR: 3385, 3240, 3180, 3115 ($NH_2 \rightleftarrows NH$) 1660, 1653 (C=N).

Oxime of α-*nitrobenzoylacetic acid* (IV)

(a) A soln of II (4 g) in 5% NaOH aq (30 ml) was warmed at 60° over a steam bath for 6 hr; filtration of the cooled mixture gave 0·8 g (23·5%) of III (m.p. and mixed m.p. identical).

After an additional 10 hr heating, a small volume of Et_2O added to the cooled soln caused the separation of a Na-salt as white needles (1·4 g) (alkaline residual products after calcination). After dissolving the Na-salt in water (25 ml) and carefully acidifying with dil HCl, IV (1 g, 27·2%) was precipitated as colourless needles, m.p. 117° dec (from diisopropyl ether with a few drops of EtOH), identical in IR spectrum and m.m.p. with an authentic sample.[5]

(b) The same product was obtained from III (1 g) and 5% NaOH aq (5 ml) by heating for 2 hr over a steam bath and separating IV as described under (a).

Hydrolytic cleavage of IV

Compound IV (0·4 g) was suspended in 20% H_2SO_4 aq (30 ml) and heated for 2 hr over a steam bath. After the evolution of CO_2 ceased, the reaction mixture was very slowly cooled to room temp and the bright colourless platelets, m.p. 103–104° (diisopropyl ether) which separated were identical in every respect with a sample of ω-nitroacetophenone.[6]

3-*Phenyl*-4,5-*diaminoisoxazole* (V) *monohydrochloride.* To a stirred solution of III (5 g) in dioxan distilled over $NaBH_4$ (150 ml), a suspension of 10% Pd–C (0·2 g) in water (10 ml) was added under a slow N_2 flow and cooling to 10°.

During 1·5 hr a soln of $NaBH_4$ (2·5 g) in water (10 ml) was added dropwise and stirring was continued for an additional 4 hr. The reaction mixture, after removal of the catalyst by filtration, was concentrated under mild conditions to a small volume, diluted with water and extracted several times with ether. The combined ether extracts, dried over $CaCl_2$,* were saturated with gaseous dry HCl, yielding 2 g of V monohydrochloride, m.p. 120° dec, which was used without further purification. (Found: C, 50·69; H, 5·06; N, 19·83; Cl, 16·62. Calc. for $C_9H_{10}N_3OCl$: C, 51·07; H, 4·76; N, 19·86; Cl, 16·75%).

3-*Phenyl*-4,5-*diacetylaminoisoxazole* (VIII)

(a) The monohydrochloride (0·1 g) was dissolved in Ac_2O (30 ml) over a steam bath. The faint violet-coloured soln, decomposed with iced water (20 ml), gave white needles of VII (0·08 g), m.p. 202–203° (EtOH). (Found: C, 60·55; H, 5·24; N, 16·30. Calc. for $C_{13}H_{13}N_3O_3$: C, 60·22; H, 5·05; N, 16·21%); IR: 3333, 3135 (NH); 1698, 1672 (CO).

(b) The same product was obtained under similar experimental conditions from VI (0·05 g) and Ac_2O (1 ml).

* When the ethereal extracts of V were dried with Na_2SO_4 or $MgSO_4$, the monohydrochloride came down as an oily paste.

3-Phenyl-4-amino-5-acetylaminoisoxazole (VI)

A suspension of 10% Pd–C (0·1 g), in water (10 ml), was added to a soln of II (1 g) in dioxan (100 ml) and to the cooled mixture, in an atmosphere of N_2, a soln of $NaBH_4$ (1·0 g) in water was added (0·5 hr) under vigorous stirring which was continued for an additional 2 hr. The reaction mixture, after removal of the catalyst, was concentrated under mild conditions to a small volume, diluted with water (20 ml) and carefully neutralized to pH 7 with dil H_2SO_4. After standing overnight at 0°, 0·7 g of VI separated as white small prisms, m.p. 105–106° (BzH). (Found: C, 60·95; H, 5·37; N, 19·51. Calc. for $C_{11}H_{11}N_3O_2$: C, 60·82; H, 5·10; N, 19·35%); IR: 3338; 3230, 3120 (NH_2 and NH); 1695 (CO).

3-Phenylisoxazolo[4.5-b]*pyrazine* (VIII)

To a stirred soln of V monohydrochloride (0·5 g) in water (5 ml) a soln of glyoxal–bisulphite complex (from glyoxal 0·2 g and $NaHSO_3$ 0·35 g) in water (5 ml) was added. After standing overnight at 0°, the light cream-coloured ppt was filtered off and dried. Purification was achieved by elution on silicagel through a short column using benzene as eluant, collecting VIII (0·5 g) as white needles, m.p. 143·5–144·5° (diisopropyl ether). (Found: C, 67·07; H, 3·71; N, 21·38. Calc. for $C_{11}H_7N_3O$: C, 67·00; H, 3·58; N, 21·31%); UV (EtOH): λ_{max} 230, 301 mμ (log ε 4·04, 4·07).

3-Phenyl-5,6-dimethylisoxazolo[4.5-b]*pyrazine* (IX)

To a soln of V monohydrochloride (0·5 g) in water (10 ml) diacetyl (1 ml) was added under vigorous magnetical stirring. After standing for 12 hr at 0° the white ppt (0·5 g) was filtered off and dried; crystallization from diisopropyl ether gave IX as white needles, m.p. 134–135°. (Found: C, 69·12; H, 4·94; N, 18·90. Calc. for $C_{13}H_{11}N_3O$: C, 69·32; H, 4·92; N, 18·66%); UV (EtOH): λ_{max} 228, 306, 327 (f) mμ (log ε 4·13, 4·13, 3·95).

3,5,6,-Triphenylisoxazolo[4.5-b]*pyrazine* (X)

To a saturated ethanolic soln of benzil (0·7 g), V monohydrochloride (0·3 g) was added at room temp with vigorous stirring. The soln obtained was chilled and after standing overnight, 0·3 g of X were collected; recrystallization from benzene gave colourless small prisms, m.p. 216–217°. (Found: C, 79·09; H, 4·39; N, 12·02. Calc. for $C_{23}H_{15}N_3O$: C, 79·07; H, 4·33; N, 12·03%); UV (dioxan): λ_{max} 238, 256 mμ (log ε 4·37, 4·21).

3-Phenyl-5,6,7,8-tetrahydroisoxazolo[4.5-b]*quinoxaline* (XII)

To a magnetically stirred ethereal soln of V (1·5 g), cooled in an ice-bath and kept in a dark place, 1,2-cyclohexanedione (1·3 g) in anhydrous ether (30 ml) was added. After 36 hr removal of the solvent left an oily residue, which after washing with warm water gave a deep red solid which recrystallized from EtOH as cream-coloured needles (0·8 g), m.p. 156–157°. (Found: C, 71·85; H, 5·44; N, 16·84. Calc. for $C_{15}H_{13}N_3O$: C, 71·69; H, 5·21; N, 16·72%); UV (EtOH): λ_{max} 230, 313, 333 (f) mμ (log ε 4·13, 4·16, 3·97).

3-Phenyl-6,7,8,9-tetrahydroisoxazolo[4.5-b]5H-*cyclohepta*[b]*pyrazine* (XIII)

Using a similar procedure, an ethereal soln of V (1·0 g) and 1,2-cycloheptanedione (1·5 g) yielded XIII as white needles (1·0 g), m.p. 148–149° (MeOH). (Found: C, 72·17; H, 5·87; N, 15·98. Calc. for $C_{16}H_{15}N_3O$: C, 72·43; H, 5·70; N, 15·84%); UV (EtOH): λ_{max} 228, 308, 328·5 (f) mμ (log ε 4·15, 4·17, 3·99).

3-Phenyl-5,6-bis(bromomethyl)isoxazolo[4.5-b]*pyrazine* (XI)

(a) To a magnetically stirred ethereal soln of V (1·0 g), 1,4-dibromo-2,3-butanedione (2·0 g) dissolved in anhydrous ether (50 ml) was added. After nearly 1 hr, a ppt separated and after standing overnight at room temp, XI (1·8 g) was collected and crystallized as ivory platelets m.p. 166–167° (EtOH). (Found: C, 41·06; H, 2·52; N, 11·12; O, 4·17; Br, 41·96. Calc. for $C_{13}H_9N_3OBr_2$: C, 40·78; H, 2·37; N, 10·97; O, 4·20; Br, 41·70%); M.W. (mass spectrum) 383; UV (EtOH): λ_{max} 234, 315 mμ (log ε 4·29, 4·14).

(b) To a soln of IX (0·3 g) in CCl_4 (10 ml), N-bromosuccinimide (0·55 g) and a trace of α,α′-azoisobutyronitrile were added and the mixture was refluxed 8 hr, until the starting material disappeared on TLC. The deep yellow coloured soln was filtered and the solvent removed. The residue (0·5 g) crystallized from EtOH, m.p. 166–167°, undepressed with a sample of XI prepared as described under (a).

3-Phenyl-5,8-dibromo-5,6,7,8-tetrahydroisoxazolo[4.5-b]*quinoxaline* (XIV)

To a soln of XII (0·6 g) in CCl_4 (200 ml), N-bromosuccinimide (0·95 g) and a trace of α,α′-azoisobutyro-

nitrile were added and the mixture refluxed 2 hr. The deep yellow-coloured suspension was cooled with ice and the solid separated by filtration. After drying, the solvent was removed at room temp and the residue (1·0 g), dissolved in CCl_4 (30 ml). Cooling and addition of diisopropyl ether (60 ml) precipitated light cream-coloured small prisms of XIV, m.p. 197–198°. (Found: C, 44·32; H, 2·88; N, 9·94; Br, 38·74. Calc. for $C_{15}H_{11}N_3OBr_2$: C, 44·05; H, 2·71; N, 10·28; Br, 39·06%); UV (EtOH): λ_{max} 233, 323 mμ (log ε 4·29, 4·09).

3-*Phenylisoxazolo*[4.5-b]*quinoxaline* (XV)

An ethanolic soln of XIV (0·4 g) and Et_3N (0·4 g) was gently heated under reflux for 1 hr. The reaction mixture was poured onto iced HCl. The crude brown product, filtered off and dried, was chromatographed on preparative TLC plates (cm 30 × 45—1 mm Kieselgel with UV indicator); after elution with cyclohexane–AcOEt (70:30) the heavy fluorescent (254 mμ) small strip at R_f 0·45 was collected and eluted with MeOH yielding XV (50 mg), absolutely identical in m.p., mixed m.p. and IR spectrum with a sample prepared according to literature.[2]

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