New Syntheses of Condensed Heterocycles from Isoxazole Derivatives. V. Pyrrolo[3,4-*b*]pyridin-4-ones

G. Dattolo, E. Aiello, S. Plescia, G. Cirrincione and G. Daidone

Istituto di Tecnica Farmaceutica dell'Università di Palermo, Via Archirafi, 32, 90123 Palermo, Italy

Received June 3, 1977

Hydrogenolysis with Raney-Nickel or iron powder in acetic acid of 2,5-diphenyl-4-nitro-3-(3,5-R,R-4-isoxazolyl)pyrrolyl ketones, prepared by the Grignard reaction of 2,5-diphenylpyrrole and 3,5-R,R-4-isoxazolecarboxilic acid chlorides followed by nitration, afforded directly the desired 6*H*-pyrrolo[3,4-*b*]pyridin-4-ones.

J. Heterocyclic Chem., 14, 1021 (1977)

In connection with our continuing interest in isoxazole chemistry (1-3) and with a study directed toward the synthesis of heterocycles fused to the pyrrole nucleus (4), we wish to report a new synthesis of pyrrolo[3,4-*b*]-pyridin-4-ones. The basic synthetic approach to the desired ring system was established by a route starting from the key intermediates prepared by the Grignard reaction of pyrroles and acyl chlorides. At this point it was desirable to explore the scope of this reaction utilizing the 3,5-R,R-4-isoxazolecarboxilic acid chlorides as acylating agents, both from the point of view of the production of compounds of biological importance incorporating a pyrrole nucleus and potentially interesting bicyclic system acetyl and benzoyl-substituted pyrrolo-[3,4-*b*]pyridinones of type VI.

The starting materials, 2,5-diphenyl-3-(3,5-R,R-4-isoxazolyl)pyrrolyl ketones (IIIa,b), were prepared by the Grignard reaction using 2,5-diphenylpyrrole (I) and IIa,b. Nitration of IIIa,b in nitromethane with a mixture of nitric acid and acetic anhydride at -15° gave the nitro derivatives IVa,b in 75-80% yield. Catalytic hydrogenation on W-2-Raney-Nickel (Method A) of IVa,b caused reduction of the nitro group and isoxazole ring opening (5) to give directly in low yield (10%) the desired pyrrolo-pyridinones (VIa,b).

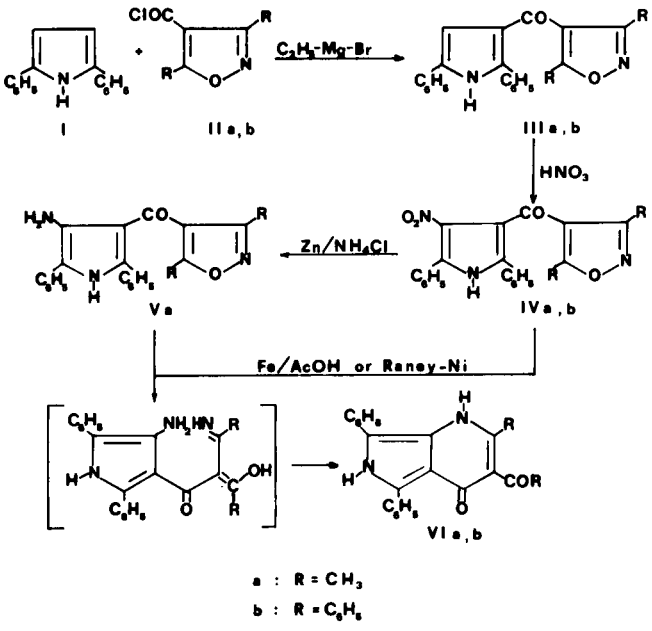
The structure of the products VIa,b were readily determined on the basis of the nmr, ir spectra and elemental analytical data. The ir spectra showed two NH bands at 3400-3440 and 3200-3260 cm^{-1} and C=O bands at 1610-1640 and 1660-1670 cm^{-1} due to the cyclic carbonyl group and the acetyl or the benzoyl group, respectively.

The low yield of compounds VIa,b prompted us to explore another possible route leading to VIa,b, which accounted for the preliminary reduction of the nitro group, ring opening of the isoxazole nucleus and subsequent cyclization. However, with iron powder in acetic acid, as the reducing agent, (Method B), surprisingly, we succeeded in preparing VIa,b directly in good yield in one step. Moreover, a review of literature revealed that this was the first example of isoxazole ring opening with iron in acetic acid.

When reduction of compound IVa, taken as an example, was carried out in ethanol-water medium with zinc and ammonium chloride, ring opening did not occur, but the amino derivative Va only was isolated, as expected.

The structure proof of Va rested upon its correct elemental analysis as well as spectroscopic data (nmr, ir). In fact, the nmr spectrum exhibited a NH_2 signal at δ 5.10 (2H), exchangeable with deuterium oxide, beside other signals for substituent protons. The infrared spectrum showed ν C=O at 1620 cm^{-1} due to the carbonyl group and bands at 3200, 3370, 3470 cm^{-1} attributable to the NH and NH_2 groups. By the action of Raney-Nickel or iron in acetic acid on the amino derivatives Va, VIa was obtained directly.

Most of the compounds described in this work were tested for their biological and pharmacological properties by Bristol Laboratories, Syracuse, New York. Only compound IVa demonstrated noteworthy activity, histamine release inhibition, at MED of 50 mcg./ml. using an "in vitro" assay.



EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were determined in nujol mulls with a Perkin-Elmer 137 spectrophotometer; nmr spectra (DMSO-d_6, unless otherwise specified) were obtained with a Jeol C-60 spectrometer (TMS as the internal reference).

2,5-Diphenyl-3-(3,5-R,R-4-isoxazolyl)pyrrolyl Ketones (IIIa,b).

To a stirred mixture of 2,5-diphenylpyrrole (40 mmoles), absolute ether (150 ml.) and magnesium (40 mmoles), an ethereal solution of ethyl bromide (40 mmoles) was added dropwise with cooling in an ice bath as evolution of ethane began. The mixture was then refluxed for one hour and after cooling at 0°, 3,5-R,R-isoxazole-4-carboxylic acid chloride (6,7) (IIa,b) in absolute ether (300 ml.) was added dropwise with stirring. After standing at room temperature overnight, the solution was refluxed for one hour and the precipitate was filtered off, shaken with aqueous ammonium chloride solution and then with an aqueous sodium bicarbonate soluiton. The residue was air dried and recrystallized from ethanol, yield 15-22%.

IIIa.

This compound had m.p. 253°; ir, cm^{-1}: 3230 (NH) 1630 (CO); nmr, δ: 2.20 (6H, s, 2 x CH_3) 6.88 (1H, d, CH, J = 1.5 Hz) 7.15-8.00 (10H, m, 2 x C_6H_5) 11.82 (1H, d, NH, J = 1.5 Hz).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.38; H, 5.42; N, 8.11.

IIIb.

This compound had m.p. 188°; ir, cm^{-1}: 3200 (NH) 1590 (CO); nmr, δ: 6.95 (1H, d, CH, J = 0.75 Hz) 7.10-7.90 (20H, m, 4 x C_6H_5) 12.00 (1H, d, NH, J = 0.75 Hz).

Anal. Calcd. for $C_{32}H_{22}N_2O_2$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.40; H, 4.85; N, 5.98.

2,5-Diphenyl-4--nitro-3-(3,5-R,R-4-isoxazolyl)pyrrolyl Ketones (IVa,b).

A mixture of nitric acid (d = 1.52) (20 mmoles) and acetic anhydride (20 mmoles) was added dropwise with stirring to a suspension of IIIa,b (20 mmoles) in nitromethane (40 ml.) at -15°. The resultant solution was allowed to warm to room temperature, neutralized with sodium bicarbonate and extracted with ether (4 x 100 ml.). The extracts were dried (sodium sulfate), yield 75-80% of IVa,b, which were recrystallized from ethanol.

IVa.

This compound had m.p. 212°; ir, cm^{-1}: 3180 (NH) 1630 (CO); nmr, δ: 2.22 (3H, s, CH_3) 7.25-7.90 (10H, m, 2 x C_6H_5) 12.80 (1H, broad, NH).

Anal. Calcd. for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.42; N, 10.85. Found: C, 68.35; H, 4.62; N, 10.98.

IVb.

This compound had m.p. 252°; ir, cm^{-1}: 3110 (NH) 1650 (CO); nmr, δ: 7.20-7.70 (20H, m, 4 x C_6H_5) 12.40 (1H, broad, NH).

Anal. Calcd. for $C_{32}H_{21}N_3O_4$: C, 75.13; H, 4.14; N, 8.22. Found: C, 75.26; H, 4.22; N, 8.30.

2,5-Diphenyl-4-amino-3-(3,5-dimethyl-4-isoxazolyl)pyrrolyl Ketone (Va).

A mixture of 1 g. of IVa in ethanol (50 ml.) and water (10 ml.), 5 g. of zinc (chips) and 10 g. of ammonium chloride, was refluxed for one hour. After a further addition of 5 g. of zinc and 10 g. of ammonium chloride the mixture was refluxed for 5 hours. After adding water, the mixture was made alkaline with ammonia and was extracted with ether (4 x 100 ml.). The extracts were dried (sodium sulfate) and evaporated to give a solid residue which was recrystallized from ethanol, yield 80%, m.p. 95-96°; ir, cm^{-1}: 3200, 3370, 3470 (NH and NH_2) 1620 (CO); nmr, δ: 1.97 (3H, s, CH_3) 2.22 (3H, s, CH_3) 5.10 (2H, s, NH_2) 7.10-7.80 (10H, m, 2 x C_6H_5) 11.30 (1H, s, NH).

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.01; H, 5.42; N, 11.78.

Pyrrolo[3,4-*b*]pyridinones (VIa,b).

Method A.

A mixture of 2 mmoles of IVa,b or Va, 75 ml. of ethanol and *ca.* 1 g. of Raney-Nickel (8) was hydrogenated in a Parr apparatus at 45 psi for 8 hours at room temperature. Removal of the catalyst and evaporation of ethanol left a brown residue which was purified by column chromatography (20 x 3 cm) of silica gel (25 g.). Elution with benzene-ethyl acetate (95:5) gave a product VIa,b which was recrystallized from ethanol (yield 10%).

VIa.

This compound had m.p. 299°; ir, cm^{-1}: 3440 (NH) 3260 (NH) 1660 (CO) 1640 (CO); nmr (pyridine-d_5), δ: 2.70 (3H, s, CH_3) 3.00 (3H, s, CH_3) 7.10-8.60 (10H, m, 2 x C_6H_5) 11.70 (1H, broad, NH) 13.30 (1H, broad, NH).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.44; N, 8.20.

VIb.

This compound had m.p. 320°; ir, cm^{-1}: 3400 (NH) 3200 (NH) 1670 (CO); nmr, δ: 6.90-7.70 (20H, m, 4 x C_6H_5) 10.80 (1H, broad, NH) 12.50 (1H, broad, NH).

Anal. Calcd. for $C_{32}H_{22}N_2O_2$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.40; H, 4.80; N, 6.00.

Method B.

A solution of 2 mmoles of IVa,b or Va in acetic acid (50 ml.) was heated at 70°, when iron powder (1.5 g.) was added over a period of one hour. After the addition was complete, the mixture was kept at 70° for 7 hours, then poured into crushed ice and extracted with ethyl acetate. The organic layer was dried (sodium sulfate) and evaporated under reduced pressure to give a solid residue which was purified by column chromatography (20 x 3 cm) of silica gel (25 g.). Elution with benzene-ethyl acetate (95:5) gave the desired product, which was recrystallized from ethanol, yield 50-60%. The products were identical (m.p. and mixed m.p., ir, nmr) with those obtained by the above method A.

REFERENCES AND NOTES

(1) E. Aiello, *J. Heterocyclic Chem.*, **8**, 1035 (1971).

(2) E. Aiello, O. Migliara and V. Sprio, *ibid.*, **9**, 1119 (1972).

(3) E. Aiello, O. Migliara, L. Ceraulo and S. Petruso, *ibid.*, **11**, 339 (1974).

(4) E. Aiello, G. Dattolo and S. Plescia, *ibid.*, **13**, 645 (1976).

(5) G. S. d'Alcontres, *Gazz. Chim. Ital.*, **80**, 441 (1950).

(6) F. P. Doyle and J. H. C. Nayler, U. S. Patent, 2,996,501; Appl. Apr. 10, 1961; British Patent, March 31, 1961; *Chem. Abstr.*, **56**, P5972g (1962).

(7) M. Betti and S. Berlingozzi, *Gazz. Chim. Ital.*, **51**, II 229 (1921).

(8) R. L. Augustine, "Catalytic Hydrogenation", M. Dekker, Inc., New York 1965, p. 147.