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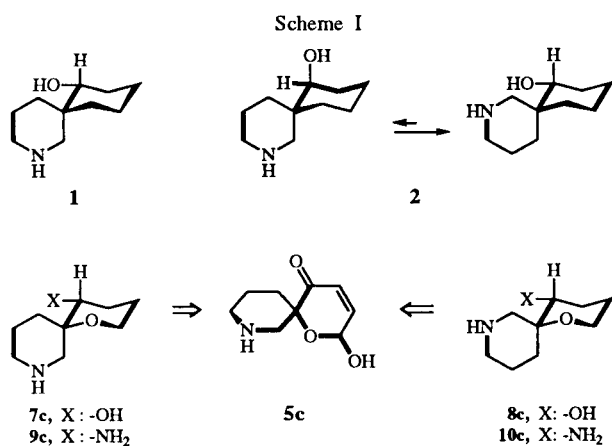
2-Hydroxy-8-(or 9-)aza-1-oxaspiro[5.5]undec-3-en-5-ones derived from their corresponding 2-furfuryl alcohols were used as key intermediates for the convenient synthesis of several novel 8- and 9-aza-1-oxaspiro[5.5]undecane derivatives.

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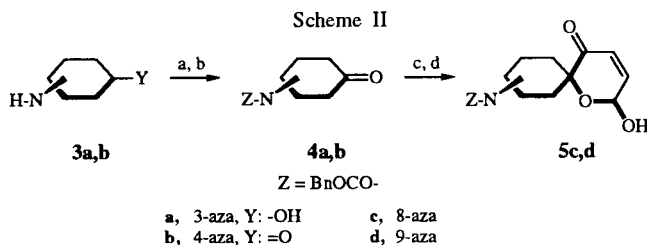
Azaspiro[5.5]undecanes are important structural features of a growing variety of naturally occurring compounds with considerable current importance and interest [1]. Especially the 2-azaspiro[5.5]undecane moiety comprise the skeleton of ($\pm$)-Nitramine **1** and its diastereoisomer ($\pm$)-Isonitramine **2**, which are alkaloids isolated from plants of the *Nitraria* family [2] and have shown considerable biological activity [3]. These unusual carbon skeletons have also reported to be components of molecules with significant biological activity such as histrionicotoxin [4], antiarrhythmic drug candidate MK-499 [5], σ -receptor ligands [6] *etc.* Thus, they have attracted a great deal of synthetic work directed towards the facile and convenient synthesis of their derivatives and analogues [7].

incorporation of a wide variety of substituents and functionalities leading to a wide variety of derivatives.

As substrates for our synthetic route we have used the 3- and 4-(1-benzoyloxycarbonyl) piperidinones **4a** and **4b** which were prepared almost quantitatively from the readily available 3-piperidinol **3a** (the corresponding ketone is unstable) and 4-piperidinone **3b** respectively. Treatment of **4a,b** with 2-furyllithium yielded the corresponding 2-furfurylalcohols, which in the presence of 3-chloroperbenzoic acid (*m*-CPBA) undergo an oxidation-rearrangement sequence on the furan nucleus [9] affording the pyranone derivatives **5c,d** (Scheme II). The overall yield for the synthesis of these intermediates was 56% and 60% (for 8- and



In the course of our ongoing investigation concerning the preparation of biologically active oxo and azaheterocycles from furan [8], we were interested to study the synthesis and use of 6-hydroxy-2-spiropyran-3(6*H*)-ones **5c** and **5d** as key intermediates for the facile and efficient preparation of several novel biologically interesting 8- and 9-aza-1-oxaspiro[5.5]undecane derivatives. This synthetic approach also leads to the synthesis of novel oxygen containing isosteres of ($\pm$)-Nitramine and ($\pm$)-Isonitramine (compounds **7c** and **8c** respectively - Scheme I). It is evident that the multitude of the reactions which can be carried out on the α,β -unsaturated ketone system as well as the hydroxy and oxo groups of these synthetic intermediates allow the



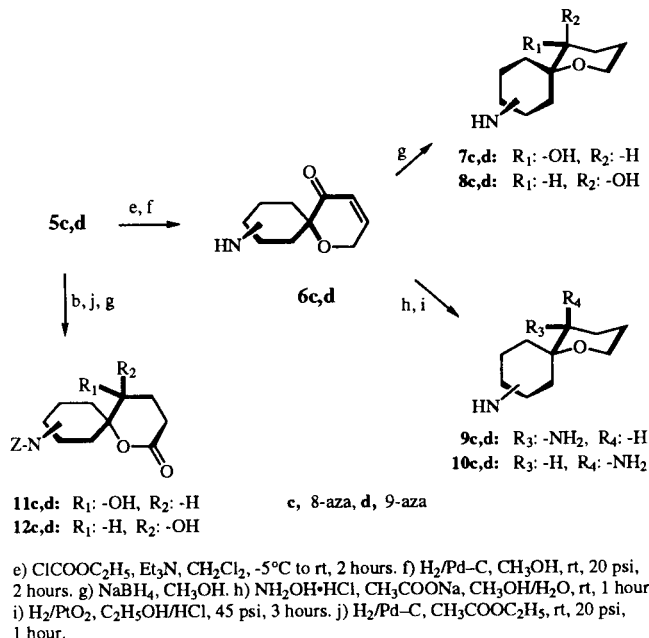
a) Z-Cl, Et₃N, CH₂Cl₂, 0° C to rt, 30 minutes. b) Jones reagent, (CH₃)₂CO, 0° C to rt, 30 minutes. c) 2-Furyllithium, THF, -5° C to rt, 3 hours. d) *m*-CPBA, CH₂Cl₂, rt, 3 hours.

9-aza products respectively). The hydroxy groups at C-2 were eliminated by conversion to their corresponding allylic ethyl carbonates and successive treatment with hydrogen in the presence of palladium catalyst. Under these conditions the allylic carbonates were hydrogenolysed, the double bonds were hydrogenated and the *N*-benzyloxycarbonyl groups were removed simultaneously yielding the target ketones **6c** and **6d**. Reduction of the latter compounds with sodium borohydride furnished the desired oxygen containing isosteres **7c,d** and **8c,d** as mixtures of diastereomers (2:1), which easily separated by flash chromatography (see experimental). Ketones **6c** and **6d** were transformed in high yields to their corresponding oximes which by hydrogenation (Scheme III) afforded the derivatives **9c,d** and **10c,d** as 4:1 mixtures (by ¹H nmr) of diastereoisomers.

Using a similar synthetic pathway, pyranones **5a** and **5b** by Jones oxidation, hydrogenation and subsequent reduc-

tion were easily transformed to the δ -lactone derivatives **11c,d** and **12c,d** of these compounds which are well known structural features of many natural products.

Scheme III



In conclusion the synthetic route presented provides a convenient route to the not readily available functionalized 8- and 9-aza-1-oxaspiro[5.5]undecanes which are valuable intermediates for the synthesis of natural products and their analogues. Further synthetic applications concerning the use of this strategy for the design of other aza-1-oxaspiro[5.5]undecane derivatives are currently under progress.

EXPERIMENTAL

The complete experimental details and analytical data for the synthesis of the presented compounds as well as preliminary assays of their biological activity will be reported as a full paper in the near future. In this communication we disclose only the experimental and analytical data of selective final products and key intermediates.

General Procedures.

Melting points are in degrees Centigrade and were determined in open capillary tubes with a Büchi melting point apparatus and are uncorrected. Reaction progress was followed with analytical thin-layer chromatography (tlc) performed on 0.25 mm silica gel precoated plastic plates with fluorescent indicator UV₂₅₄ (Merck). All column chromatography was done by the flash chromatography technique using 32-63 μm silica gel packing (Merck). Proton magnetic resonance (^1H nmr) spectra were recorded on Varian 360 EM (60 MHz) or on General Electric QE 300 (300 MHz) spectrometers in the indicated solvents.

Chemical shifts are reported in parts per million downfield from tetramethylsilane as internal standard (δ scale); multiplicities indicated by s (singlet), d (doublet), t (triplet), m (multiplet) or br (broadened). Infrared (ir) spectra were obtained on a Perkin Elmer Model 283B (4,000-200 cm^{-1}) spectrophotometer, from samples prepared in accordance with the potassium bromide disk technique, unless otherwise stated. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100%), m (medium, 34-66%), and w (weak, 0-33%). Microanalytical data were provided by the Microanalytical Service Laboratories of the University of Illinois, USA and University of Thessaloniki, Greece. *n*-Butyllithium was purchased from Merck and titrated prior to use. Furan was distilled immediately prior to use. Other reagents and catalysts were purchased as analytical reagent grade. Tetrahydrofuran (THF) was distilled from sodiumbenzophenone immediately prior to use. All other solvents were used as received.

3-(1-Benzyloxycarbonyl)piperidinone (**4a**).

To an ice cold stirred solution of 3-piperidinol (8.6 g, 85 mmoles) in methylene chloride (60 ml) and triethylamine (11.8 ml, 85 mmoles), 14.6 g (85 mmoles) of benzylchloroformate was added dropwise. The reaction mixture was allowed to reach the room temperature and the stirring was continued for additional 30 minutes. The solvent was evaporated under reduced pressure and the resulted slurry was chromatographed to give the 3-(1-benzyloxycarbonyl)piperidinol as a colorless oil (19 g, 95% yield). A fraction of 3.5 g (15 mmoles) of the above alcohol dissolved in 60 ml of ice cold acetone were treated with 4 ml of Jones, reagent [10]. The reaction mixture was brought at room temperature and stirred for 30 minutes. Then the inorganic by-products were eliminated by decantation, the liquid layer was evaporated under reduced pressure and the resulted residue was partitioned in ethyl acetate (200 ml) and water (50 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to a colorless oil (3.33 g, 96%); ir ν_{max} 1720 s [C=O], 1685 s [O-C(O)-N], 2980 s, 2890 m [C-H], 3050 w, 750 s, 695 m [aromatic]; ^1H nmr (60 MHz, deuteriochloroform): δ 7.05 [s, 5H, aromatic], 5.00 [s, 2H, CH_2O], 3.90 [s, 2H, H-C(2)], 3.55 [t, J = 5.9, 2H, H-C(6)], 2.15 [t, J = 5.9, 2H, H-C(4)], 1.85 [m, 2H, H-C(5)]

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3$ (233.27): C, 66.94; H, 6.48; N, 6.00. Found: C, 67.18; H, 6.63; N, 5.93.

2-Hydroxy-8-benzyloxycarbonyl-8-aza-1-oxaspiro[5.5]undec-3-en-5-one (**5c**).

To a solution of freshly distilled furan (15 ml) in anhydrous THF (50 ml), *n*-butyllithium in hexane (15%, 50 ml) was added dropwise under nitrogen while the temperature was maintained below -5° . The reaction was allowed to reach the rt and was stirred for an additional hour. The mixture was cooled to 0° and a solution of **4a** (11.66 g, 50 mmoles) in 150 ml anhydrous THF was added dropwise over a period of 30 minutes and the stirring was continued at rt for 3 hours. Then the mixture was poured into ice water (100 ml), stirred for 15 minutes and the product was taken by extraction with ethyl acetate (2 x 150 ml). The organic layers, were pooled together, washed with water, dried over magnesium sulfate and evaporated under reduced pressure yielding *N*-benzyloxycarbonyl-3-hydroxy-3-(2-furyl)piperidine as a yellowish oil (11.3 g, 75%). The above furfuryl alcohol was dissolved in methylene chloride (100 ml) and *m*-chloro-

perbenzoic acid (80%, 9.70 g, 45 mmol) was added in portions under stirring, while the temperature was kept between 7 and 15°. After being stirred at rt for 3 hours the mixture was cooled and the precipitated solid (*m*-chlorobenzoic acid) was filtered. The filtrate was washed successively with 20% potassium iodide, 30% sodium thiosulfate, concentrated bicarbonate and water, dried over magnesium sulfate and evaporated to give 9.76 g (82%) of **5c**; mp 82–83°; ν_{max} 3400 s [OH], 1685 s [broad, conj C=O and -O-C(O)-N], 2950 s, 2870 m [C-H], 3070 w, 740 s, 695 m [aromatic]; ^1H nmr (300 MHz, deuteriochloroform): δ 7.05 [s, 5H, aromatic], 6.52 [dd, $J = 10.3, 2.1$, 1H, H-C(3)], 5.68 [dd, $J = 10.3, 0.9$, 1H, H-C(4)], 5.35 [dd, $J = 2.1, 0.9$, 1H, H-C(2)], 5.15 [br, disappeared on addition of deuterium oxide, OH], 5.00 [s, 2H, CH₂O], 2.95 [t, $J = 6.2$, 2H, H-C(9)], 2.85 [s, 2H, H-C(7)], 1.70 [m, 4H, H-C(10,11)].

Anal. Calcd. for C₁₇H₁₉NO₅ (317.34): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.12; H, 6.17; N, 4.51.

8-Aza-1-oxaspiro[5.5]undecan-5-one (**6c**).

To a solution of compound **5c** (1.46 g, 4.6 mmol), triethylamine (0.9 g, 8.9 mmol) in methylene chloride (80 ml) cooled to -5°, ethyl chloroformate (1.20 g, 11 mmol) was added under stirring in such a rate that the temperature was maintained below 0°. The reaction was allowed to proceed at room temperature and stirred for 2 hours. The reaction mixture was washed with water, dried over magnesium sulfate and evaporated to dryness yielding 1.54 g (86%) of the 2-ethyl carbonate derivative, which was dissolved in ethyl acetate (100 ml) and methanol (20 ml) and 0.2 g of 10% Pd/C was added as catalyst. The mixture was treated with hydrogen under 20 psi pressure and rt for 2 hours. The catalyst was filtered and the filtrate was evaporated under reduced pressure to give the title product as a colorless oil (0.42 g, 63%); ν_{max} 3320 m [NH], 1720 s [C=O], 2940 s, 2870 m [C-H]; ^1H nmr (300 MHz, deuteriochloroform): δ 3.72 (t, $J = 5.6$, 2H, H-C(2)), 2.85 [m, 2H, H_c-C(7,9)], 2.60 [m, 2H, H_a-C(7,9)], 2.35 [m, 2H, H-C(4)], 2.01 [m, 2H, H-C(3)], 1.65 [m, 5H, H-C(10,11), NH].

Anal. Calcd. for C₉H₁₅NO₂ (169.22): C, 63.88; H, 8.93; N, 8.28. Found: C, 64.01; H, 8.87; N, 8.16.

5-Hydroxy-8-aza-1-oxaspiro[5.5]undecane (**7c** and **8c**).

To an ice cold stirred solution of compound **6c** (0.42 g, 2.5 mmol) in 10 ml methanol, 0.03 g (0.8 mmol) of sodium borohydride was added portionwise. After the addition was completed, the stirring was continued for an additional hour at room temperature. Then the reaction mixture was partitioned in methylene chloride/water (80:20 vol/vol) and the organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure yielding 0.40 g (93% total yield) of a viscous light yellow oil. The latter was identified as a diastereomeric mixture (2:1 by ^1H nmr) of the title compounds, which were separated by flash chromatography using chloroform/methanol/25% ammonia (46/50/4) as eluant.

Analytical and spectral data of the more mobile major (0.27 g) diastereomer, compound **7c** are as follows: mp 106–108°; ν_{max}

max 3340–3060 m [OH, NH], 2950 s, 2870 m [C-H]; ^1H nmr (300 MHz, deuteriochloroform): δ 3.75 [t, $J = 5.4$ Hz, 2H, H-C(2)], 3.48 [dd, $J_{4,5a} = 9.9$ Hz, $J_{4,5e} = 3.5$ Hz, 1H, H-C(5)], 3.33 [br, 2H, disappeared on addition of deuterium oxide, OH and NH], 2.95 [m, 2H, H_c-C(7,9)], 2.65 [d, $J = 11.9$ Hz, 1H, H_a-C(7)], 2.55 [m, 1H, H_a-C(9)], 2.25 [m, 2H, H-C(4)], 2.0–1.4 [m, 6H, H-C(3, 10, 11)].

Anal. Calcd. for C₉H₁₇NO₂ (171.24): C, 63.13; H, 10.01; N, 8.18. Found: C, 63.36; H, 9.84; N, 8.27.

The less mobile minor (0.13 g), diastereomer **8c** had mp 111–113°; ν_{max} 3320–3100 m [OH, NH], 2950 s, 2870 m [C-H]; ^1H nmr (300 MHz, deuterioacetone): δ 3.72 [t, $J = 5.5$ Hz, 2H, H-C(2)], 3.62 [dd, $J_{4,5} = 11$ and 3.6 Hz, 1H, H-C(5)], 3.10 [br, disappeared on addition of deuterium oxide, OH, NH], 2.92 [m, 2H, H_c-C(7,9)], 2.55 [m, 2H, H_a-C(7,9)], 2.30 [m, 2H, H-C(4)], 2.0–1.3 [m, 6H, H-C(3,10,11)].

Anal. Calcd. for C₉H₁₇NO₂ (171.24): C, 63.13; H, 10.01; N, 8.18. Found: C, 63.23; H, 9.92; N, 8.32.

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