A Simple Synthesis of Heterocyclic Ring Systems Containing the 1,3-Oxazine Nucleus

C. Altomare, A. Carotti*, G. Casini and M. Ferappi

Dipartimento Farmaco-Chimico, Università di Bari,
via Amendola 173, 70126 Bari, Italy

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An easy, one-step conversion of aldol adducts **1** into spiro-derivatives of partially hydrogenated [1,3]oxazino[2,3-*a*]isoquinoline **5**, [1,3]oxazino[2,3-*a*]phthalazine **6** and [1,3]oxazino[3,2-*a*]quinoline **7** is reported.

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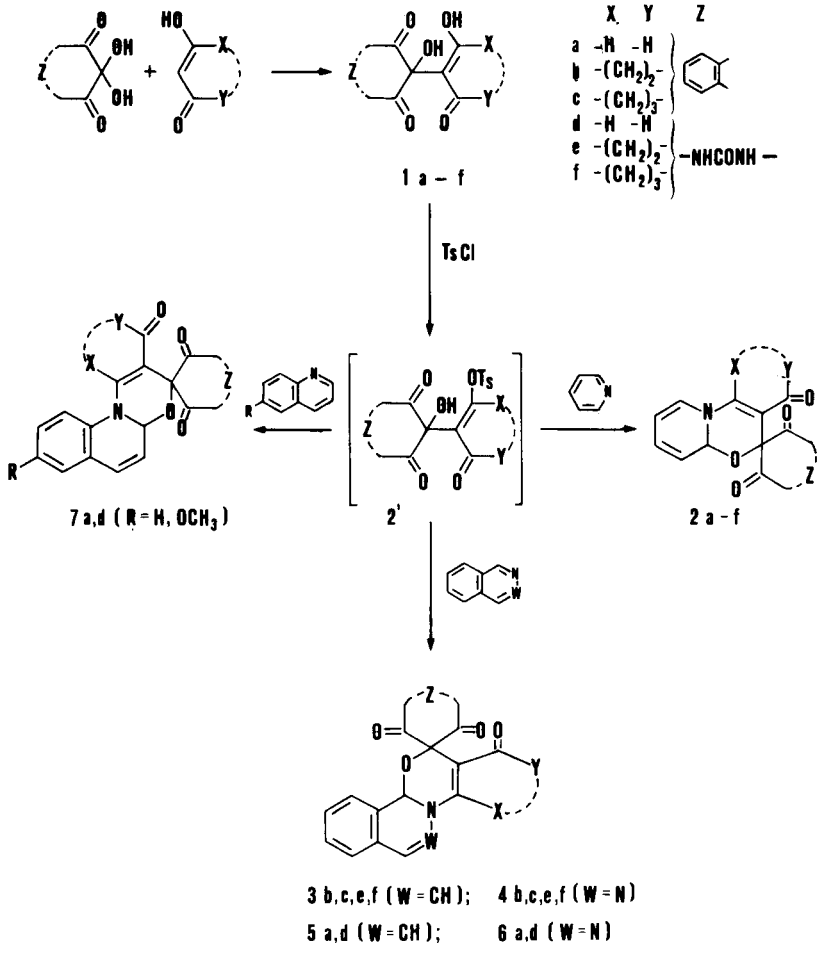
In a first paper of this series [1] we described the synthesis of partially hydrogenated pyrido[2,1-*b*][1,3]oxazine **2a**, cyclopenta[*d*]pyrido[2,1-*b*][1,3]oxazine (**2b**) and pyrido-[1,2-*a*][3,1]benzoxazine (**2c**) all carrying the 1,3-dioxoindane moiety as a spiro-substituent. Our interest in the preparation of potential biologically active compounds prompted us to similarly synthesize some derivatives of new heterocyclic steroid systems, the 8-aza-11-oxagonapentaene **3** [2] and the 7,8-diaza-11-oxagonapentaene **4** [3].

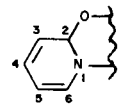
The present paper reports a further application of such a synthesis by first preparing compound **1d**, carrying a different spiro-substituent (the pharmacophore barbituric nucleus), and by using this adduct and the formerly described ones **1a,b,c,e,f** [1-3] we obtained derivatives of the heterocyclic ring systems **5**, **6**, **7**. To the best of our knowledge the last ring has been synthesized for the first time. The synthesis of all compounds containing the 1,3-oxazine moiety was accomplished according to the following scheme.

SCHEME



Table

Parameters of Dihydropyridine Ring Protons [a] of Compounds **2d-f**



Compound	H-2	H-3	H-4	H-5	H-6	J_{2-3}	J_{3-4}	J_{4-5}	J_{5-6}
2d	6.30	5.56	6.28	5.40	6.86	3	9	6.5	7
2e	6.60	5.62	6.30	5.40	6.85	3	9	6.5	7.5
2f	6.18	5.60	6.36	5.42	7.08	3	9.5	6.5	7.5

[a] Numbering of the dihydropyridine ring protons refers to that indicated in the head of the table and does not correspond to the correct one of the pyridooxazine structures **2**.

Starting from easily obtainable aldol adducts **1** spiro derivatives **2-7** were directly produced in good yields, by using tosyl chloride and the corresponding aromatic bases through the reaction sequence outlined in the scheme. In contrast with the normal behaviour of pyridine, isoquinoline and phthalazine, reaction with tosyl chloride and quinoline on adducts **1** afforded the expected oxazine derivatives only in the case of adducts **1a,d** and this behaviour could be related to both the low nucleophilic character and the greater steric hindrance of the quinoline nitrogen atom that could prevent nucleophilic substitution of the tosyloxy group on the cyclic tosylate intermediates **2'b,c, e,f**. Steric hindrance has been previously taken into account to explain similar results observed in the reaction of adducts **1b,c** with tosyl chloride and 2-methylpyridine [1].

The pharmaceutical interest for some compounds reported in this paper resides on some structural analogy of **2c, f** with the cannabinoids nucleus [4,5] while even closer analogy could be found in derivatives **5-7** with respect to the benzo[*a*]quinolizidine nucleus which is present on some reserpine-like antipsychotic drugs used in therapy like tetrabenzazine [6] and benzquinamide [7].

Preliminary pharmacological screening on compounds **6a,d** reveals that both compounds exert a mild antidepressant effect in the test of reserpine induced ptosis without any action on 5-HTP potentialisation.

EXPERIMENTAL

Melting points were determined by the capillary method on a Dr. Tottoli (Büchi) or on Electrothermal (Mark II) apparatus and are uncorrected. Elemental analyses were made by the technical staff of our department using a Hewlett-Packard 185 C,H,N autoanalyser. The ir spectra were recorded as potassium bromide pellets on a Perkin-Elmer spectrophotometer Model 283; only the most significant absorption bands were reported. The nmr spectra were taken on a Varian EM-390, 90 MHz instrument using tetramethylsilane as internal standard and dimethylsulfoxide-d_6 as solvent (unless otherwise indicated); chemical shifts were expressed in δ (ppm) and the coupling constants in Hz; the following abbreviations were used: s, singlet; d, doublet; dd, double doublet; m, multiplet(s); br, broad signal; exchange with deuterium oxide was used to identify protons on oxygen and nitrogen atoms.

Synthesis of 5-Hydroxy-5-bisformilmethylbarbituric Acid **1d**.

An aqueous solution (5 ml) of malonaldehyde bisdimethylacetal (1.64 g, 10 mmoles) and alloxane tetrahydrate (2.30 g, 10 mmoles) was heated for 1 hour at 55° with stirring. A pure crystalline product precipitated on cooling (1.97 g, 92% yield), mp >350° dec; ir: ν max 3220, 3100, 2880, 2560, 1760, 1730, 1705, 1640, 1560 cm^{-1}; nmr: δ 8.70 (s, 2H, CHO + =C*H*-OH), 8.2-9.2 (s, br, 2H, OH), 11.40 (s, 2H, NH).

Anal. Calcd. for $C_7H_6N_2O_6$: C, 39.26; H, 2.82; N, 13.08. Found: C, 39.15; H, 2.92; N, 12.69.

Preparation of Pyridooxazine Derivatives **2d-f**.

Tosyl chloride (0.42 g, 2.2 mmoles) was added to a stirred, ice-cooled solution of **1d-f** (2 mmoles) in dry pyridine (2 ml, 25 mmoles). Stirring and cooling were maintained over a period of 3 hours and then the reaction mixture was poured on ice and the precipitate was collected and crystallized to give:

Compound **2d**.

This compound was obtained in a 67% yield, mp >350° dec from acetone; ir: ν max 3200, 3080, 1720, 1705, 1615, 1560 cm^{-1}; nmr [8]: δ 8.32 (s, 1H, C*H*=C-CHO), 9.15 (s, 1H, CHO), 11.80 (s, 2H, NH).

Anal. Calcd. for $C_{12}H_9N_3O_5$: C, 52.37; H, 3.30; N, 15.27. Found: C, 52.06; H, 3.31; N, 15.00.

Compound **2e**.

This compound was obtained in a 58% yield, mp >350° dec from aqueous dimethylsulfoxide; ir: ν max 3290, 3240, 1730, 1705, 1690, 1595, 1560 cm^{-1}; nmr [8]: δ 2.30 (m, 2H, CH_2, part masked), 2.90 (m, 2H, CH_2), 11.75 (s, 2H, NH).

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: C, 55.81; H, 3.68; N, 13.95. Found: C, 55.65; H, 3.88; N, 13.69.

Compound **2f**.

This compound was obtained in a 72% yield, mp 276-280° dec from aqueous dimethylsulfoxide; ir: ν max 3220, 3080, 1760, 1690, 1590, 1540 cm^{-1}; nmr [8]: δ 2.0 (m, 2H, CH_2-C*H*$_2$-CH_2), 2.3-3.2 (m, 4H, C*H*$_2$-CH_2-C*H*$_2$), 11.65 (s, 2H, NH).

Anal. Calcd. for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33. Found: C, 57.02; H, 4.39; N, 12.95.

Preparation of [1,3]Oxazino[2,3-*a*]isoquinolines **5a,d** [1,3]Oxazino[2,3-*a*]-phthalazines **6a,d** and [1,3]Oxazino[3,2-*a*]quinolines **7a,d**.

A solution of adduct **1a,d** (2 mmoles) and suitable heteroaromatic base (isoquinoline and phthalazine, 8 mmoles; quinoline and 6-methoxyquinoline, 20 mmoles) in dry dioxane (3-4 ml) was stirred for 1 hour and then tosyl chloride (0.42 g, 2.2 mmoles) was added portionwise. After 6-12 hours stirring at room temperature the reaction mixture was poured on ice-cooled diluted hydrochloric acid and the precipitate so formed was collected, washed with water and crystallized to give the following:

Compound **5a**.

This compound was obtained in a 95% yield, mp 235-237° dec from chloroform-hexane; ir: ν max 1750, 1715, 1645, 1615, 1570 cm^{-1}; nmr (deuteriochloroform): δ 5.80 (d, 1H, H-7, J_{6-7} = 8), 6.45 (d, 1H, H-6), 7.03 (s, 1H, H-11b), 7.1-7.4 (m, 4H, H-8-11), 7.74 (s, 1H, H-4), 7.8-8.2 (m, 4H, indane), 9.10 (s, 1H, CHO).

Anal. Calcd. for $C_{21}H_{13}NO_4$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.39; H, 3.89; N, 3.90.

Compound **5d**.

This compound was obtained in a 70% yield, mp 253-255° dec from ethanol; ir: ν max 3320, 1760, 1720, 1700, 1595, 1565 cm^{-1}; nmr: δ 5.97 (d, 1H, H-7, J_{6-7} = 8), 6.80 (s, 1H, H-11b), 6.90 (d, 1H, H-6, part masked), 7.30 (s, 4H, H-8-11), 8.40 (s, 1H, H-4), 9.14 (s, 1H, CHO), 11.90 (s, 2H, NH).

Anal. Calcd. for $C_{16}H_{11}N_3O_5$: C, 59.08; H, 3.41; N, 12.92. Found: C, 58.89; H, 3.24; N, 13.06.

Compound **6a**.

This compound was obtained in 82% yield, mp 245-247° dec from xylene; ir: ν max 1740, 1710, 1650, 1630, 1600, 1590, 1565 cm^{-1}; nmr: δ 6.93 (s, 1H, H-11b), 7.2-7.7 (m, 4H, H-8-11), 7.95 (s, 1H, H-7), 8.15 (s, 4H, indane), 8.70 (s, 1-H, H-4), 9.20 (s, 1H, CHO).

Anal. Calcd. for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14. Found: C, 70.11; H, 3.38; N, 7.90.

Compound **6d**.

This compound was obtained in a 91% yield, mp 302-304° from aqueous dimethylsulfoxide; ir: ν max 3200, 3075, 1710, 1620, 1600, 1560 cm^{-1}; nmr: δ 6.85 (s, 1H, H-11b), 7.58 (s, 4H, H-8-11), 7.93 (s, 1H, H-7), 8.65 (s, 1H, H-4), 9.24 (s, 1H, CHO), 11.96 (s, 2H, NH).

Anal. Calcd. for $C_{15}H_{10}N_4O_5$: C, 55.22; H, 3.09; N, 17.17. Found: C, 55.52; H, 3.07; N, 17.19.

Compound **7a** (R = H).

This compound was obtained in a 73% yield, mp 256-258° dec from xylene; ir: ν max 1745, 1705, 1640, 1605, 1570, 1500 cm^{-1}; nmr: δ 5.77 (dd, 1H, H-5, $J_{5\text{-}6}$ = 10, $J_{5\text{-}4a}$ = 3), 6.44 (dd, 1H, H-4a, $J_{4a\text{-}6}$ = 1.5), 6.85 (dd, 1H, H-6), 7.0-7.9 (m, 4H, H-7-10), 8.15 (s, 4H, indane), 9.27 (s, 1H, H-1), 9.36 (s, 1H, CHO).

Anal. Calcd. for $C_{21}H_{13}NO_4$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.84; H, 3.90; N, 3.92.

Compound **7a** (R = OCH_3).

This compound was obtained in a 51% yield, mp 230-232° dec from xylene; ir: ν max 1735, 1710, 1630, 1605, 1580, 1500 cm^{-1}; nmr: δ 3.85 (s, 3H, CH_3), 5.92 (dd, 1H, H-5, $J_{5\text{-}6}$ = 10, $J_{5\text{-}4a}$ = 3), 6.50 (dd, 1H, H-4a, $J_{4a\text{-}5}$ = 3, $J_{4a\text{-}6}$ = 1.5), 6.87 (dd, 1H, H-6, part masked), 6.9-7.3 (m, 2H, H-7 + H-9), 7.59 (d, 1H, H-10, $J_{9\text{-}10}$ = 9.5), 8.05 (s, 4H, indane), 8.92 (s, 1H, H-1), 9.09 (s, 1H, CHO).

Anal. Calcd. for $C_{22}H_{15}NO_5$: C, 70.77; H, 4.05; N, 3.75. Found: C, 71.12; H, 4.01; N, 3.68.

Compound **7d** (R = H).

This compound was obtained in a 95% yield, mp 245-246° dec from ethanol; ir: ν max 3260, 3110, 1760, 1730, 1710, 1665, 1600, 1570, 1500 cm^{-1}; nmr: δ 5.90 (dd, 1H, H-5, $J_{5\text{-}6}$ = 10, $J_{5\text{-}4a}$ = 3), 6.37 (dd, 1H, H-4a, $J_{4a\text{-}5}$ = 3, $J_{4a\text{-}6}$ = 1.5), 6.87 (dd, 1H, H-6), 7.1-7.8 (m, 4H, H-7-10), 9.20 (s, 1H, H-1), 9.35 (s, 1H, CHO), 11.92 (s, 2H, NH).

Anal. Calcd. for $C_{16}H_{11}N_3O_5$: C, 59.08; H, 3.41; N, 12.92. Found: C, 58.80; H, 3.57; N, 12.89.

Compound **7d** (R = OCH_3).

This compound was obtained in a 53% yield, mp 258-260° dec from ethanol; ir: ν max 3300, 3220, 3110, 1760, 1720, 1690, 1600, 1580, 1500 cm^{-1}; nmr: δ 3.77 (s, 3H, CH_3), 5.79 (dd, 1H, H-5, $J_{5\text{-}6}$ = 10, $J_{5\text{-}4a}$ = 3), 6.32 (dd, 1H, H-4a, $J_{4a\text{-}5}$ = 3, $J_{4a\text{-}6}$ = 1.5), 6.82 (dd, 1H, H-6, part masked), 6.9-7.1 (m, 2H, H-7 + H-9), 7.55 (d, 1H, H-10, $J_{9\text{-}10}$ = 9.5), 9.09 (s, 1H, H-1), 9.24 (s, 1H, CHO), 11.84 (s, 2H, NH).

Anal. Calcd. for $C_{17}H_{13}N_3O_6$: C, 57.46; H, 3.69; N, 11.83. Found: C, 57.85; H, 3.52; N, 11.95.

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[8] The nmr parameters of dihydropyridine ring protons are listed in the Table.