CHEMICAL AND CATALYTIC REDUCTIVE ISOMERIZATION OF [1,3]OXAZINO[2,3-a]ISOQUINOLINES TO [1,3]OXAZINO[3,2-b]ISOQUINOLINES

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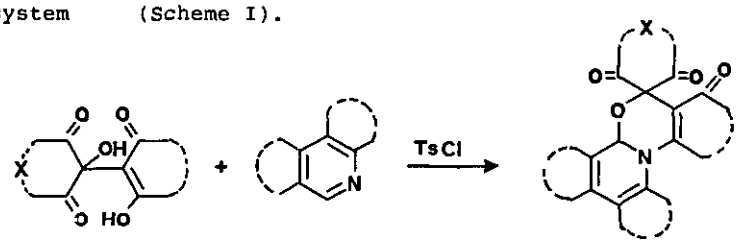
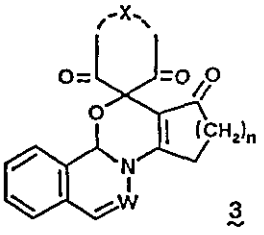
Abstract - The title reductive isomerization leading to 7, which contain a new heterocyclic ring system, has been carried out with Pd on C and more efficiently with $NaBH_4$. A possible pathway for the formation of 7 as well as of other hydrogenolysis products is discussed.

A simple and efficient conversion of aldol adducts of general structure 1 to polycondensed heterocycles 2 containing the 1,3-oxazine nucleus, has been realized by using tosyl chloride (TsCl) and different heteroaromatic bases as reagents system[1-5] (Scheme I).



1 Scheme I 2

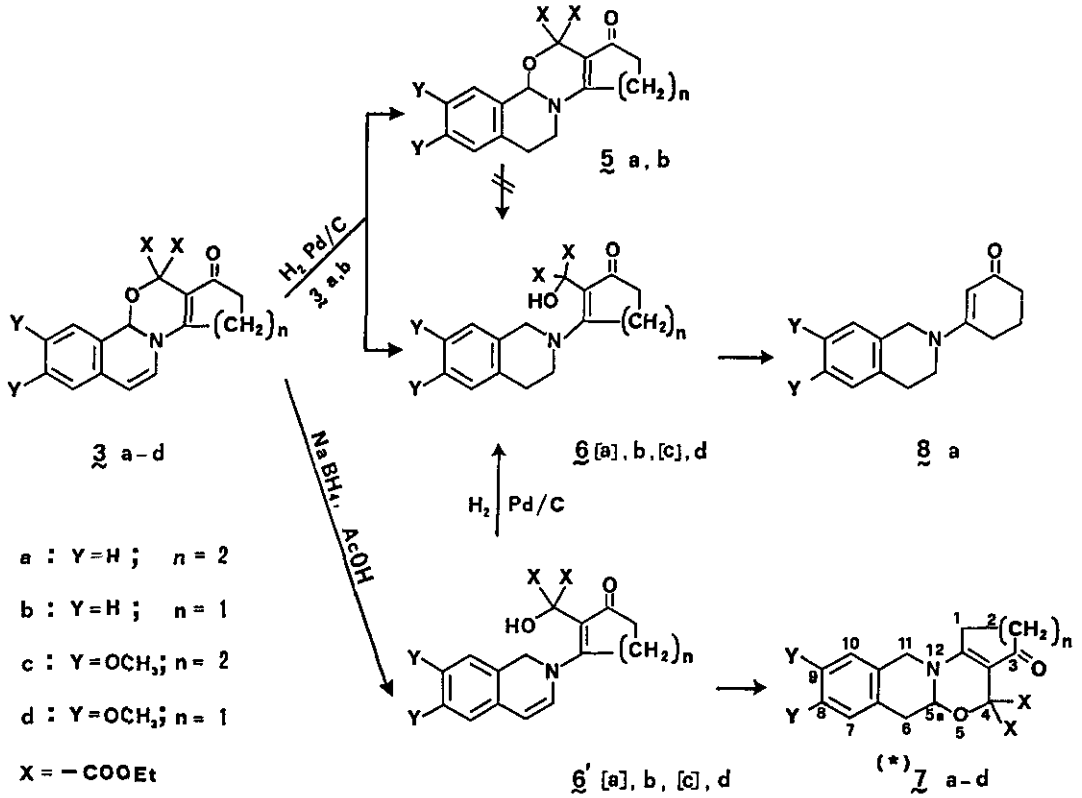
When aldol adducts 1 deriving from 1,3-cyclopentanedione or 1,3-cyclohexanedione and isoquinoline or phthalazine have been utilized, the above reaction constituted a valid entry to new classes of heterosteroids that are 8-aza-11-oxagonanes and D-homogonanes 3, and 7,8-diaza-11-oxagonanes and D-homogonanes 4.



3 (W = −CH=), 4 (W = N); n = 1,2

In order to increase the structural analogy with the natural estrogens several compounds 3 carrying a spiro-substituent[6] or a bis-ethoxycarbonyl group[5] at C-12 have been reduced with H_2 and Pd on carbon. As a continuation of this research we subjected compounds 3 to further catalytic reduction and to sodium borohydride reduction and in this paper we wish to report the interesting results obtained from such investigation.

Under atmospheric pressure, with 5 % Pd on carbon as catalyst compounds 3a,b were easily reduced to the corresponding 6,7-dihydroderivatives 5a,b[5] whereas simply by using a more active catalyst (10 % Pd on carbon) besides compounds 5a,b also products deriving from the hydrogenolysis of C_9-O_{11} bond were isolated. Compound 3a produced 5a (50 % yield), the enaminone 8a (7 %) and the [4,5]-benzo[1,3]oxazino[3,2-b]isoquinoline derivative 7a (5 %), whereas under identical experimental conditions compounds 3b, gave the expected 6,7-dihydroderivative 5b and the enaminone 6b, which unlike 8a still presented the 2-hydroxydiethylmalonate moiety. The catalytic reduction seems therefore to proceed according to the pathway delineated in the following scheme:



(*) The numbering refers to compounds 7b,d

Compound 8a was clearly derived by a retro-aldolic reaction from an intermediate hydrogenolysis product (either 6'a or 6a) followed or preceded by hydrogenation of the double bond.

Since isolated compounds 5 did not afford compounds 6 under catalytic reduction with Pd on carbon the latter could arise only from the intermediate derivatives 6' and thus hydrogenolysis of C_9-O_{11} bond must precede the Δ^6 double bond reduction.

The reductive isomerization of compound 3a, formally containing the [4,5]benzo-[1,3]oxazino[2,3-a]isoquinoline heterocyclic ring system, to 7a took place thus through a first hydrogenolysis of the C_9-O_{11} bond and the subsequent intramolecular nucleophilic addition of the hydroxyl group to the 3,4 double bond of the 1,2-dihydro-isoquinoline moiety. This transformation is by far the most interesting aspect of the above reaction pathway being moreover, to the best of our knowledge, the heterocyclic ring system in 7a unknown.

We decided then to explore the possibility of obtaining similar heterocycles in higher yield from 3a,b and from the newly prepared dimethoxyderivatives 3c,d, by reduction with $NaBH_4$ in acetic acid.

As auspicated, compound 3a,c afforded [1,3]oxazino[3,2-b]isoquinoline derivatives 7a,c in good yield, but unexpectedly compounds 3b,d yielded only compounds 6'b,d, which could be considered as intermediates in the formation of 7b,d. However 6'b,d could be almost quantitatively converted to 7b,d in chloroform at room temperature via a strong acid catalysis (p-toluenesulfonic acid).

Some aspects of the described reactions deserve some discussion.

The fact that hydrogenolysis of 3 preceded the saturation of the Δ^6 double bond may be explained by the formation of a more delocalized and hence more stable transient 9-carbonium ion during the hydrogenolytic cleavage of the C_9-O_{11} bond; this is consistent with the results of $NaBH_4$ attack on 3 in acid medium, giving that cleavage as the only reduction path, eventually followed by cyclization to 7.

The isolation of the intermediates 6'b,d in the $NaBH_4$ reaction speaks for a less favoured cyclization to 7b,d, that needs a stronger acid catalysis. This could arise from some steric strain in the polycondensed system in 7b,d due to the smaller five membered ring.

Further studies are planned in order to explore the scope and limitations of the interesting reductive isomerization reaction described above with the aim of

synthesizing new heterocyclic ring systems of chemical and pharmaceutical interest.

EXPERIMENTAL

Melting points were determined by the capillary method on a Dr Tottoli apparatus (Büchi) and were not corrected. Elemental analyses were made on a Hewlett-Packard 185 C,H,N analyzer and were in good agreement (±0.40 %) with calculated values. Ir spectra were recorded using Kbr disks on a Perkin-Elmer 283 spectrophotometer, only the most significant and diagnostic absorption bands being reported (OH,CO and C=C stretchings). ^{1}H-Nmr spectra were recorded on a Varian XL-200 or EM 390 spectrometer using TMS as internal standard; the following abbreviations being used: a(ax) axial proton; e(eq) equatorial proton; s, singlet; d, doublet; dd, double doublet; t, triplet; qt, quartet; qn, quintet; m, multiplet. Exchange with deuterium oxide (D_2O) was used to identify hydroxyl protons. A careful ^{1}H-NMR spectra analysis of some [1,3]-oxazino[2,3-a]isoquinoline derivatives similar to compounds 3a-d have been reported in details by us in references 5 and 6 and it was not been repeated in this experimental section. *Chromatographic separations were carried out on silica gel columns* (0.060-0.200 mm., Merck).

General Method for the Preparation of the 8-Aza-11-oxa-12,12bis(ethoxycarbonyl)-17-oxo-gonane and D-Homo-gonane Derivatives ([1,3]Oxazino[2,3-a]isoquinoline derivatives) 3.

Compounds 3a,b were prepared according to the procedure described previously[5]. Compounds 3c,d were prepared as follows:

Appropriate diethyl 2-hydroxy-2, 2'-hydroxy-5'(6')-oxocycloalken-1'-yl malonate (5 mmol) and 6,7-dimethoxyisoquinoline (4.73 g., 25 mmol) were dissolved in anhydrous tetrahydrofuran (25 ml) and TsCl (1.05 g., 5.5 mmol) was then added portionwise. The reaction mixture was heated at ~55 °C for 16 h and, after cooling, poured on cold water (150 ml). The resulting precipitate was collected, washed with water and dried to give:

2,3-Dimethoxy-8-aza-11-oxa-12,12bis(ethoxycarbonyl)-17-oxo-D-homogona-1,3,5(10),6,13 Pentaene 3c (65 % yield) mp 193-194 °C from chloroform-hexane, ir, ν max: 1750, 1740, 1640, 1590 cm^{-1}; ^{1}H-nmr (chloroform-d)δ: 1.26(t,3H,CH_3-C, J=7.1),

1.34(t,3H,CH_3-C,J=7.1), 1.94-2.22(m,2H,H-16), 2.26-2.86(m,4H,H-15,H-17), 3.86(s, 3H,-OCH_3), 3.88(s,3H,-OCH_3), 4.14-4.42(m,4H,2-CH_2-O), 5.66(d,1H,H-6, J=7.8), 6.10(s,1H,H-9), 6.53(d,1H,H-7,J=7.8), 6.53(s,1H,H-1, overlapped with the H-7 signal), 7.16(s,1H,H-4);

2,3-Dimethoxy-8-aza-11-oxa-12,12-bis(ethoxycarbonyl)-17-oxogona-1,3,5(10),6,13 Pentaene 3d (75 % yield) mp 203-204 °C from chloroform-hexane, ir, νmax: 1760, 1740, 1680, 1645, 1600 cm^{-1} ; ^{1}H-nmr(chloroform-d) δ :1.25(t,3H,CH_3-C, J=7.1), 1.33(t,3H,CH_3-C,J=7.1), 2.40-2.70(m,2H,H-15), 2.70-3.00(m,2H,H-16), 3.86(s,3H, -OCH_3), 3.92(s,3H,-OCH_3), 4.14-4.42(m,4H,2-CH_2-O), 5.68(d,1H,H-6, J=7.7), 6.22(s,1H,H-9), 6.40(d,1H,H-7,J=7.7), 6.54(s,1H,H-1), 7.23(s,1H, H-4).

Sodium Borohydride Reduction of Compounds 3a-d: General Procedure

Compound 3 (1 mmol) was dissolved (3a,b) or suspended (3c,d) in glacial acetic acid (20 ml) and sodium borohydride (0.57 g., 15 mmol) was then added portionwise to the ice-cooled solution with vigorous stirring. The reaction mixture was allowed to warm to room temperature and stirring was continued for another 0.5 h. The reaction solution was neutralized with a saturated $NaHCO_3$ water solution and extracted with chloroform. The residue obtained after drying the organic phase over Na_2SO_4 and elimination of the solvent in vacuo, was crystallized from ethyl ether to produce 6'b,d, and 7a,c whose physical and spectroscopic data are as follows:

Diethyl 2-Hydroxy-2-[2'-(1,2-dihydro-2-isoquinolyl)-5'-oxocyclopentenyl]-malonate 6'b (90 % yield) mp 148-149 °C decomp. from ethyl ether, ir, νmax: 3450, 1730, 1675, 1630, 1570 cm^{-1} ; ^{1}H-nmr(chloroform-d) δ : 1.09(t,6H,2CH_3-C,J=7.1), 2.35-2.60(m,2H,-CH_2-CH_2-CO), 2.70-2.95(m,2H,CH_2-CO), 3.70-4.40(m,4H,CH_2-O), 4.66(s,1H,OH,exch.D_2O), 4.76(s,2H,CH_2-N), 5.98(d,1H,-CH=CH-N,J=8.0), 6.90(d,1H, -CH=CH-N,J=8.0), 6.90-7.34(m,4H,arom.,partially overlapped to =CH-N signal).

Diethyl 2-Hydroxy-2-[2'-(1,2-dihydro-6,7-dimethoxy-2-isoquinolyl)-5'-oxocyclopentenyl]malonate 6'd (90 % yield) mp 166-167 °C decomp. from ethyl ether, ir, ν max :3460, 1745, 1720, 1670, 1640, 1560 cm^{-1} ; ^{1}H-nmr(chloroform-d) δ : 1.07(t, 6H,2CH_3-C,J=7.1), 2.30-2.56(m,2H,-CH_2-CH_2-CO), 2.64-2.90(m,2H,CH_2-CO), 3.70(s, 6H,2O-CH_3), 3.70-4.40(m,4H,2CH_2-O), 4.63(s,3H,CH_2-N and O-H, exch. with D_2O), 5.80(d,1H,-CH=CH-N,J=8.0), 6.50(s,2H,arom.), 6.80(d,1H,-CH=CH-N, J=8.0).

5H,12H-5,5-Bis-(ethoxycarbonyl)-1,2,3,4,6a,7-hexahydro-4-oxo-benzo[4,5][1,3] oxazino[3,2-b]isoquinoline 7a (65 % yield) mp 134-136 °C decomp. from ethyl

ether, ir, νmax: 1750, 1730, 1615, 1550 cm^{-1}; ^{1}H-nmr(chloroform-d)δ: 1.26(t,3H, CH_3-C,J=7.1), 1.30(t,3H,CH_3-C,J=7.1), 1.96-2.22(m,2H,H-2), 2.26-2.54(m,2H,H-1), 2.56-2.90(m,2H,H-3), 3.15(dd,1H,H-7ax,Jgem=16.0, Jaa=9.4), 3.31(dd,1H,H-7eq, Jgem=16.0,Jea=4.6), 4.12-4.26(m,4H,2CH_2-O), 4.59(d,1H,H_A,CH_2-N-AB system, J=15.2), 4.71(d,1H,H_B,CH_2-N,AB system,J_{AB}=15.2), 4.78(dd,1H,H-6a, Jaa=9.4, Jea=4.6, partially overlapped to the H_B signal), 7.02-7.26(m,4H,arom.).

5H,12-H-5,5-Bis(ethoxycarbonyl)-9,10-dimethoxy-1,2,3,4,6a,7-hexahydro-4-oxo-benzo[4,5][1,3]oxazino[3,2-b]isoquinoline 7c (92 % yield) mp 167-168 °C decomp. from ethyl ether, ir, νmax: 1745, 1735, 1630 1570 cm^{-1}, ^{1}H-nmr(chloroform-d) δ: 1.24(t,3H,CH_3-C,J=7.1), 1.28(t,3H,CH_3-C,J=7.1), 1.83-2.20(m,2H,H-2), 2.20-2.50(m,2H,H-1), 2.50-2.83(m,2H,H-3), 3.02(dd,1H,H-7ax,Jgem=15.1,Jaa=9.2), 3.16(dd,1H,H-7eq,Jgem=15.1,Jea=4.5), 3.83(s,3H,O-CH_3), 3.86(s,3H,O-CH_3), 4.05-4.45(m,4H,2 CH_2-O), 4.45(d,1H,H_A,CH_2-N,AB system,J_{AB}=14.9 partially overlapped to the CH_2-O signals), 4.60(d,1H,H_B,CH_2-N,AB system,J_{AB}=14.9), 4.70(dd,1H,H-6a, Jaa=9.2, Jae=4.5, partially overlapped to the H_B signal), 6.60(s,1H,H-11), 7.68(s,1H,H-8).

Cyclization of Diethyl-2-hydroxymalonate Derivatives 6'b,d to [1,3]Oxazino[3,2-b] isoquinoline derivatives 7b,d.

A solution of compound 6' (1 mmol) and p-toluenesulfonic acid (19 mg., 0.1 mmol) in $CHCl_3$ (20 ml) was stirred at room temperature for 5 h. The reaction mixture was washed with a saturated $NaHCO_3$ water solution (5 ml), with water (5 ml) and dried over Na_2SO_4. The residue obtained after the evaporation of the solvent in vacuo was crystallized from ethyl ether to give:

3H,4H,11H,4,4-Bis-(ethoxycarbonyl)-3-oxo-1,2,5a,6-tetrahydro-cyclopenta[4,5][1,3]oxazino[3,2-b]isoquinoline 7b (90 % yield), mp 89-91 °C from ethyl ether, ir, ν max: 1740, 1665, 1580 cm^{-1}; ^{1}H-nmr(chloroform-d) δ: 1.27(t,3H, CH_3-C, J=7.1), 1.29(t,3H,CH_3-C,J=7.1), 2.30-2.56(m,2H,H-1), 2.60-2.86(m,2H,H-2), 3.11(dd,1H,H-6ax,Jgem=14.8,Jaa=9.6), 3.36(dd,1H,H-6eq,Jgem=14.8,Jea=4.4), 4.00-4.43(m,4H, 2CH_2-O), 4.52(d,1H, H_A,CH_2-N,AB system,J_{AB}=15.2), 4.69(d,1H,H_B,CH_2-N, AB system, J_{AB}=15.2), 4.87(dd,1H,H-5a,Jaa=9.6,Jea=4.4), 7.00-7.40(m,4H, arom.).

3H,4H,11H,4,4-Bis-(ethoxycarbonyl)-8,9-dimethoxy-3-oxo-1,2,5a,6-tetrahydro-cyclopenta[4,5][1,3]oxazino[3,2-b]isoquinoline 7d (90 % yield), mp 176-178 °C decomp. from ethyl ether, ir, νmax: 1755,1740,1675,1595 cm^{-1}; ^{1}H-nmr(chloroform-d) δ :1.29(t,3H,CH_3-C,J=7.1), 1.27(t,3H,CH_3-C,J=7.1), 2.30-2.56(m,2H,H-1),

2.60-2.86(m,2H,H-2), 3.02(dd,1H,H-6ax,Jgem=14.8,Jaa=9.6), 3.30(dd,1H,H-6eq, Jgem=14.8,Jea=4.4), 3.86(s,3H,O-CH_3), 3.90(s,3H,O-CH_3), 4.05-4.43(m,4H,2-CH_2-O), 4.49(d,1H,H_A,CH_2-N,AB system,J_{AB}=15.2), 4.66(d,1H,H_B,CH_2-N,AB system, J_{AB}=15.2), 4.87(dd,1H,H-5a,Jaa=9.6,Jea=4.40), 6.63(s,1H,H-10), 6.73(s,1H,H-7).

Catalytic Reduction of Compounds 3a,b

Compounds 3a,b were reduced in dioxane solution under atmospheric pressure using Pd on carbon (10 %) as catalyst. When the complete disappearance of the starting material was detected by TLC analysis, the catalyst was filtered off and the mixture obtained after solvent evaporation *in vacuo* was separated by chromatography on a silica gel column (ethyl acetate as eluant) to give, from 3a: 5a (50 % yield)[5], 7a (5 % yield) and N-(3-oxo-cyclohexenyl)-1,2,3,4-tetrahydroisoquinoline 8a (7 % yield) oil product, ir, ν max: 1585, 1535 cm^{-1}; ^{1}H-nmr(chloroform-d) δ: 2.03(qn,2H,-CH_2-CH_2-CH_2-,J=6.0), 2.30(t,2H,-CH_2-CH_2-CH_2-,J=6.0), 2.53(t,2H,-CH_2-CO,J=6.0), 2.90(t,2H,-CH_2-CH_2-N-,J=5.9), 3.57(t,2H,-CH_2-CH_2-N-, J=5.9), 4.47(s,2H,$\Phi$$CH_2$-N-), 5.33(s,1H,=CHCO), 7.00-7.33(m,4H,arom.); from 3b: 5b (32 % yield)[5] and 6b (48 % yield)[5].

Catalytic Reduction of Compounds 6'b,d

Compounds 6'b,d were reduced in dioxane solution under atmospheric pressure using Pd on carbon (5 %) as catalyst. The residue obtained after filtration of the catalyst and evaporation of the solvent solution *in vacuo* was crystallized to give from 6'b: 6b (90 % yield)[5]; from 6'd: diethyl 2-hydroxy-2-[2'-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)-5'-oxocyclopentenyl]malonate 6d (90 % yield), mp 58-59 °C decomp., from ethyl ether; ir, ν max: 3450, 1735, 1650, 1550 cm^{-1}; ^{1}H-nmr (chloroform-d) δ: 1.22(t,6H,2CH_3-C,J=7.1), 2.22-2.46(m,2H, -CH_2-CH_2-CO), 2.70-2.94(m,4H,CH_2-CO and -CH_2-CH_2-N), 3.72(t,2H,-CH_2-CH_2-N, J=5.9), 3.83(s,6H,2-OCH_3), 4.06-4.40(m,4H,2-CH_2-O), 4.62(s,3H,Φ-CH_2-N and OH exch. with D_2O), 6.50(s,1H,arom.), 6.59(s,1H,arom.).

REFERENCES

1) A.Carotti, G.Casini, M.Ferappi, and G.M.Cingolani, J.Heterocyclic Chem., 17, 1577 (1980).

2) A.Carotti, Il Farmaco, Ed.Sci., 26, 146 (1981).

3) C.Altomare, A.Carotti, and F.Campagna, J.Heterocyclic Chem., 20, 1751 (1983).

4) C.Altomare, A.Carotti, G.Casini, and M.Ferappi, J.Heterocyclic Chem., 21, 777 (1984).

5) F.Campagna, C.Altomare, A.Carotti, G.Casini, and M.Ferappi, Steroids, 47, 307 (1986).

6) C.Altomare, F.Campagna, A.Carotti, and W.E.Steinmetz, Heterocycles, 23, 1933 (1985).

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