Study of the Transformation Products of the Oxime of 2,7-Dioxo-3-methyl-5-phenyl-2,3,5,6-tetrahydrocyclopenta[*f*]benzoxazole

Didier Barbry* and Daniel Couturier

Laboratoire de Synthèse Organique, Université des Sciences et Techniques de Lille Flandres-Artois, 59655 - Villeneuve d'Ascq Cédex - France

Noureddine Abdellatifi, Daniel Lesieur, Charles Lespagnol

Institut de Chimie Pharmaceutique, 3 rue du Professeur Laguesse, 59045 - Lille Cédex - France

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Beckmann rearrangement of the title compound gave only a derivative of an isoquinoline structure and its catalytic hydrogenation afforded the *cis* isomer of 1-amino-3-phenyl-1,2-dihydroindenes.

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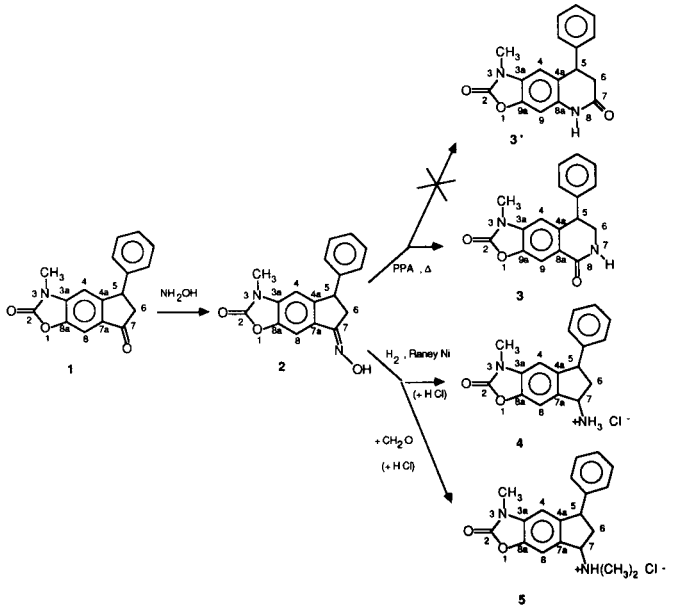
Introduction.

In an attempt to obtain compounds which combine the sedative properties of benzoxazolinone with the antidepressant activity of isoquinoline derivatives or with the neuroleptic properties of the 1-amino-3-phenyldihydroindenes, we have studied the Beckmann rearrangement and the catalytic hydrogenation of the title compound **2**.



SCHEME 1 - TRANSFORMATION PRODUCTS OF THE OXIME OF 2,7-DIOXO-3-METHYL-5-PHENYL-2,3,5,6-TETRAHYDROCYCLOPENTA(f)BENZOXAZOLE

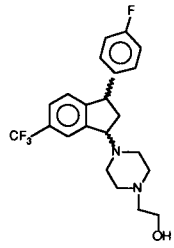
Results and Discussion.

Beckmann Transposition of **2**.

The synthesis of 2,7-dioxo-3-methyl-5-phenyl-2,3,5,6-tetrahydrocyclopenta[f]benzoxazole **1** has been previously described [1]. Compound **2** was obtained by treatment of **1** with hydroxylamine. Previous studies on the structure of the more stable isomer of indanone oxime have established its *E*-configuration on the basis of the coupling constant $^2J(^{13}C,^{15}N)$ [2]. Beckmann rearrangement of 3-phenyl-1-indanone oxime with phosphorus pentachloride has been reported to give 4-phenyl-2-quinolone in 15% yield [3]. More recently, Robba *et al* [4] have not obtained the products of Beckmann rearrangement of 3-trifluoroacetylamino-1-indanone oxime with sulfuric acid or phosphorus pentachloride. Heating **2** with PPA at 120° gave the isoquinolone **3** in 60% yield. The structure of this compound was established by ^1H nmr spectroscopy. The two H-6 protons are non equivalent (δ at 3.68 and 3.83 ppm) and constitute at 400 MHz the AB part of an ABMX spectrum which was reduced into an ABX by NH irradiation. The value of 3 Hz of the coupling constant (NH, H-6) was only compatible with vicinal protons of the isoquinolone. This Beckmann transposition is regiospecific.

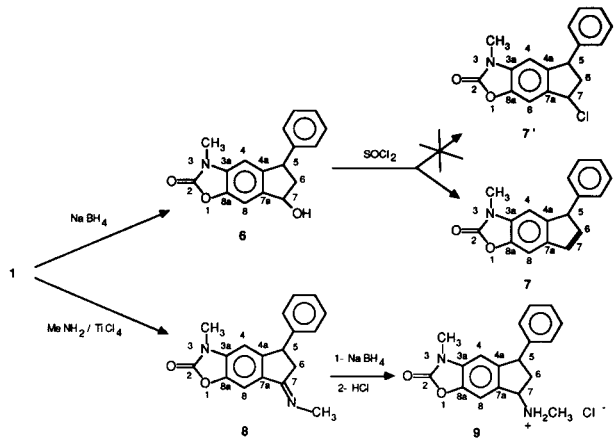
Catalytic Hydrogenation of **2**.

Hydrogenation of **2** under 700 psi with Raney nickel at 80° followed by treatment with hydrogen chloride affords 7-amino-3-methyl-2-oxo-5-phenyl-2,3,5,6-tetrahydrocyclopenta[*f*]benzoxazole hydrochloride **4**. Its *N*-dimethyl derivative **5** was obtained by the same reaction in the presence of formalin. Structures of **4** and **5** are related to the stereochemistry of 1,3-disubstituted 1,2-dihydroindenes and the geometry of these compounds has been little studied. Bogeso *et al* [5] have reported the synthesis of 1-piperazino-3-phenyl-1,2-dihydroindenes whose stereochemistry has been established by X-ray diffraction. In the case of tefludazine correlation with ^1H nmr spectroscopy (80 MHz) [6] has displayed that, in the *cis* compound, H-1 and H-3 (δ = 4.17 and 4.45 ppm) appeared as broadened triplets (J = 9.5 and 8.5 Hz) whereas in the *trans* isomer, the two protons merged at 4.5 ppm (one of these would be a doublet of doublets (J = 8.5 and 4.25 Hz) with a pseudoaxial amino group and a pseudoequatorial phenyl substituent. Protons 5 and 7 of **4** and **5** appear at 80 MHz as triplets with coupling constants close to 8 Hz; H-5 resonates at 4.4 ppm for the two compounds whereas H-7 appears at 4.79 for **4** and at 5.36 ppm for **5**. This similarity with the results of Bogeso *et al* allows to believe that **4** and **5** are the *cis* isomers (chemical shift differences between



SCHEME 2 - TEFLUDAZINE

H-3 of tefludazine and H-7 of **4** and **5** are those between amines and their salts). More evidences were obtained by trying to prepare aminophenyldihydroindenes by the same methods as those used by Bogeso *et al* [5] (Scheme 3). Reduction of **1** with sodium borohydride gave the *cis* alcohol **6** whose treatment with thionyl chloride afforded the indene **7** and not the chloro compound **7'**, however treatment of **1** with methylamine in the presence of titanium (IV) chloride followed by reduction of the imine led to **9**. This compound exhibited a ^{1}H nmr spectrum similar to those of **4** and **5**. Bogeso *et al* [5] have assigned the *cis* structure to the product of reduction of their imine. Thus **9** as **4** and **5** are the *cis* stereoisomers and these reactions are stereospecific.



SCHEME 3 - SYNTHESIS OF SALTS OF 7-AMINO-3-METHYL-2-OXO-5-PHENYL-2,3,5,6-TETRAHYDROCYCLOPENTA(f)BENZOXAZOLE

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were performed by the central Microanalytical Department of CNRS (Vernaison, France). The ir spectra were recorded on a Perkin-Elmer 297 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker wp 80 or AM 400 instrument in 5 mm tubes using standard pulses sequence and TMS as internal reference. Compound **1** was previously described [1].

3-Methyl-7-oximino-2-oxo-5-phenyl-2,3,5,6-tetrahydrocyclopenta-[*f*]benzoxazole **2**.

A mixture of ketone **1** (5.58 g, 20 mmoles), hydroxylamine hydrochloride (2.78 g, 40 mmoles) ans sodium acetate (3.28 g, 40 mmoles) in ethanol (150 ml) was refluxed for six hours with stirring. The hot mixture was filtered, the solvent was removed under vacuum, the pulverized residue, was washed with water and recrystallized from benzene to afford 4.71 g of **2** (yield 80%), mp 219°; ir (neat): 3170, 2800-2860, 1750-1770, 1605 cm^{-1}; ^{1}H nmr (acetone-d_6): 400 MHz δ 2.78 (dd, 1H, H-6, ^{3}J(5,6) = 4.13 Hz, I ^{2}J(6,6')I = 18.7 Hz), 3.34 (s, 3H, N-Me), 3.50 (dd, 1H, H6', ^{3}J(5,6') = 8.63 Hz), 4.57 (dd, 1H, H-5), 6.84 (s, 1H, H-4), 7.23 (m, 5H, phenylring protons), 7.41 (s, 1H, H-8), 10.93 (s, 1H, N-OH) ppm.

Anal. Calcd. for $C_{17}N_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52; O, 16.31. Found: C, 69.09; H, 4.93; N, 9.27; O, 16.40.

2,8-Dioxo-3-methyl-5-phenyl-2,3,5,6,7,8-hexahydropyrido[4,3-*f*]-benzoxazole **3**.

A mixture of oxime **2** (7.7 g, 24 mmoles) and PPA (120 g) was heated at 120° for 1.5 hours and poured into cold water (500 g). The precipitate was washed with water until neutral and dried. The residue was pulverized and refluxed for two hours in chloroform (500 ml). After filtering, the solvent was removed under vacuum and the residue was recrystallized from benzene to afford 4.24 g of **3** (yield 60%), mp 274°; ir (neat): 3030-3160, 2880, 1760, 1665, 1600 cm^{-1}; ^{1}H nmr deuteriochloroform): 400 MHz δ 3.30 (s, 3H, N-Me), 3.69 (m, 1H, H-6, ^{2}J(6,6')I = 12.3 Hz, ^{3}J(6,7) = 3 Hz), 3.83 (m, 1H, H-6', ^{3}J(6',7) = 3Hz), 4.34 (dd, 1H, H-5 ^{3}J(5,6) = 5.2 Hz, ^{3}J(5,6') =7.5 Hz), 6.17 (s, 1H, H-7), 6.52 (s, 1H, H-4), 7.21 (m, 5H, phenyl ring protons), 8.00 (s, 1H, H-9) ppm; ^{13}C nmr deuteriochloroform): 100 MHz δ 28.3, 44.5, 47.2, 106.9, 109.6, 124.0, 127.6, 128.4, 128.9, 135.2, 138.5, 140.3, 141.8, 154.3, 165.2 ppm.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52; O, 16.31. Found: C, 69.30; H, 5.05; N, 9.37; O, 16.28.

7-Amino-3-methyl-2-oxo-5-phenyl-2,3,5,6-tetrahydrocyclopenta[*f*]-benzoxazole Hydrochloride **4**.

A mixture of **2** (3.53 g, 12 mmoles), Raney nickel (0.4 g) and methanol (150 ml) was heated at 80° for seven hours under a hydrogen atmosphere (700 psi). After filtering, the solvent was removed under vacuum and the residue was diluted with ethanol (50 ml). Dry hydrogen chloride was bubbled through the solution and the salt precipitated slowly. After filtering and drying, the ammonium salt was recrystallized to give 2.05 g of **4** (yield 54%), mp 284°; ir (neat): 2860, 1765 1590 cm^{-1}; ^{1}H nmr (DMSO-d_6): 400 MHz δ 2.08 (m, 1H, H-6, ^{2}J(6,6')I = 12.0 Hz), 2.99 (m, 1H, H-6'), 3.23 (s, 3H, N-Me), 4.34 (t, 1H, H-5, ^{3}J(5,6) = ^{3}J(5,6') = 8.8 Hz), 4.79 (dt, 1H, H-7, ^{3}J(6,7) = ^{3}J(6',7) = ^{3}J(6',7) = 8.3 Hz), 6.61 (s, 1H, H-4), 7.32 (m, 5H, phenyl) ring protons), 7.83 (s, 1H, H-8), 9.00 (d, 3H, $+NH_3$) ppm; ^{13}C nmr (DMSO-d_6): 100 MHz δ 28.0, 41.4, 48.1, 53.1, 105.0, 105.5, 126.8, 128.2, 128.6, 132.5, 133.3, 141.1, 141.7, 143.2, 154.0 ppm.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.41; N, 8.84; Cl, 11.19. Found: C, 64.18; H, 5.47; N, 8.61; Cl, 10.88.

7-Dimethylamino-3-methyl-2-oxo-5-phenyl-2,3,5,6-tetrahydro-cyclopenta[*f*]benzoxazole Hydrochloride **5**.

A 52% yield (2.15 g) of this compound was obtained by the same work-up as above for 18 hours of hydrogenation with formalin (48 mmoles), mp 254°; ir (neat): 2880-2900, 2400-2560, 1760, 1600 cm^{-1}; ^{1}H nmr (deuteriochloroform): 400 MHz δ 2.03 (m, 1H, H-6, ^{2}J(6,6')I = 13.2 Hz), 2.60 and 2.90 (2s, 2 x 3H, $+NMe_2$), 2.99 (m, 1H, H-6'), 3.27 (s, 3H, N-Me), 4.47 (t, 1H, H-5,

$^3J(5,6) = {}^3J(5,6') = 8.5$ Hz), 5.36 (t, 1H, H-7, $^3J(6,7) = {}^3J(6',7) = 7.9$ Hz), 6.51 (s, 1H, H-4), 7.26 (m, 5H, phenyl ring protons), 8.17 (s, 1H, H-8), 13.0 (bs, 1H, +NH) ppm; ^{13}C nmr (deuteriochloroform): 100 MHz δ 28.1, 34.8, 35.2, 42.1, 47.9, 68.2, 104.9, 107.7, 127.5, 127.9, 129.1, 129.9, 133.5, 142.3, 142.4, 142.7, 154.4 ppm.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_2$: C, 66.17; H, 6.13; N, 8.12; Cl, 10.28. Found: C, 65.83; H, 6.28; N, 7.78; Cl, 10.27.

7-Hydroxy-3-methyl-2-oxo-5-phenyl-2,3,5,6-tetrahydrocyclopenta-[*f*]benzoxazole **6**.

A mixture of **1** (5.58 g, 20 mmoles), sodium borohydride (1.51 g, 40 mmoles) and methanol (400 ml) was stirred for two hours at room temperature and then filtered. The solvent was removed under vacuum, the residue was diluted with water (30 ml) and extracted with chloroform (3 × 30 ml) and the organic layers were dried over calcium chloride. The solvent was removed under vacuum and the residue crystallized from 50% ethanol to give 4.78 g of **6** (yield 85%), mp 173°; ir (neat): 3380, 2880-2950, 1760, 1605 cm^{-1}; ^1H nmr (deuteriochloroform): (400 MHz δ 1.98 (m, 1H, H-6, $I^2J(6,6')$ I = 12.5 Hz), 2.35 (s, 1H, OH), 3.05 (m, 1H, H-6'), 3.27 (s, 3H, N-Me), 4.18 (t, 1H, H-5, $^3J(5,6) = {}^3J(5,6') = 8.2$ Hz), 5.30 (t, 1H, H-7, $^3J(6,7) = {}^3J(6',7) = 6.3$ Hz), 6.46 (s, 1H, H-4), 7.30 (m, 5H, phenyl ring protons), 7.37 (s, 1H, H-8) ppm; ^{13}C nmr (deuteriochloroform): 100 MHz δ 28.1, 47.2, 48.3, 74.7, 104.5, 105.6, 126.8, 128.2, 128.7, 132.1, 139.8, 141.4, 142.1, 143.9, 155.0 ppm.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; O, 17.06. Found: C, 72.79; H, 5.32; N, 4.88; O, 17.01.

3-Methyl-2-oxo-5-phenyl-2,3-dihydro-5*H*-cyclopenta[*f*]benzoxazole **7**.

A solution of thionyl chloride (1.19 g, 10 mmoles) in chloroform (10 ml) was added dropwise to the alcohol **6** (2.81 g, 10 mmoles) diluted with chloroform (40 ml). The mixture was stirred at room temperature for six hours and then filtered. The solvent was removed under vacuum and the residue was crystallized from cyclohexane to afford 1.84 g of **7** (yield 70%), mp 155°; ir (neat): 1760, 1595-1610, 865 cm^{-1}; ^1H nmr (deuteriochloroform): (400 MHz δ 3.32 (s, 3H, N-Me), 4.58 (m, 1H, H-5), 6.57-6.88 (2 dd, 2H, H-6 and H-7, $^3J(6,7) = 5.6$ Hz, $^3J(5,6) = I\ {}^4J(5,7)$ I = 1.75 Hz), 6.82 (s, 1H, H-4), 7.19 (m, 6H, H-8 and phenyl ring protons) ppm; ^{13}C nmr (deuteriochloroform): (100 MHz δ 27.1, 55.4, 102.2, 103.4, 126.0, 126.7, 127.8, 128.7, 130.0, 137.8, 139.2, 140.9, 143.4, 154.0 ppm.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32; O, 12.15. Found: C, 77.80; H, 4.87; N, 5.16; O, 12.17.

3-Methyl-7-methylamino-2-oxo-5-phenyl-2,3,5,6-tetrahydrocyclopenta[*f*]benzoxazole Hydrochloride **9**.

A solution of methylamine (2.60 g, 84 mmoles) in THF (20 ml) was slowly added to a cooled solution of ketone **1** (3.34 g, 12 mmoles) and titanium (IV) chloride (1.23 g, 6.5 mmoles) in THF (80 ml). The mixture was stirred at room temperature for twenty hours and then filtered. The solvent was removed under vacuum and the residue was diluted with methanol (150 ml). Sodium borohydride (0.75 g, 20 mmoles) was then added portionwise and the mixture was stirred at room temperature for four hours and filtered. The solvent was removed under vacuum and the residue was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). The organic layers were dried over calcium chloride. The solvent was removed under vacuum and the residue was diluted with ethanol (50 ml). Dry hydrogen chloride bubbled through the solution and the salt precipitated slowly. After filtering and drying, the ammonium salt was recrystallized from ethanol to give 1.19 g of **9** (yield 30%), mp 289°; ir (neat): 2900, 2710, 1770, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): (400 MHz δ 2.14 (m, 1H, H-6, I $^2J(6,6')$ I = 12.3 Hz), 2.62 (d, 3H, +NMe), 2.98 (m, 1H, H-6'), 3.23 (s, 3H, N-Me), 4.35 (t, 1H, H-5, $^3J(5,6) = {}^3J(5,6') = 9.2$ Hz), 4.82 (m, 1H, H-7), 6.63 (s, 1H, H-4), 7.36 (m, 5H, phenyl ring protons), 7.96 (s, 1H, H-8), 9.6 and 10.2 (2d, 2H, $+NH_2$) ppm; ^{13}C nmr 100 MHz δ 28.6, 30.3, 39.1, 48.3, 61.2, 105.6, 106.4, 127.4, 128.8, 129.1, 132.3, 133.3, 141.6, 142.7, 143.6, 154.5 ppm.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.79; N, 8.47; Cl, 10.71. Found: C, 65.32; H, 6.04; N, 8.67; Cl, 10.88.

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