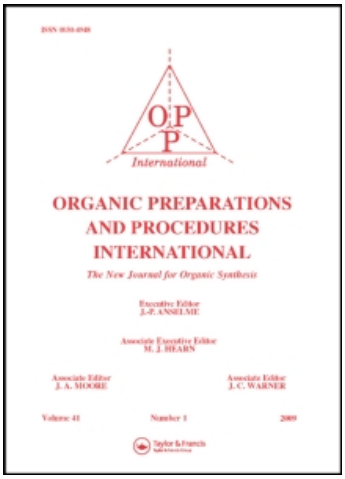



**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# PREPARATION OF REDOX DERIVATIVES OF 3α-HYDROXY-5α-PREGNANE-11,20-DIONE

Emil Pop[ab]; Marcus E. Brewster[ab]; Katalin Prókai-Tátrai[ab]; Nicholas Bodor[ab]
[a] Pharmos Corporation, Alachua, FL [b] Center for Drug Discovery, University of Florida, Gainesville, FL

**To cite this Article** Pop, Emil , Brewster, Marcus E. , Prókai-Tátrai, Katalin and Bodor, Nicholas(1994) 'PREPARATION OF REDOX DERIVATIVES OF 3α-HYDROXY-5α-PREGNANE-11,20-DIONE', Organic Preparations and Procedures International, 26: 3, 379 — 382
**To link to this Article: DOI:** 10.1080/00304949409458444
**URL:** http://dx.doi.org/10.1080/00304949409458444

# PREPARATION OF REDOX DERIVATIVES OF 3α-HYDROXY-5α-PREGNANE-11,20-DIONE

*Submitted by* (09/20/93)

Emil Pop*, Marcus E. Brewster, Katalin Prókai-Tátrai and Nicholas Bodor

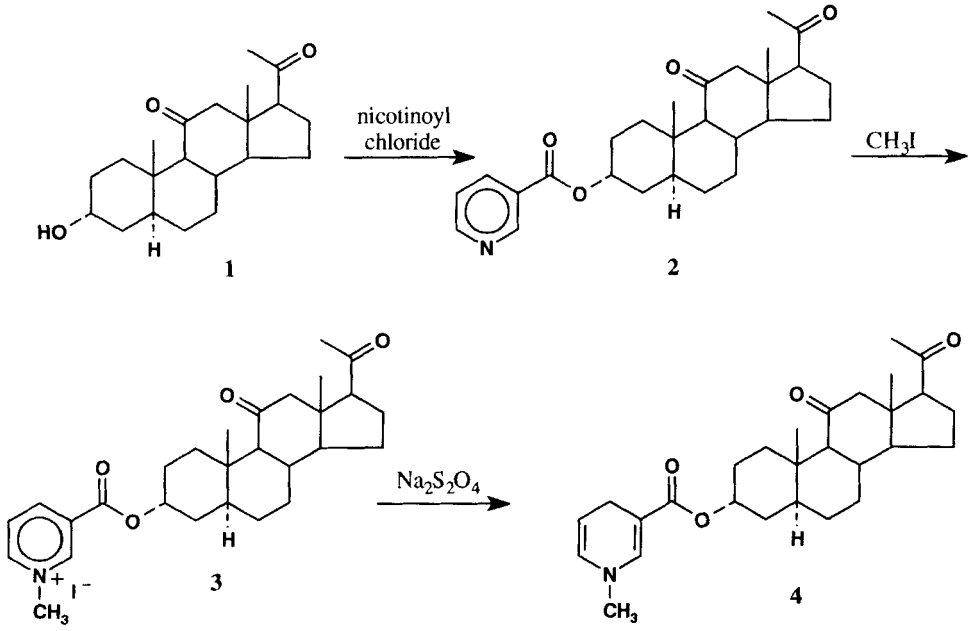
*Pharmos Corporation, 2 Innovation Drive, Alachua, FL 32615*

*Center for Drug Discovery, University of Florida, Gainesville, FL 32610*



3α-Hydroxy-5α-pregnane-11,20-dione (Alfaxalone, **1**), a steroid anesthetic introduced to both human and veterinary medicine in 1971 was favorably received by clinicians.[1] In spite of a remarkable therapeutic index and safety profile, an unacceptable incidence of adverse allergic reactions (estimated between 0.1 and 0.25%) resulted in withdrawal of Althesin®, the alfaxalone formulation for humans.[2] However, evidence indicates that the allergic responses can be attributed to the formulation.[3] In order to improve the central nervous system delivery and selectively reduce peripheral side effects, the chemical delivery system (CDS)[4,5] approach has been applied to **1**. The CDSs are based on a dihydropyridine ↔ pyridinium salt redox system, analogous to the endogenous NADH ↔ $NAD^+$ coenzyme system. Two synthetic procedures for the attachment of the 1,4-dihydropyridine moiety to **1** are described herein.

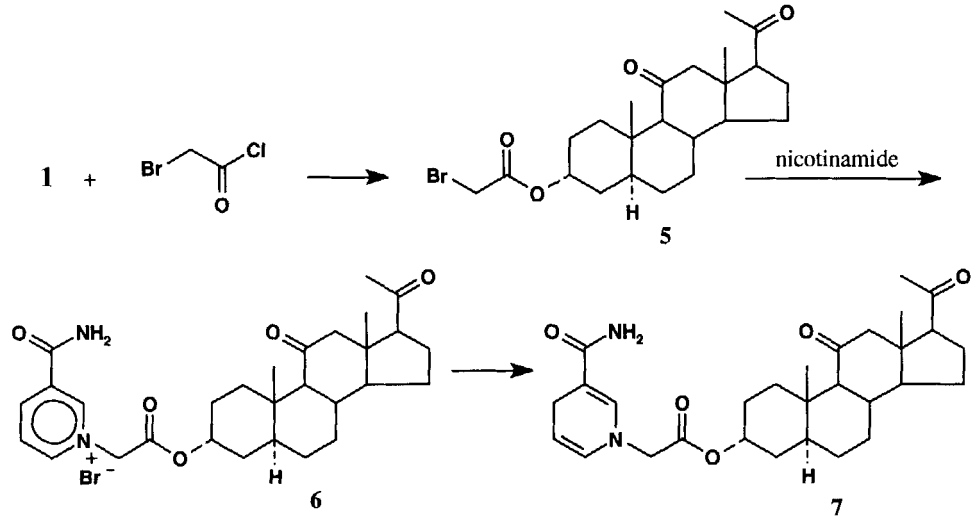
The only possible synthetic handle for preparation of reversible derivatives of **1** is the 3 hydroxylic functionality. The epimerization at C-3 during functionalization has to be avoided since the 3 conformer (betaxolon) is inactive. As shown in Scheme 1, alfaxalone was esterified with nicotinoyl chloride in pyridine. The resulting 3-nicotinate (**2**) was N-alkylated with methyl iodide giving the




**Scheme 1**

pyridinium quaternary salt **3**. Regioselective reduction of **3** with sodium dithionite in a biphasic system (aqueous sodium bicarbonate and ethyl acetate) gave the 1-methyl-1,4-dihydronicotinate of **1**, *i. e.*, CDS **4**.[6] Preferential formation of the 1,4 isomers of the dihydropyridines arises from thermodynamic control.[7]

The synthesis of another type of CDS, **7**, in which the redox moiety is attached to the drug *via* the pyridine nitrogen as a substitute acetate[8,9] is illustrated in Scheme 2. The 3-hydroxyl group of **1** was acylated with bromoacetyl chloride in chloroform in the presence of triethylamine. The bromoacetate **5** was reacted with nicotinamide in acetonitrile at room temperature to produce the quaternary salt **6**. The CDS **7** was then obtained by reducing **6** as described above.




**Scheme 2**



## EXPERIMENTAL SECTION

Uncorrected melting points were determined with a Fisher melting-point apparatus. Elemental microcombustion analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. Ultraviolet spectra (UV) were determined on a Hewlett-Packard 8451A diode array spectrophotometer. $^1$HNMR spectra were recorded on a Varian XL 200 MHz (FT) spectrometer and chemical shifts are reported as parts per million (δ) relative to TMS. Coupling constants (J) are reported in Hz. Mass spectra were recorded on a Kratos, MS 80-RFA instrument. Fast atom bombardment (FAB) ionization was performed by xenon beam (6 KeV) using samples in glycerol.[10] Thin layer chromatography (TLC) was performed on EM Reagents DC-aluminum foil plates (0.2 mm thickness silica gel 60). A mixture of methanol:chloroform, 1:8 was used as eluant. All chemicals were reagent grade.

**3-{[(Pyridinyl)carbonyl]oxy}-5-pregnane-11,20-dione (2).**- To a solution of 3.40 g (10 mmol) of 5-pregnane-3-ol-11,20-dione (Alfaxalone, **1**; SIGMA) in 10 mL dry pyridine, was added 1.90 g (10.6 mmol) of nicotinoyl chloride at 0-5°. The reaction mixture was stirred at 20-25° for 20 hrs, poured

into ice (100 g) and extracted with ethyl acetate (2 x 150 mL). The organic layer was extracted with water (2 x 50 mL) and dried ($MgSO_4$). Removal of solvent *in vacuo* and recrystallization of the crude product (methanol:ether) afforded **2** (white solid, 3.29 g, 75% yield) mp 175-177°; $R_f$: 0.72. $^1H$ NMR (DMSO-$d_6$): δ 0.51 (s, 3H), 1.01 (s, 3H), 1.21-1.42 (m, 5H), 1.60-1.64 (m, 3H), 1.77-1.92 (m, 8H), 2.11 (s, 3H), 2.21-2.57 (m, 5H), 5.31 (s, 1H), 7.40-7.44 (m, 1H), 8.30-8.33 (m, 1H), 8.78 (d, 1H, J = 3.18), 9.26 (s, 1H).

*Anal.* Calcd. for $C_{27}H_{36}NO_4$: C, 73.93; H, 8.27; N, 9.12. Found: C, 73.71; H, 8.34; N, 9.21.

**1-Methyl-3-{[5-pregnane-11,20-dione-3-yl)oxy]carbonyl}pyridinium Iodide (3).**- A solution of 1.00 g (2.27 mmol) of **2** and 0.44 g (1 mL) (30 mmol) methyl iodide in 50 mL acetone was stirred at 20-25° for 16 h. Addition of 100 mL diethylether to the reaction mixture precipitated **3**; recrystallization (methanol: ether) yielded 1.09 g (83% yield) of **3** (off-white solid), mp 240-245° (decomp). M.S. (FAB) $C^+$(m/z): 451. UV (MeOH) $\lambda_{max}$: 218, 265 nm. $^1H$ NMR (DMSO-$d_6$): δ 0.52 (s, 3H), 1.03 (s, 3H), 1.20-1.41 (m, 5H), 1.62-1.66 (m, 3H), 1.81-1.86 (m, 8H), 2.07 (s, 3H), 2.12-2.81 (m, 5H), 4.60 (s, 3H), 5.31 (d, 1H, J = 6.12), 9.33 (d, 1H, J = 3.89), 9.62 (s, 1H).

*Anal.* Calcd. for $C_{28}H_{39}INO_4$: C, 58.06; H, 6.51; I, 21.91; N, 2.41
Found: C, 57.82; H, 6.59; I, 21.84; N, 2.37

**3{[(1-Methyl-1,4-dihydropyridine-3-yl)carbonyl]oxy}-5-pregnane-11,20-dione (4).**- To a solution of 0.58 g (1 mmol) of **3** in 150 mL deaerated water and 150 mL of ethyl acetate, was added a mixture of 0.70 g (4 mmol) of sodium dithionite and 0.33 g (6 mmol) of sodium bicarbonate with stirring at 20-25°, under argon 1 h. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 100 mL) and the combined organics with cold water (2 x 100 mL). After drying ($MgSO_4$) and removing the solvent *in vacuo* 0.32 g (70% yield) of **4** was obtained (yellow solid), mp 138-41° (decomp). $R_f$: 0.87. UV (MeOH) $\lambda_{max}$: 210, 360 nm. $^1H$ NMR (DMSO-$d_6$): δ 0.52 (s, 3H), 0.98 (s, 3H), 1.09-1.21 (m, 5H), 1.31-1.92 (m, 11H), 2.11 (s, 3H), 2.31-2.25 (m, 3H), 2.67-2.87 (m, 5H), 2.98-3.07 (m, 5H), 4.67-4.74 (m, 1H), 4.86 (bs, 1H), 5.86 (d, 1H, J = 6.11), 7.01 (s, 1H).

*Anal.* Calcd. for $C_{28}H_{40}NO_4$: C, 73.97; H, 8.86; N, 3.07. Found C, 73.78; H, 8.51; N, 2.88

**3-Bromoacetyl-5-pregnane-11,20-dione (5).**- A solution of 1.00 g (6 mmol) of bromoacetyl chloride in 10 mL chloroform was added dropwise to a solution of 2.22 g (6 mmol) of **1** and 0.64 g (6 mmol) triethylamine in 20 mL chloroform at 0-5°. The reaction mixture was stirred at 20-25° for 24 h, then extracted with water (2 x 50 mL), and dried over $Na_2SO_4$. After removing the solvent *in vacuo* 2.44 g (90% yield) of **5** was obtained as an oil. $R_f$ 0.67. $^1H$ NMR (DMSO-$d_6$) similar to **1**. The methylene protons of the bromoacetyl group (s, 2H) are at 3.97 ppm. The compound was used in the following step:

**3-Carbamoyl-1-{[(5-pregnane-11,20-dione-3-yl)oxy]-2-oxoethyl}pyridinium Bromide (6).**- To a solution of 1.50 g (3.3 mmol) of **5** in 30 mL acetonitrile, 0.40 g (3.3 mmol) of nicotinamide was added. The mixture was stirred at 20-25° for 24 hrs then poured into 100 mL of diethyl ether. The precipitate was filtered off and recrystalized from acetone: ether to afford 1.73 g (91% yield) of **6** (off-white solid) mp 95-100° (dec), UV (MeOH) $\lambda_{max}$: 212.5, 266.5 nm. MS (FAB) $C^+$(m/z): 495. $^1H$

NMR (DMSO-$d_6$): δ 5.02 (bs, 1H), 5.75 (s, 2H), 8.31-8.39 (m, 2H), 8.78 (s, 1H), 9.22-9.28 (m, 2H), 9.72 (s, 1H) (the rest similar to **3**).

*Anal.* Calcd. for $C_{29}H_{39}BrN_2O_5$: C, 60.51;H, 6.83; Br, 13.88; N, 4.86.
Found: C, 60.83; H, 6.97; Br, 13.71; N, 4.51

**3-{[(3-Carbamoyl-1(4*H*)-pyridin-1-yl)methoxy]carbonyl}-5-pregnane-11,20-dione (7).**- Reduction of 0.31 g (5.4 mmol) of **6** dissolved in 100 mL deaerated water and 50 mL ethyl acetate with 0.37 g (2.16 mmol) sodium dithionite and 0.27 g (3.24 mmol) sodium bicarbonate (2 hrs at 20-25° C, cf. **4**) afforded 1.88 g (70% yield) of **7** (hygroscopic yellow solid) mp 95-98° (decomp) $R_f$: 0.74. UV (MeOH) $\lambda_{max}$: 220, 348 nm. $^1$H NMR ($CDCl_3$): δ 3.81 (s, 2H), 4.77-4.79 (m, 1H); 5.07 (bs, 1H), 5.68 (d, 1H, J = 7.11), 7.05 (s, 1H) (rest similar to **4**).

*Anal. Calcd. for* $C_{29}H_{40}N_2O_5$; C, 70.13; H, 8.12; N, 5.64. Found: C, 69.85; H, 8.35; N, 5.53

**Acknowledgments.**- The authors would like to thank Dr. L. Prokai for mass spectra determinations and Kathe Burkhead for her editorial expertise and assistance in preparing the manuscript.

## REFERENCES

1. P. J. Wright and J. W. Dundee, *Anaesthesia*, **37**, 1209 (1982).

2. M. Morgan and J. G. Whitman, *ibid.*, **40**, 121 (1985).

3. L. W. Hall and K. W. Clarke, "*Veterinary Anesthesia*", 8th Ed., p. 305, Bailliere Tindall, London, 1977.

4. N. Bodor, *Drugs of the Future*, **6**, 165 (1981).

5. N. Bodor, *Ann. N.Y. Acad. Sci.*, **507**, 289 (1987).

6. U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 2 (1972).

7. E. Pop, M. E. Brewster, M.-J. Huang and N. Bodor, *J. Mol. Structure (Theochem)*, **283**, 27 (1993).

8. E. Pop,E. Shek, T. Murakami and N. Bodor, *J. Pharm. Sci.*, **78**, 609 (1989).

9. E. Pop, W. Anderson, K. Prókai-Tátrai, J. Vlasak, M. E. Brewster and N. Bodor, *Med. Chem. Res.*, **2**, 16 (1992).

10. L. Prókai, B. Hsu, H. Farag and N. Bodor, *Anal. Chem.*, **61**, 1723 (1989).

********