Synthesis of Granatanine-3-spiro-5′-hydantoin-*N*-ω-hydroxyalkyl Esters

G. G. Trigo (1), C. Avendaño, P. Ballesteros and A. Sastre

Department of Organic and Pharmaceutical Chemistry, School of Pharmacy,
Universidad Complutense, Madrid-3, Spain

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Synthetic methods to prepare *N*-ω-hydroxyalkyl-*nor*-psuedopelletierine and granatanine-3-spiro-5′-hydantoin *N*-ω-hydroxyalkylbenzylic and diphenylacetic esters are analyzed. The Bucherer-Bergs synthesis used by us to obtain some other granatanine-spirohydantoins (2), originates the hydrolysis of the ester group.

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Introduction.

The central anticholinergic activity found by Ribbentrop, *et al.*, (3) in some *N*-ω-hydroxyalkylgranatanine esters I (4,5) and 3-*nor*-granatanols *N*-substituted esters II (6) (Figure 1) and the anticonvulsivant activity of the hydantoin ring led us to prepare compounds **3a** and **3b**. The synthesis of these compounds was designed following the two ways showed in Scheme I.

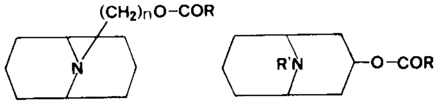
Results and Discussion.

Compound **2a** was prepared by reaction of **1a** with diphenylacetyl chloride while **2b** was obtained by *trans*-esterification from **1a**. Compounds **1a** and **1b** were prepared following the general Robinson-Schöpf procedure (7).

When **2a** and **2b** were dissolved with potassium cyanide and ammonium carbonate in 50% aqueous ethanol at 55-60° according to the Bucherer-Bergs proceudre (8), compounds **2a** and **2b** were recovered. The same reaction, in sealed flask at 65°, gave compound **1a** and the potassium salt of the acid originated by saponification of the ester group (Figure 2).

Since no literature references about the Bucherer-Bergs reaction on ketones including ester groups have been found, this reaction was assayed with compound **5** (Figure 3). The carbonyl group was transformed in this case in the corresponding spirohydantoin, but the ester group was also hydrolyzed.

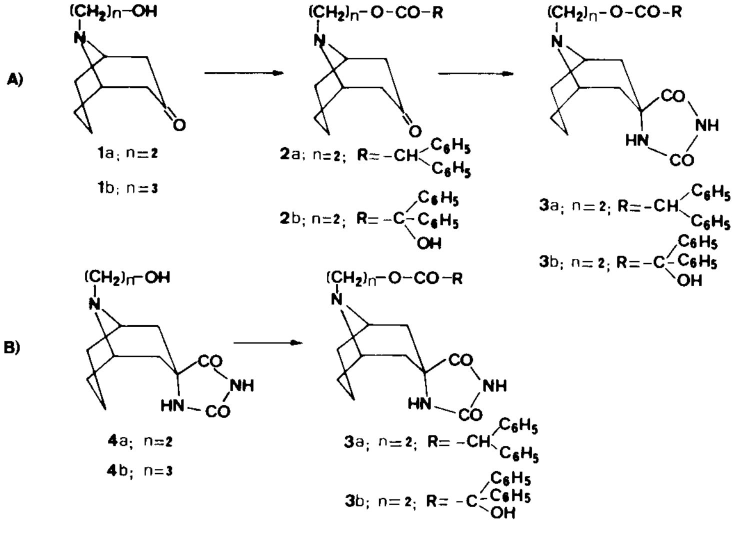
These results seem to point out that the way A) shown in Scheme I is not reliable to obtain compounds **3a** and **3b**.



I   II

Figure 1

Scheme I



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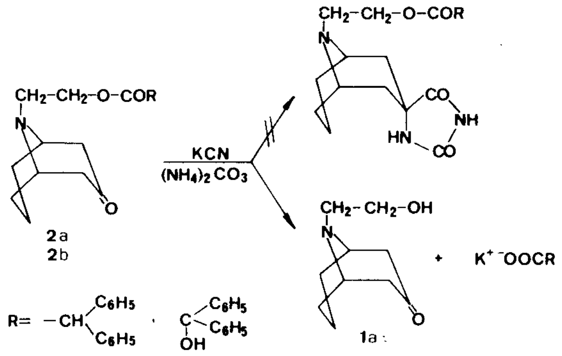

Figure 2

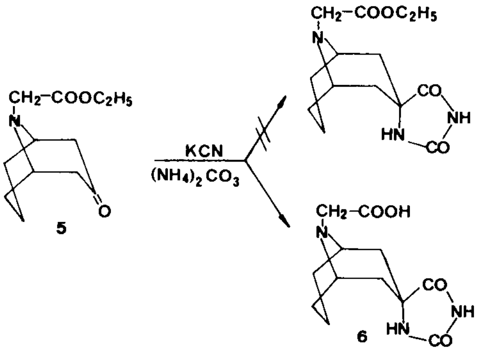

Figure 3

Compound **4b** was prepared from **1b** following the method used for **4a** (2). Compound **4a** gave **3a** by treatment with diphenylacetyl chloride. The high melting point of **4a** made impossible the *trans*esterification method to obtain **3b**, which was then prepared by reaction of the *N*-β-chloroethyl derivative **7** with potassium benzylate.

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 577 spectrophotometer.

N-β-Hydroxyethyl-*nor*-pseudopelletierine (**1a**) and *N*-γ-Hydroxypropyl-*nor*-pseudopelletierine (**1b**).

These compounds were obtained following reference (4).

N-β-Hydroxyethyl-*nor*-psuedopelletierine Diphenylacetic Ester (**2a**).

Five g. (0.027 mole) of **1a** was heated under reflux with 6.3 g. (0.027 mole) of diphenylacetyl chloride and 27.2 ml. of pyridine. After 8 hours the solvent was removed under vacuum. The residue was triturated with ethyl acetate and 8 g. of **2a** hydrochloride was obtained, yield 68%, m.p. 209-210° (from absolute ethanol); ir (potassium bromide): 1710 and 1750 (C=O) cm^{-1}.

Anal. Calcd. for $C_{24}H_{28}ClNO_3$: C, 69.62; H, 6.81; N, 3.38; Cl, 8.57. Found: C, 69.74; H, 6.83; N, 3.62; Cl, 8.89.

Compound **2a** hydrochloride was neutralized with 0.1 *N* sodium hydroxide giving **2a**, m.p. 105-106°; ir: 1705 and 1737 (C=O) cm^{-1}.

N-β-Hydroxyethyl-*nor*-psuedopelletierine Benzylic Ester (**2b**).

Ten g. (0.05 mole) of **1a**, 14.2 g. (0.05 mole) of methyl benzylate and 0.14 g. (0.006 mole) of sodium were heated at 80°/30 for 3 hours. After 7 additional hours at 130°/30, the reaction mixture was cooled and acidified with 6*N* hydrochloric acid. Twenty-one g. of **2b** hydrochloride was precipitated with ether, yield 90%, m.p. 191-192° (from 2-propanol), ir (potassium bromide): 1725 and 1750 (C=O) cm^{-1}.

Anal. Calcd. for $C_{24}H_{28}ClNO_4$: C, 67.03; H, 6.56; N, 3.25. Found: C, 66.60; H, 6.61; N, 3.24.

Compound **2b** hydrochloride was neutralized with 0.1 *N* sodium hydroxide giving **2b**, m.p. 80-81°; ir (potassium bromide): 1625 and 1736 (C=O); 3470 (OH) cm^{-1}.

Bucherer-Bergs Synthesis on *N*-β-Hydroxyethyl-*nor*-pseudopelletierine Benzylic Ester.

a) Compound **2b** hydrochloride (8.6 g., 0.02 mole) was dissolved by heating in 105 ml. of 50% ethanol/water and a solution of 16 g. (0.02 mole) of potassium cyanide and 5.7 g. (0.06 mole) of ammonium carbonate in 25 ml. of water was added. The solution was heated under reflux at 55-60° for 5 hours. After cooling, **2b** was recovered.

b) In a "Sovirel" sealed flask, 5.6 g. (0.01 mole) of **2b**, 0.8 g. (0.01 mole) of potassium cyanide and 27 g. (0.03 mole) of ammonium carbonate in 140 ml. of 50% ethanol/water were heated at 65° for 8 days, then the solution was cooled and 6 *N* hydrochloric acid was added to adjust *p*H = 7. The solvent was removed under vacuum and the residue extracted with absolute ethanol. Potassium benzylate crystallized. When the ethanolic solution was concentrated, the residue was identified as **1a**.

N-Ethoxycarbonylmethyl-*nor*-pseudopelletierine (**5**).

Acetonedicarboxylic acid (8.3 g., 0.057 mole), 20.5 ml. (0.057 mole) of a 25% aqueous glutardialdehyde solution, 8 g. (0.057 mole) of ethyl glycocolate hydrochloride and 17.5 g. of sodium acetate were dissolved in 36 ml. of water. The *p*H of the mixture was adjusted to a value of 3 with 3 *N* hydrochloric acid and the resulting mixture was permitted to stand at room temperature for a period of 3 days. Thereafter the admixture was made alkaline using potassium carbonate and the alkaline mixture extracted several times with chloroform. The extract obtained was dried, concentrated and the residue distilled. The yield amounts to 3.25 g. (25%) of **5** having a b.p. 0.05 112.5°; ir (liquid film): 1715 and 1755 (C=O) cm^{-1}. The hydrobromide had m.p. 209-210° (from absolute ethanol), ir (potassium bromide) 1730 and 1760 (C=O); 2550 ($\overset{+}{N}$-H) cm^{-1}.

Anal. Calcd. for $C_{12}H_{20}BrNO_3$: C, 47.05; H, 6.58; N, 4.57; Br, 26.10. Found: C, 46.83; H, 6.36; N, 4.43; Br, 26.13.

Bucherer-Bergs Synthesis on *N*-Ethoxycarbonylmethyl-*nor*-pseudopelletierine.

In a "Sovirel" sealed flask, 1 g. (0.004 mole) of **5**, 0.32 g. (0.004 mole) of potassium cyanide and 1.14 g. (0.012 mole) of ammonium carbonate dissolved in 8 ml. of 50% ethanol/water were heated at 65° for 24 hours. The hydroalcoholic solution was concentrated and the residue was extracted with 96° ethanol, giving crystallized **6**, m.p. 292-294°.

Anal. Calcd. for $C_{12}H_{17}N_3O_4$: C, 53.9; H, 6.41; N, 15.72. Found: C, 53.45; H, 6.87; N, 15.74.

N-β-Hydroxyethylgranatanine-3-spiro-5'-hydantoin (**4a**).

This compound was obtained following the procedure in reference (2).

N-γ-Hydroxypropylgranatanine-3-spiro-5'-hydantoin (**4b**).

This compound was obtained following the procedure in reference (2), yield 53% (from 96° ethanol); ir (potassium bromide): 1730-1775 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.91; N, 15.71. Found: C, 58.15; H, 7.83; N, 15.76.

N-β-Hydroxyethylgranatanine-3-spiro-5′-hydantoin Diphenylacetic Ester (**3a**).

Compound **4a** (1.2 g., 0.0047 mole), 1.17 g. (0.0047 mole) of diphenylacetyl chloride and 20 ml. of pyridine were heated under reflux for 1 hour. After this time the mixture was cooled and 600 mg. of **4a** hydrochloride was recovered. The pyridine was removed under vacuum, the residue was triturated with ethyl acetate and filtered. The hygroscopic product was recrystallized from ethanol/ether and 200 mg. of **3a** hydrochloride was obtained, yield 8.73%, m.p. 174-176°; ir (potassium bromide); 1700, 1740 and 1770 (C=O) cm^{-1}.

Anal. Calcd. for $C_{26}H_{30}ClN_3O_4$: C, 64.51; H, 6.24; N, 8.67. Found: C, 64.16; H, 6.34; N, 8.38.

N-β-Chloroethylgranatanine-3-spiro-5′-hydantoin (Hydrochloride) (**7**).

Five hundred mg. (0.0015 mole) of **4a** and 1 ml. of thionyl chloride were heated with stirring under reflux for 0.5 hour. The reaction mixture was cooled and benzene was added and 550 mg. of **7** was recovered by filtration, yield 90%, m.p. 289-291° (from absolute ethanol); ir (potassium bromide): 1710 and 1770 (C=O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{19}Cl_2N_3O_2$: C, 42.35; H, 5.62; N, 12.34. Found: C, 42.69; H, 5.90; N, 12.66.

N-β-Hydroxyethylgranatanine-3-spiro-5′-hydantoin Benzylic Ester (**3b**).

One g. (0.003 mole) of **7** was dissolved in 15 ml. of dimethyl sulfoxide and 1.4 g. (0.006 mole) of potassium benzylate was added. The solution was heated at 98-100° for 2 hours. Dimethyl sulfoxide was removed under vacuum and the residue was dispersed with water and chloroform. The crude was dissolved in hydrochloric ethanol and 247 mg. of **3b** hydrochloride was obtained when ethylic ether was added, yield, 13.5%, m.p. 190° (from ethanol/ether); ir (potassium bromide): 1695, 1725 and 1750 (C=O) cm^{-1}.

Anal. Calcd. for $C_{26}H_{30}ClO_5N_3 \cdot 1\frac{1}{2}H_2O$: C, 59.24; H, 6.31; N, 7.97. Found: C, 59.30; H, 6.73; N, 7.72.

REFERENCES AND NOTES

(1) Author to whom correspondence should be addressed.

(2) G. G. Trigo, C. Avendaño, P. Ballesteros and A. González, *J. Heterocyclic Chem.*, **15**, 833 (1978).

(3) A. Ribbentrop and W. Schaumann, *Arzneim.-Forsch.*, **15**, 857 (1965).

(4) K. Stach and O. Dold, Belgian Patent 610,768 (1962); *Chem. Abstr.*, 13815 (1962).

(5) K. Stach and O. Dold, *Arzneim.-Forsch.*, **13**, 1015 (1963).

(6) K. Stach and O. Dold, *ibid.*, **15**, 856 (1965).

(7) C. Schöpf, G. Lehmann and W. Arnold, *Angew. Chem.*, **50**, 783 (1937).

(8a) H. T. Bucherer and W. Steiner, *J. Prakt. Chem.*, **140**, 291 (1934); (b) H. T. Bucherer and V. A. Lieb, *ibid.*, **141**, 5 (1934).