Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

New N-Substituted (±)-Dehydronorglaucine Analogs

Violeta Benedetti-Doctorovich [a], Fu-Yung Huang [a], John Lambropoulos [a], Edward M. Burgess [a] & Leon H. Zalkow [a]

[a] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Ga, 30332-0400, USA

Published online: 23 Sep 2006.

To cite this article: Violeta Benedetti-Doctorovich, Fu-Yung Huang, John Lambropoulos, Edward M. Burgess & Leon H. Zalkow (1995) New N-Substituted (±)-Dehydronorglaucine Analogs, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:22, 3701-3709, DOI: 10.1080/00397919508015508

To link to this article: http://dx.doi.org/10.1080/00397919508015508

SYNTHETIC COMMUNICATIONS, 25(22), 3701-3709 (1995)

NEW N-SUBSTITUTED (±)-DEHYDRONORGLAUCINE ANALOGS.

Violeta Benedetti-Doctorovich, Fu-Yung Huang, John Lambropoulos, Edward M. Burgess and Leon H. Zalkow*.

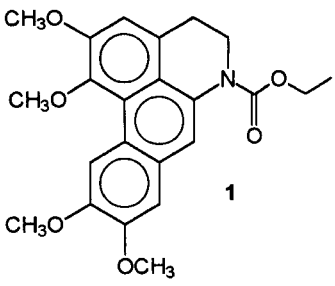
School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Ga 30332-0400, USA.

Abstract: The aporphine alkaloid N-carbethoxydehydronorglaucine (**1**) was found to have promising *in vitro* antitumor activity, but poor water solubility. We report the synthesis of **1**, the efficient hydrolysis of its urethane group and the further transformation into several new dehydronorglaucine analogs.

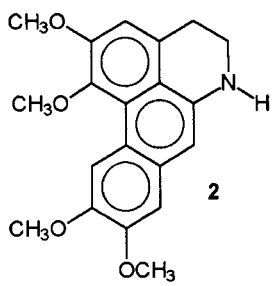
Screening in the National Cancer Institute (NCI) *in vitro* disease-oriented primary antitumor screen, consisting of 60 human tumor cell lines[1], revealed that N-carbethoxydehydronorglaucine (**1**) showed interesting activity. Using the COMPARE program[1], the cell line response pattern was similar to that of tubulin binding agents such as taxol. However, the lack of water solubility preclude further development of this interesting compound. To overcome this problem, a synthetic program was initiated to prepare water soluble analogs for eventual *in vivo* evaluation. The procedure of

*To whom correspondence should be addressed.

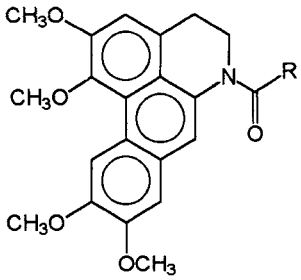
Cava et. al.[2] was followed in the preparation of N-carbethoxy-dehydronorglaucine (**1**). However, it was found that on scale-up, the yield in



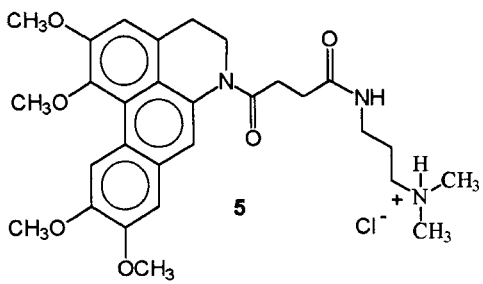
1



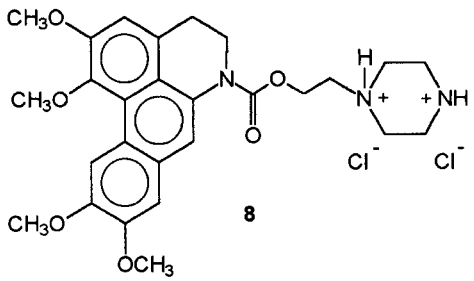
2



R=CH_2CH_2COOH (**3**)
R=$CH_2CH_2CH_2COOH$ (**4**)
R=$N(CH_3)_2$ (**6**)
R=$O(CH_2)_2Br$ (**7**)



5



8

the last step, involving non-oxidative photocyclization of 1-(6'-bromo-3',4'-dimethoxybenzylidene)-6,7-dimethoxy-3,4-dihydroiso-quinoline-N-ethyl-

carbamate to give **1**, could be greatly improved by substituting n-butanol for t-butanol as the solvent.

The first step in the synthesis of analogs involves hydrolysis of the urethane group. This has been previously reported, in poor yield[3], using acidic conditions. We have found that by using an aqueous solution of potassium hydroxide in isopropanol, the free amine **2** could be obtained in 78% yield.

By condensing **2** with succinic and glutaric anhydrides, respectively, in the presence of pyridine, the amide acids 2-(N-carbonyldehydro-norgalucine)ethanoic acid (**3**) and 3-(N-carbonyldehydronorgalucine) propanoic acid (**4**) were obtained. By treating a solution of **3** and CDI in acetonitrile with 3-(dimethylamino)-1-propylamine the amide amine **5** was obtained. Also by treating **2** with N,N-dimethylcarbamyl chloride in pyridine, the urea **6** was obtained. When **2** was treated with 2-bromoethyl-chloroformate in pyridine a mixture of N-(2-bromocarbethoxy)-dehydro-norglaucine (**7**) and the chloro analog were obtained. However, with acetone as solvent, the reaction rapidly gave only **7**. Treatment of **7** with piperazine in acetone followed by treatment with hydrogen chloride gave **8** in good yield.

Compound **2**, as its HCl salt and compound **5,** showed weak selectivity in the melanoma panel cell lines, while the other compounds mentioned showed no selectivity in the National Cancer Institute (NCI) *in vitro* disease-oriented primary antitumor screen.

EXPERIMENTAL SECTION

Melting points were determined on a Koffler hot-stage equipped with a digital thermometer and are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform solutions with a Varian Gemini-300 (300 MHz) spectrometer. Chemical shifts are reported downfield (δ) relative to TMS. Mass spectra were recorded on a VG Analytical 70-SE mass spectrometer equipped with a 11-250J data system, and all exact mass determinations were recorded at 10000 resolution. All microanalyses were performed by Atlantic Microlab, Norcross, GA.

(±)-N-carbethoxydehydronorglaucine (1): A solution of 1-(6'Bromo-3',4'-dimethoxybenzylidene)-6,7-dimethoxy-3,4-dihydroisoquinoline N-ethyl carbamate (3.00 g, 6.12 mmol) prepared as previously described[2], potassium t-butoxide (3.5 g), n-butanol (400 mL) and benzene (1.2 L) was stirred under nitrogen at RT while being irradiated (Cortex filter) with a Hanovia 450 W lamp. After 2.5 days, the pale yellow reaction mixture was concentrated *in vacuo* and ether (40 mL) was added. After refrigeration overnight, 925 mg of white crystals were collected by filtration. An additional 450 mg of product was obtained by chromatography on silica gel using a Chromatotron (Harrison Research, Inc.). Yield 55%. mp 158-160° C (lit. m.p. 159-161° C)[2] . ^{1}H NMR ($CDCl_3$) δ(ppm): 1.37 (t, 3H, J=7.1 Hz), 3.22 (t, 2H, J=5.5 Hz), 3.92 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 4.10 (m, 2H), 4.32 (q, 2H, J=7.1 Hz), 7.08 (s, 1H), 7.18 (s, 1H), 7.77 (s, 1H), 9.21 (s, 1H);

EIMS *m/e* 413 (5), 412 (25), 411 (100), 397 (3), 396 (13), 368 (4), 338 (6), 324 (3), 323 (4), 322 (9), 308 (4), 294 (3), 292 (4), 264 (3); EIMS *m/e* M^+=411.1682 ($C_{23}H_{25}NO_6$ requires 411.1682).

(±)-Dehydronorglaucine (2): A mixture of (±)-N-carbethoxydehydronorglaucine (**1**, 250 mg, 0.61 mmol) and 5 mL of a 10% KOH solution in i-propanol, saturated with water, was refluxed for 5 hs. in an oxygen free nitrogen atmosphere. Water (20 mL) was added to the cooled solution and the resulting precipitate was collected by filtration, washed with water and dried, giving (±)-dehydronorglaucine (160 mg, 0.47 mmol, 78% yield). ^{1}H NMR ($CDCl_3$) δ(ppm): 3.25 (t, 2H), 3.50 (t, 2H), 3.90 (s, 3H), 4.00 (s, 3H), 4.02 (s, 6H), 4.30 (bb, 1H), 6.6 (s, 1H), 6.95 (s, 1H), 7.02 (s, 1H), 9.10 (s, 1H). The hydrochloride salt was prepared with HCl gas giving **2.HCl** in quantitative yield. m.p.=198-200° C with decomposition (CH_3OH) (lit.[3,4] 221-222° C (CH_3OH)). EIMS *m/e* M^+=339.1471 ($C_{20}H_{21}NO_4$ requires 339.1471). Anal. cald. for $C_{20}H_{21}NO_4$: C, 70.77; H, 6.24; N, 4.13. Found: C, 70.70; H, 6.27; N, 4.13.

2-(N-carbonyldehydronorgalucine)ethanoic acid (3): A solution of (±)-dehydronorglaucine (**2**, 300 mg, 0.88 mmol) and succinic anhydride (900 mg, 9.0 mmol) in pyridine (15 mL) was stirred at room temperature under N_2 for 20 hr. The solvent was removed by evaporation and the precipitate was dissolved in chloroform. This solution was treated with water saturated with $NaHCO_3$. The aqueous layer was acidified with HCl 1N, and the organic

layer was separated, dried and the solvent removed under reduced presure, affording 2-(±)-(N-carbonyldehydronorglaucine)ethanoic acid (**3**, 250 mg, 0.57 mmol, 64 % yield).m.p.=111-113° C (CH_3OH),^{1}H-NMR ($CDCl_3$) δ(ppm): 2.70 (t, 2H), 2.95 (t, 2H), 3.20 (t, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 4.20 (bb, 1H), 7.1 (s, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 9.20 (s, 1H).MS-FAB$^+$ *m/e* 439.1574 (M^+= $C_{24}H_{25}NO_7$ requires 439.1631. Anal. calcd. for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found : C, 65.71; H, 5.85; N, 3.08.

3-(N-carbonyldehydronorgalucine)propanoic acid (4). A solution of (±)-dehydronorglaucine (**2**, 350 mg, 1.03 mmol) and glutaric anhydride (900 mg, 7.90 mmol) in pyridine (18 mL) was treated in the same manner as previously described, to afford 3-(carbonyl-N-dehydronorgalucine) propanoic acid (**4**, 450 mg, 0.99 mmol, 96% yield) ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.0 (m,2H), 2.40 (t, 2H), 2.70 (t, 2H), 3.20 (t, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 4.20 (bb, 1H), 7.1 (s, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 9.20 (s, 1H). m.p.=157-159° C (CH_3OH). EIMS *m/e* 453.1787 (M^+ $C_{25}H_{27}NO_7$ expected 453.1787). Anal calcd. for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.01; N, 3.09. Found : C, 6.19; H, 6.01; N, 3.07.

N-[carbonyl-(3(dimethyl-amino)-1-propyl-ethylamide] - dehydronorglaucine (5). A stirred solution of **3** (290 mg, 0.66 mmol) in acetonitrile (7.25 mL) and CDI (carbonildiimidazol) (145 mg, 0.90 mmol) was heated to 45° C for 5 min. After cooling to room temperature a solution of 3-

(dimethyl-amino)-1-propylamine (94µl, 0.75 mmol) in acetonitrile (0.7 mL) was added over a period of 20 min. After 30 min. the solvent was evaporated and the precipitate was dissolved in chloroform (50 mL), then washed 5 times with 3 volumns of water, dried over Na_2SO_4 and concentrated to afford **5** (290 mg, 0.55 mmol, 84% yield). ^{1}H-NMR ($CDCl_3$) δ(ppm):9.18 (s, 1H), 7.14 (s, 1H), 7.05 (s, 1H), 6.92 (br. s, 1H), 4.12 (br. t, 2H), 4.03 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.89 (s, 3H), 3,26 (q, J=5.9 Hz, 2H), 3.15 (br. t, 2H), 2.90 (t, J=6.3 Hz, 2H), 2.54 (br. t, 2H), 2.46(t, J=6.6Hz, 2H), 2.27 (s, 6H), 1.67(m, 2H). The hydrochloride salt was prepared with HCl gas to give **5**.HCl quantitatively. mp= 206-208° C (methanol-isopropanol).^{1}H-NMR ($CDCl_3$) δ(ppm): 9.20 (s, 1H), 7.44 (bs, 1H), 7.20 (s, 1H), 7.09 (s, 1H), 4.09 (bb, 2H), 4.06 (s, 3H), 4.05 (s, 3H), 4.03 (s, 3H), 3.93 (s, 3H), 3.41 (q, J=6.0Hz, 2H), 3.18 (bb, 4H), 2.97 (br. t, J=6.7Hz, 2H), 2.78 (bb., 6H), 2.52 (bb, 2H), 2.08 (br. t, J=5.5Hz, 2H). EIMS *m/e* 523.2687 (M^+ $C_{29}H_{37}N_3O_6$ requires 523.2682). Anal. cald. for $C_{29}H_{38}$ Cl N_3O_6 : C, 62.19; H, 6.84; N, 7.50. Found: C, 62.12; H, 6.80; N, 7.55.

N-(N-dimethylcarbamoyl)dehydronorglaucine (6). To a solution of (±)-dehydronorglaucine **2** (265 mg, 0.78 mmol) in pyridine (5 mL), carbamyl chloride (50µl, 0.55 mmol) was added and the solution was heated to reflux. After 3 hr., a similar amount of carbamyl chloride was added and the mixture maintained for 3 additional hours. The solvent was evaporated under reduced pressure, the resulting solid disolved in chloroform and washed 3

times with water. The gummy product was purified with a Chromatotron run with hexane:ethylacetate (1:1), yielding **6** (97 mg, 0.24 mmol, 30% yield), mp=208-209°C (i-propanol). ^{1}H-NMR ($CDCl_3$) δ(ppm): 9.18 (s, 1H), 7.07 (s, 1H), 7.03 (s, 1H), 6.83 (s, 1H), 4.05 (s, 3H), 4.03 (s, 6H), 3.93 (s, 3H), 3.87 (t, J=6Hz, 2H), 3.25 (t, J=6Hz, 2H), 2.90 (s, 6H). EIMS *m/e* 410.1846 (M^+ $C_{23}H_{26}N_2O_5$ requires 410.1812). Anal cald. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.83. Found : C, 67.20; H, 6.34; N, 6.90.

N-(2-bromocarbethoxy)-dehydronorglaucine (7). To a stirred suspension of (±)-dehydronorglaucine **2** (250 mg, 0.74 mmol) in acetone (10 mL), bromoethyl-chloroformate (83.5µl, 0.78 mmol) was added. After 15 min. the mixture was poured into ethyl acetate (70 mL) and washed with water. After evaporation of the solvent the product **7** was obtained (330 mg, 0.67 mmol, 91% yield). mp=111°C (i-propanol).^{1}H-NMR ($CDCl_3$) δ(ppm): 9.20 (s, 1H), 7.82 (s, 1H), 7.20 (s, 1H), 7.07 (s, 1H), 4.54 (t, J=6Hz, 2H), 4.10 (t, J=5.5Hz, 2H), 4.06 (s, 3H), 4.03 (s, 3H), 4.01 (s, 3H), 3.92 (s, 3H), 3.61 (t, J=6Hz, 2H), 3.22 (t, J=5.5Hz, 2H). EIMS *m/e* 489.0793 (M^+ $C_{23}H_{24}BrNO_6$ expected 489.0787). Anal. calcd. for $C_{23}H_{24}BrNO_6$: C, 56.34; H, 4.93; N, 2.86. Found : C, 56.33; H, 4.97; N, 2.73.

N-(2-(N-piperazine)carbethoxy)-dehydronorglaucine (8). A suspension of **7** (130 mg, 0.26 mmol), K_2CO_3 (40 mg) and piperazine (260 mg, 3.02 mmol) in acetone (4 mL), was stirred at r.t. for 16 hr. The solution was poured into water, extracted with ethyl acetate and washed 3 times with water. After drying and evaporation of the organic layer, **8** was obtained (110

mg, 0.22 mmol, 84% yield). ^{1}H-NMR ($CDCl_3$) δ(ppm): 9.20 (s, 1H), 7.75 (s, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 4.38 (t, J=6Hz, 2H), 4.09 (t, J=5.5Hz, 2H), 4.06 (s, 3H), 4.03 (s, 6H), 3.92 (s, 3H), 3.22 (t, J=5.5Hz, 2H), 2.92 (t, J=6Hz, 4H), 2.72 (t, J=6Hz, 2H), 2.56 (bb., J=14Hz, 4H). The hydrochloride salt was prepared with HCl gas to give **11**.HCl quantitatively. ^{1}H-NMR (D_2O) δ(ppm): 8.38 (s, 1H), 7.16 (s, 1H), 7.01 (s, 1H), 6.82 (s, 1H), 4.40 (br. t, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.50 (s, 3H), 3.32 (br.b, 2H), 3.20 (br. b, 6H), 3.02 (br. t, 2H). MS-FAB+ *m/e* 496.2387 (M^++1 $C_{27}H_{34}N_3O_6$ requires 496.2447). Anal. calcd. for $C_{27}H_{34}Cl\,N_3O_6$: C, 60.95; H, 6.44; N, 7.90. Found: C, 60.92; H, 6.56; N, 7.81.

Acknowledgement: We gratefully acknowledge support of this work by NCI contract N01-CM-17570. We thank Dr. Daniel Lednicer of NCI for his advice and help.

References:

1. Boyd, M.R.; *Principles & Practises of Oncology*, 1989, 3, 1.

2. Cava, M. P. ; Stern, P.; Wakisaka, K.; *Tetrahedron*, 1973, 29, 2249.

3. Gupta, S.; Bhakuni, D. S.; *Synthetic Comunications*, 1989, 19, 393.

4. Guinaudeau, H.; Le Boeuf, M.; Cave A., *J. Nat. Prod*, 1975, 38, 275.

5. Physical and spectra data of (±)-dehydronorglaucine hydrochloride we prepared is different from that previously described [3,4]. This is probably due to a mistaken formula reported in the elemental analysis which has one additional atom of carbon [4].

(Received in the USA 14 April 1995)