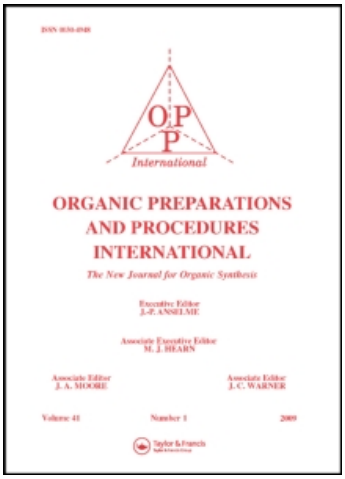


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

CONVENIENT SYNTHESIS OF 6-METHYL, 8-METHYL AND 6,8-DIMETHYL DERIVATIVES OF 5-HYDROXY-1,2,3,4-TETRAHYDRO-2-QUINOLINONE

Dominique Blondet[a]; Francette Laure[a]; Jean-Claude Pascal[a]
[a] Recherche Syntex France, Montlhery, France

To cite this Article Blondet, Dominique , Laure, Francette and Pascal, Jean-Claude(1993) 'CONVENIENT SYNTHESIS OF 6-METHYL, 8-METHYL AND 6,8-DIMETHYL DERIVATIVES OF 5-HYDROXY-1,2,3,4-TETRAHYDRO-2-QUINOLINONE', Organic Preparations and Procedures International, 25: 2, 223 — 228
To link to this Article: DOI: 10.1080/00304949309457950
URL: http://dx.doi.org/10.1080/00304949309457950

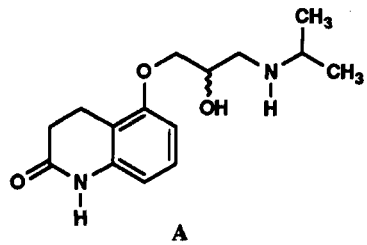
ORGANIC PREPARATIONS AND PROCEDURES INT., 25 (2), 223-228 (1993)

CONVENIENT SYNTHESIS OF 6-METHYL, 8-METHYL AND 6,8-DIMETHYL DERIVATIVES OF 5-HYDROXY-1,2,3,4-TETRAHYDRO-2-QUINOLINONE

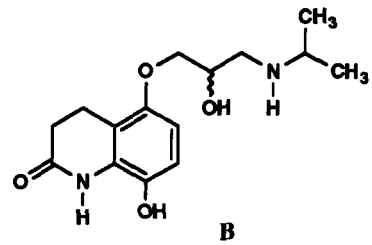
Dominique Blondet*, Francette Laure and Jean-Claude Pascal

Recherche Syntex France
Leuville-sur-Orge, 91310 Montlhery, FRANCE

Carteolol **A** bearing the 1,2,3,4-tetrahydro-2-quinolinone ring is a β-blocking agent used for glaucoma treatment.[1] One of its major metabolites has been reported[2] to be compound **B** resulting from hydroxylation at position 8 of the heterocycle. Since we were interested in developing more metabolically stable derivatives possessing the above heterocyclic structure,[3] we decided to prepare 8-substituted-1,2,3,4-tetrahydro-2-quinolinone compounds. Earlier we described the synthesis of 5-hydroxy-8-methoxy-1,2,3,4-tetrahydro-2-quinolinone[4] and now report the preparation of the methyl analogues.



A

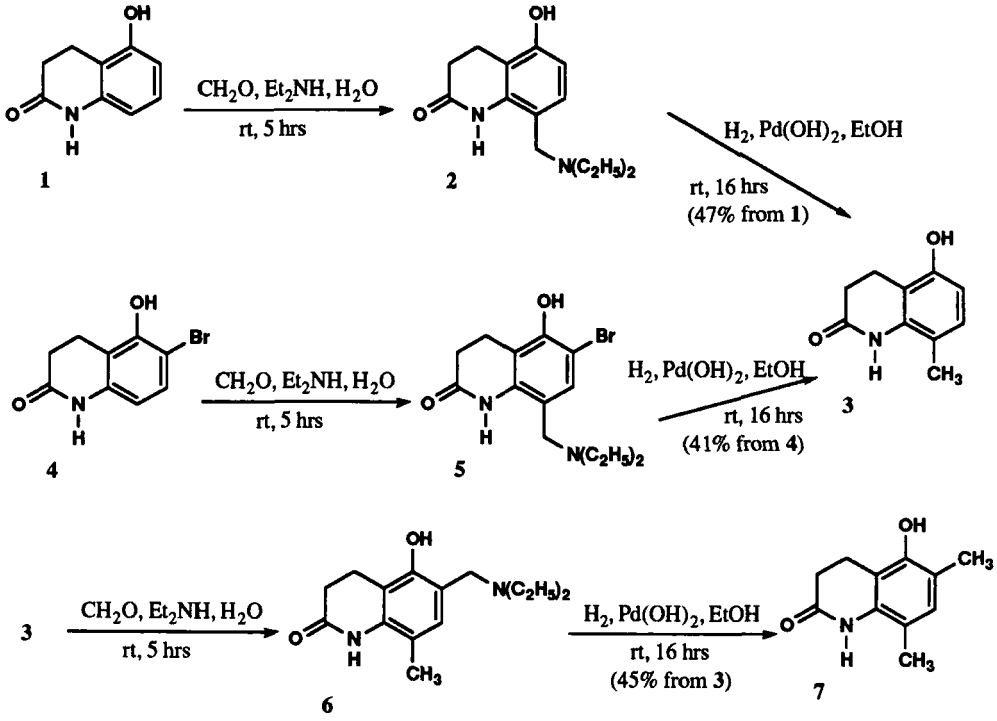


B

One of the simplest methods of introducing a methyl group on a phenol ring is *via* the Mannich reaction[5] followed by catalytic hydrogenation. On the basis of this strategy and by the use of easily available 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (**1**)[6] with aqueous formaldehyde and diethylamine, we obtained a single product whose structure was established by NMR as the corresponding Mannich base. This compound, after catalytic hydrogenation on palladium hydroxide, afforded a new compound which contains a methyl group on the aromatic ring.

In order to determine the position of the methyl substituent, the same reaction was carried out starting from two analogues (**4** and **8**) of **1**, in which the 6 or 8-position is protected by a bromine atom which can be removed by hydrogenolysis. The 6-bromo derivative **4** was obtained by direct bromination of **1**, while **8** was prepared according to the procedure of Banno and coworkers.[7] The Mannich reaction using **4** and diethylamine provided the monodimethylaminomethyl derivative **5** which was hydrogenated as above, to give the 8-methyl analogue **3** as shown clearly by ^{1}H NMR

(*ortho*-coupling of the two aromatic protons). Compound **3** has the same chromatographic and spectroscopic properties as the compound prepared from **1**. Thus, the Mannich reaction on 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone exclusively at the 8-position. This selectivity could be explained by the *ortho*-orientating effect of the lactam which in this case is more powerful than that of the phenol (*Scheme* 1). To our knowledge, there is no example in the literature of such an orientating effect of an

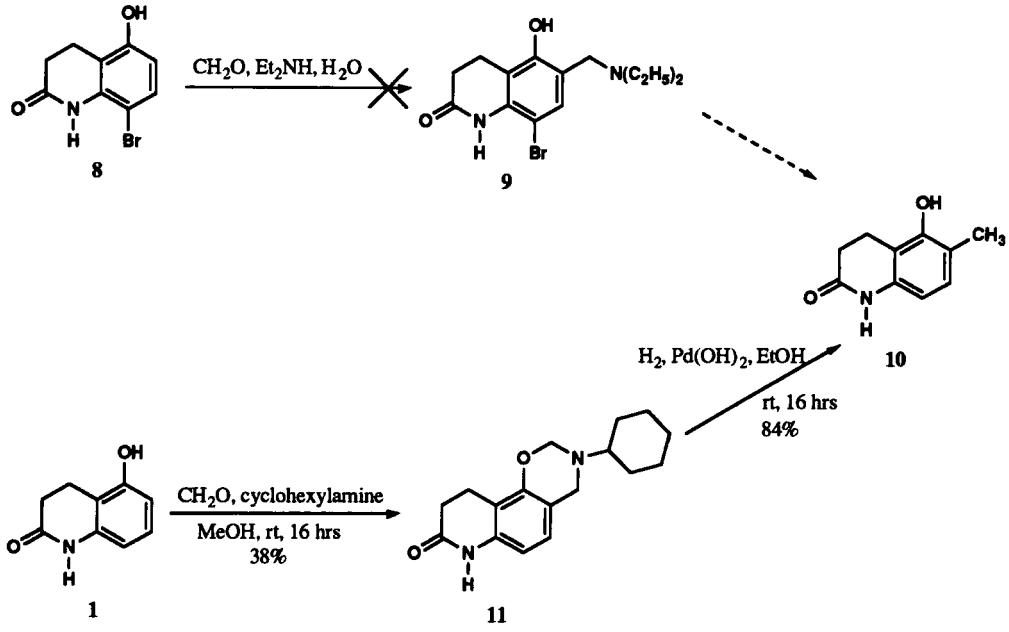


Scheme 1

amide or lactam. Lis and Marisca[9] simply reported the *para*orientating effect of the methanesulfonamide moiety in the Mannich reaction. Compound **3** itself undergoes a Mannich reaction to afford the 6,8-dimethyl derivative **7** *via* the intermediacy of Mannich base **6** (*Scheme* 1).

Attempts to prepare the 6-methyl analogue **10** employing the same strategy starting from the 8-bromo derivative **8** failed. We were able to direct the aminomethylation of **1** to position 6 by using a primary amine (e. g. cyclohexylamine) with excess of formaldehyde, leading to the formation of the benzoxazine **11**, as previously reported in the case of some naphtol compounds.[8] This 1,3-benzoxazine was then easily cleaved by hydrogenolysis to give 6-methyl derivative **10** in good yield (*Scheme* 2).

Therefore, 6-methyl and 8-methyl derivatives **10** and **3** are easily accessible from the same intermediate 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (**1**), by reaction with formaldehyde and secondary amine (Mannich reaction) or primary amine (*via* a benzoxazine heterocycle), followed by catalytic hydrogenation, respectively.



Scheme 2

EXPERIMENTAL SECTION

Mps were determined on a Kofler apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker AC 200 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. Mass spectra data were obtained using a AEI MS50 spectrometer.

8-Diethylaminomethyl-5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (2).- To a stirred suspension of 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (1, 30 g, 184 mmol) in water (300 mL) was added diethylamine (14 g, 191 mmol), followed by a 36% solution of formaldehyde in water (30 mL). The mixture was stirred for 5 hrs and the precipitate was collected and washed with ice-water (50 mL) to provide the crude Mannich base 2 which was used in the next step without further purification. An analytical sample, mp. 160°, was obtained by recrystallization from ethanol,

^1H NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 7.5 Hz, $(CH_3CH_2)_2N$), 2.60 (m, 6H, $(CH_3C\underline{H}_2)_2{}^N$ + $CH_2C\underline{H}_2CO$), 2.95 (t, 2H, J = 6.5 Hz, $CH_2C\underline{H}_2CO$), 3.73 (s, 2H, $C\underline{H}_2N(CH_2CH_3)_2$), 6.25 (d, 1H, J = 8 Hz, H6), 6.87 (d, 1H, J = 8 Hz, H_7), 8.50 (s, 1H, OH), 9.92 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 11.1, 18.4, 30.3, 46.1, 56.6, 105.9, 110.4, 116.8, 126.8, 137.7, 155.7, 172.1.

Anal. Cald for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found C, 67.65; H, 8.09; N, 11.31

6-Bromo-5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (4).- To a stirred solution of 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (1, 10 g, 61 mmol) in acetic acid (200 mL) was added dropwise a solution of bromine (10 g, 63 mmol) in acetic acid (50 mL). The mixture was stirred for 3 hrs and poured into ice-cold water (300 mL). The precipitate was collected, washed with water (50 mL) and dried. The crude mixture was purified by column chromatography on silica gel by elution with ethyl

acetate-methanol (97:3) affording first 8-bromo-5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (**8**, 2.2g, 15%), mp. 209-210°, lit.[7] 212-213% then 6-bromo-1,2,3,4-tetrahydro-2-quinolinone **4** (7.4 g, 50%): mp. 196-197°.

^{1}H NMR (DMSO-d_6): δ 2.55 (t, 2H, J = 6.5 Hz, C$\underline{H}_2$CH$_2$O), 2.88 (t, 2H, J = 6.5 Hz, CH$_2$C$\underline{H}_2$CO), 6.44 (d, 1H, J = 4 Hz, H$_8$), 7.31 (d, 1H, J = 4 Hz, H$_7$), 9.22 (s, 1H, OH), 10.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 19.4, 29.5, 103.7, 108.5, 112.5, 130.3, 138.8, 150.5, 169.7.

Anal. Cald for $C_8H_8BrNO_2$: C, 44.65; H, 3.33; N, 5.79. Found C, 44.70; H, 3.31; N, 5.84

The following compounds (crude yields) were obtained, using the same procedure as for **2** and starting respectively from **4** and **3**.

6-Bromo-8-diethylamino-5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (5), mp. 172° (EtOH), 72% yield.

^{1}H NMR ($CDCl_3$): δ 51.05 (t, 3H, J = 7.5 Hz, (C$\underline{H}_3$CH$_2$)$_2$N), 2.62 (m, 6H, (CH$_3$CH$_2$)$_2$N + C$\underline{H}_2$CH$_2$CO), 3.07(t, 2H, J = 6.5 Hz, CH$_2$C$\underline{H}_2$CO), 3.73 (s, 2H, C$\underline{H}_2$N(CH$_2$CH$_3$)$_2$), 7.05 (s, 1H, H$_7$), 7.74 (s, 1H, OH), 10.82 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 10.9, 16.6, 29.9, 46.0, 55.9, 97.5, 112.2, 118.2, 129.1,134.7, 155.0, 170.6.

Anal. Cald for $C_{14}H_{19}BrN_2O_2$: C, 51.38; H, 5.86; N, 8.57. Found C, 51.43; H, 5.82; N, 8.62

6-Diethylaminomethyl-5-hydroxy-8-methyl-1,2,3,4-tetrahydro-2-quinolinone (6), mp. 179° (EtOH), 78% yield.

^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J = 7.5 Hz, (CH~CH$_2$)2N), 2.22 (s, 3H, CH$_3$), 2.50 (m, 6H, (CH$_3$C$\underline{H}_2$)$_2$N + C$\underline{H}_2$CH$_2$CO), 2.87 (t, 2H, J = 6.5 Hz, CH$_2$C$\underline{H}_2$CO), 3.73 (s, 2H, C$\underline{H}_2$N(CH$_2$CH$_3$)$_2$), 6.75 (s, 1H, H$_7$), 8.44 (s, 1H, OH), 10.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 11.3, 16.3, 17.5, 30.1, 56.3, 110.9, 117.1, 126.5, 137.8, 156.0, 172.2.

Anal. Cald for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found C, 68.71; H, 8.40; N, 10.72

5-Hydroxy-8-methyl-1,2,3,4-tetrahydro-2-quinolinone (3).- A solution of the crude Mannich base **2** in ethanol (500 mL) was hydrogenated at room temperature over 10%-Pd (OH)$_2$ on carbon (1 g) for 16 hrs. After filtration of the catalyst and evaporation of the solvent, the crude product was recrystallized from ethanol to yield 15.2 g (47%) from 1 of a white solid, mp. 186-187°.

3 was also prepared in 41% yield from **4** *via* the Mannich base **5** using the same procedure. ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH$_3$), 2.47 (t, 2H, J = 6.5 Hz, C$\underline{H}_2$CH$_2$CO), 2.88 (t, 2H, J = 6.5 Hz, CH$_2$C$\underline{H}_2$CO), 6.32 (d, 1H, J = 7.9 Hz, H$_7$), 6.71 (d, 1H, J = 7.9 Hz,H$_6$), 8.05 (s, 1H, OH), 9.64 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 16.2, 19.0, 30.1,106.6, 110.5, 118.5, 128.4, 137.2, 152.0, 169.9.

MS (70eV): *m/z* (%): 177 (M$^+$, 100), 149 (13), 135 (19).

Anal. Cald for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found C, 67.84; H, 6.22; N, 7.85

The following compounds were obtained using the same procedure and starting from crude **6**.

6,8-Dimethyl-5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (7), from **3**, mp. 211212° (EtOH), 45% yield.

^{1}H NMR ($CDCl_3$): δ 2.15 (s, 6H, 2CH$_3$), 2.48 (t, 2H, J = 6.5 Hz, C$\underline{H}_2$CH$_2$CO), 2.90 (t, 2H, J = 6.5 Hz, CH$_2$C$\underline{H}_2$CO), 6.70 (s, 1H, H$_7$), 7.88 (s, 1H, OH), 8.85 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.8, 15.0,

29.1, 110.2, 113.1, 117.7, 128.9, 133.1, 148.6, 169.7.

MS (70eV): *m/z* (%): 191 (M^+, 100), 149 (98), 121 (50).

Anal. Cald for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found C, 69.05; H, 6.82; N, 7.37

3-Cyclohexyl-2,3,4,7,8,9, 10-heptahydro-[1,3]-oxazino-[6,5-f]-8-quinolinone (11).- To a solution of 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (15g, 92 mmol) in methanol (150 mL) was added cyclohexylamine (10.5 g, 92 mmol) and a 36% solution of formaldehyde in water (50 mL). The mixture was stirred at room temperature overnight. The precipitate was collected and recrystallized from methanol to yield 10 g (38%) of a white solid, mp. 214-215°.

^{1}H NMR (DMSO-d_6): δ 1.12 (m, 4H, $(CH_2)_2$), 1.65 (m, 6H, $(CH_2)_3$), 2.35 (t, 2H, J = 6.5 Hz, $C\underline{H}_2CH_2CO$), 2.63 (m, 1H, $C\underline{H}N$), 2.68 (t, 2H, J = 6.5 Hz, $CH_2C\underline{H}_2CO$), 3.93 (s, 2H, NCH_2), 4.95 (s, 2H, OCH_2N), 6.32 (d, 1H, J = 8.0 Hz, H_7), 6.78 (d, 1H, J = 8.0 Hz, H_8), 9.95 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 17.8, 24.8, 25.3, 29.7, 30.9, 46.1, 57.9, 80.4, 106.8, 109.7, 115.5, 125.0, 137.2, 151.6, 170.0.

MS (70eV): *m/z* (%):286 (M^+, 65), 175 (100), 112 (95).

Anal. Cald for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.79. Found C, 71.25; H, 7.70; N, 9.83

5-Hydroxy-6-methyl-1,2,3,4-tetrahydro-2-quinolinone (10).- The oxazine 11 (10 g, 35 mmol) dissolved in methanol (500 mL) was hydrogenated over 10% Pd $(OH)_2$/C (0.5g) overnight. After filtration of the catalyst and evaporation of the solvent, the crude product was recrystallized from ethanol to yield 5.2 g (84%) of a white solid, mp. 181-182°.

^{1}H NMR (DMSO-d_6): δ 2.10 (s, 3H, CH_3), 2.18 (t, 2H, J = 6.2 Hz, $C\underline{H}_2CH_2CO$), 2.83 (t, 2H, J = 6.2 Hz, $CH_2C\underline{H}_2CO$), 6.30 (d, 1H, J = 7.5 Hz, H_7), 6.88 (d, 1H, J = 7.5 Hz, H_8), 7.90 (m, 1H, OH), 9.85 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 16.3, 19.1, 30.1,106.6, 110.6, 116.6, 128.4, 137.3, 152.1,170.0.

MS (70eV): *m/z* (%): 177 (M^+, 100), 149 (23), 135 (54).

Anal. Cald for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found C, 67.81; H, 6.28; N, 7.88

REFERENCES

1. K. Nakagawa, N. Murakami, S. Yoshizaki, M. Tominaga, H. Mori, Y. Yabuchi and S. Shintani, *J. Med. Chem.*, **17**, 529 (1974).

2. H. Mori, M. Kido, N. Murakami, S. Morita, H. Kohri, K. Nagawa, T. Uno and T. Ishima, *Yakugaku Zasshi*, 97, 350 (1977). *C. A.*, **87**, 126879h (1977).

3. J. C. Pascal, L. Patmore, J. Pfister, D. Blondet and J. M. Amstrong, *U. S. Patent Application* 07/555,201 (1990), Syntex.

4. T. Persigand, F. Laure, D. Blondet and J. C. Pascal, *Synth. Commun.*, **22**, 2877 (1992).

5. M. Tramontini and L. Angiolini, *Tetrahedron*, **46**, 1791 (1990).

6. Y. Tamura, M. Terashima, Y. Higuchi and K. Ozaki, *Chem. Ind. (London)*, 1435 (**1970**).

7. K. Banno, T. Fujioka, Y. Oshiro and K. Nakagawa, *German Patent* 2,912,105 (1979); Otsuka Pharmaceutical Co., Ltd.; *C. A.*, **92**, 76316c (1980).

8. H. Mohrle and H. Foltmann, *Arch. Pharm. (Weinheim)*, **321**, 259(1988).

9. R. Lis and A. J. Mansca, *J. Org. Chem.*, **52**, 4377 (1987).

(Received July 16, 1992; in revised form January 13, 1993)