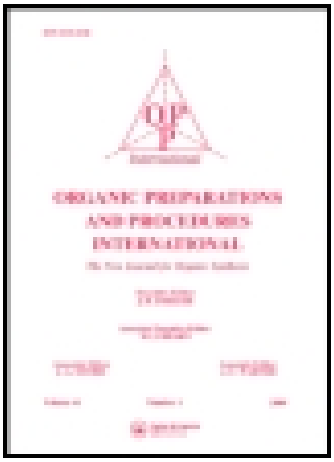


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

AN EFFICIENT SYNTHESIS OF MEQUITAZINE

Yves Guminski [a] , Valerie Fabre [b] , Patrick Lesimple [b] & Thierry Imbert [a]

[a] Division of Medicinal Chemistry, Centre de Recherche Pierre Fabre , F 81100, Castres, France

[b] Development Department , Plantes et Industries , F81603, Gaillac, France

Published online: 18 Feb 2009.

To cite this article: Yves Guminski , Valerie Fabre , Patrick Lesimple & Thierry Imbert (1999) AN EFFICIENT SYNTHESIS OF MEQUITAZINE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 31:3, 319-323, DOI: 10.1080/00304949909458326

To link to this article: http://dx.doi.org/10.1080/00304949909458326

3. L. Bernard and A. Leone, *Tetrahedron Lett.*, 499 (**1964**)

4. B. G. Hazra, V. S. Pore, S. P. Maybhate, M. V. Natekar and A. S. Rao, *Synthetic Commun.*, **19**, 1763 (1989).

5. B. G. Hazra, V. S. Pore and S. P. Maybhate, *ibid.*, **27**, 1857 (1997).

6. Chi-yi Hsing, Chien-Huan Tai and Lian-Chy Hsueh, *Hua Hsueh Pao*, **23**, 19 (1957); *Chem. Abstr.*, **52**, 12870f (1958).

7. M. Nagawa, *Takamine Kenkyujo Nempo*, **9**, 1 (1957); *Chem. Abstr.*, **55**, 1504d (1961); J. M. A. J. Batteur Jacques, Fr. Patent, 1,290,352/1962; *Chem. Abstr.*, **57**, 16489b (1962).

8. M. Karpaty, M. Hellin, M. Davidson and F. Coussemant, *Bull. Soc. Chim. France*, 1736 (**1971**).

****

AN EFFICIENT SYNTHESIS OF MEQUITAZINE

Submitted by (10/26/98)

Yves Guminski, Valerie Fabre†, Patrick Lesimple† and Thierry Imbert*

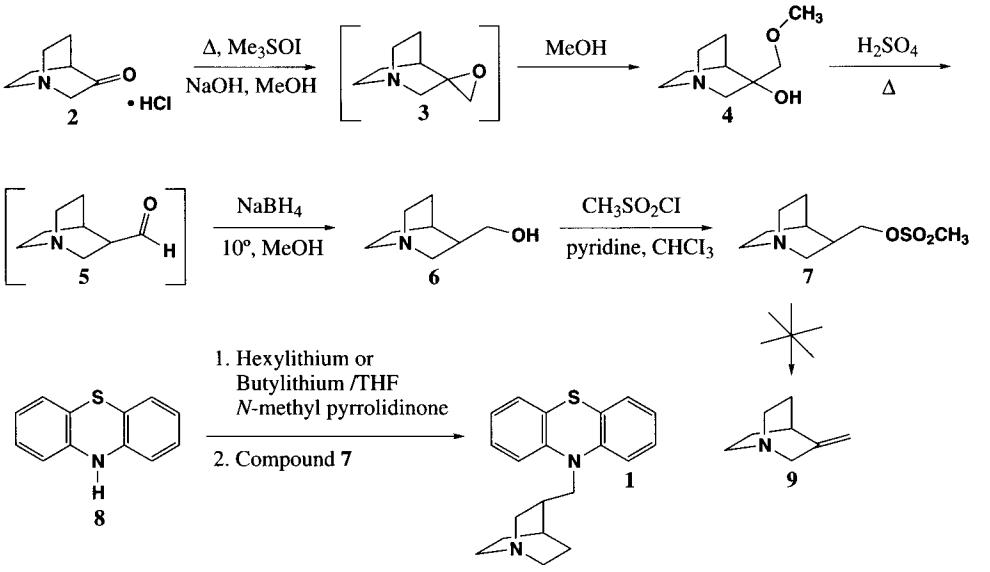
Division of Medicinal Chemistry, Centre de Recherche Pierre Fabre F 81100 Castres, FRANCE

† *Development Department, Plantes et Industries, F 81603.-Gaillac, FRANCE*

Mequitazine (**1**), a phenothiazine quinuclidine derivative known for more than two decades exhibits potent antihistamine properties and is the active constituent of some pharmaceuticals. The previously described synthesis in a patent is not satisfactory, leading to poor yields.[1] The strategy involves the preparation of the 3-hydroxymethyl quinuclidine (**6**) which was condensed *via* its chloro derivative with phenothiazine. The original six-step synthesis of **6** (5% overall yield) of Grob[2] was later modified[3] to enhance the yield to 30%. Then, another strategy,[4] using a Wittig reaction, furnished the formyl precursor **5** with no mention of the yield. Our need of large amounts of mequitazine prompted us to improve the process.

We chose to improve the preparation of 3-hydroxymethylquinuclidine (**6**), as the key intermediate, and assess the best conditions to effect the coupling reaction with phenothiazine. Our synthetic approach was based on the use of dimsylsodium reagent according to the method of Corey and Chaykovsky,[5] to yield 3-methylene quinuclidine oxide (**3**) derived from 3-quinuclidinone (**2**). Interestingly, this known 3-methylene quinuclidine oxide[6] (**3**) was prepared *in situ* by analogy with a recently described similar methodology.[7] A mixture of 3-quinuclidinone (**2**), trimethylsulfoxonium

iodide (Me_3SOI) and sodium hydroxide heated at reflux in methanol afforded directly the novel crystalline 3-methoxymethylquinuclidine-3-ol (**4**).



This one-pot conversion of **2** to **4** overcame purity problems induced by dimsylsodium route, and the difficult isolation of pure 3-methylene quinuclidine oxide (**3**), without contamination of DMSO.[6] Direct acidic dehydration and hydrolysis of **4**, with concentrated sulfuric acid, gave the relatively unstable 3-formylquinuclidine (**5**). Neutralization of the reaction medium (pH 8) with 30% sodium hydroxide, was followed by a sodium borohydride reduction in methanol. An important feature of quinuclidine chemistry is that, like with other strongly basic nitrogen compounds, quinuclidine reacts with electrophiles such as methylene chloride, to give quaternary ammonium salts. Thus, extraction with 2-butanone after basification led to pure 3-hydroxymethylquinuclidine (**6**) in 88% overall yield. This result compares advantageously with previous methods[2,3] which gave 5 and 30% yields respectively. The key step of the synthesis of **1**, remained the problematic low-yielding N-C bond formation, between phenothiazine heterocyclic nitrogen atom and quinuclidine moiety. Extensive experiments with sodium or potassium salts, ($NaNH_2$, NaH, KOH) of phenothiazine (**8**) in various solvents, as reported in patents[1,8] or in current use, did not afford useful results. The second drawback was the easy elimination of the 3-halogenomethyl quinuclidine (*i. e.* 3-chloromethyl quinuclidine) affording the *exo*-methylene adduct (**9**).[9] Careful examination of the literature indicated that lithium salts of N-aromatic heterocycles obtained from *n*-butyllithium in THF, react cleanly with mesylate electrophiles.[10] It was decided to extend this methodology to our case. Thus, alcohol **6** was converted with methanesulfonyl chloride and pyridine in chloroform to mesylate **7** in 80% yield. Interestingly, it was isolated as its pure insoluble hydrochloride salt during work-up.

Deprotonation of phenothiazine (**8**) with an alkyllithium seemed suitable, and the light yellow lithium salt generated by addition of *n*-butyllithium at 0° in THF was treated with a solution of

3-mesyloxy derivative (**7**) as its hydrochloride in N-methyl-2-pyrrolidinone. The reaction proceeded cleanly, under reflux for two hours, in contrast to sodium amide methodology.[1] The remarkable feature was the stability of the mesylate under these reaction conditions ; there was no quaternarization nor elimination to *exo*-methylene (**9**); no by-product was found. Quenching the reaction mixture by addition into ice-water and extraction with ethyl acetate and isopropyl ether (1:1), afforded an organic layer which was treated with 1N HCl solution; mequitazine hydrochloride precipitated as pure creamy crystals in 91% yield. This synthesis proved to be very efficient up to a 100 g scale. On a larger scale, for safety and ecological reason, a slight modification consisted in the use of hexyllithium instead of *n*-butyllithium to prevent the evolution of butane.

The need to prepare the biologically active S(-) enantiomer,[11] led us to attempt a diastereoselective crystallization of the stable mesylate (**7**), as its L-tartrate salt. Only two recrystallizations were required to obtain the pure enantiomer. Furthermore, it could be stored and used as its L-tartrate salt.

We described here a new efficient synthesis of mequitazine in an overall yield of 80% from commercially available 3-quinuclidinone hydrochloride (**2**). This method can be carried out to an industrial scale, up to 10 kg batches. Additionally, we have developed a new expeditious synthesis of 3-hydroxymethylquinuclidine (**6**) in 88% yield with an excellent purity, by two "one-pot" procedures. It represents a simple and convenient approach for the bulk synthesis without using hazardous or expensive reagents such as cyano compounds (KCN, TosMIC) or lithium aluminium hydride. As a result, 3-hydroxymethylquinuclidine can be a readily available useful building block for medicinal chemistry.

EXPERIMENTAL SECTION

All solvents and reagents used were obtained commercially in "pure for synthesis" grade, and were used without further purification. Melting points were determined using a capillary Electrothermal 9300, and are uncorrected. Elemental analyses were performed on a microanalyser Fisons 1108, and were within 0.4% of the theoretical values. Karl Fisher analyses were performed on a coulometer Mettler DL 37. Mass spectra were measured with a Finnigan TSQ 7000 instrument. The reaction progress was monitored by TLC on silica gel plates (60F-254, Merck art. 1.05554), and examined under UV light at 254 nm, and sprayed with Draggendorff's reagent. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution on a BRUCKER Advance DPX 400 spectrometer, chemical shifts are given in p.p.m. relative to TMS as internal standard. Optical rotations were carried out using a Perkin-Elmer 241 polarimeter. Chiral HPLC was performed on a gradient Waters 600E powerline instrument equiped with a UV variable detector 486 powerline set at 230 nm and a Chiracel OD column eluted with a mixture of Hexane/Ethanol/Diethylamine (96/4/0.01).

3-Methoxymethylquinuclidine-3-ol (4).- To a suspension of 3-quinuclidinone hydrochloride (**2**) (25 g, 0.154 mol) in methanol (200 mL) were added trimethylsulfoxonium iodide (40.9 g, 0.185 mol) and sodium hydroxide pellets (31 g, 0.77 mol) under stirring. The reaction was refluxed for 1 h. The mixture was evaporated to dryness under reduced pressure. The residue was treated with water and extracted with 2-butanone. The organic layer was washed with brine, dried over anhydrous sodium

sulfate and evaporated under reduced pressure to yield the pure 3-methoxymethylquinuclidine-3-ol (**4**) as white crystals (25 g, 95%), mp. <60°. ^{1}H NMR (400MHz, $CDCl_3$): δ 3.47 (d, 1H, *J* = 9.2 Hz, CH_2OCH_3), 3.39 (s, 3H, OCH_3), 3.23 (d, 1H, *J* = 9.2 Hz, CH_2OCH_3), 3.07 (m, 1H, OH), 2.5-2.9 (m, 5H), 2.05 (m, 1H), 1.90 (m, 1H), 1.53-1.57 (m, 2H), 1.22-1.32 (m, 2H).

3-Hydroxymethylquinuclidine (6).- A solution of compound **4** (4 g, 23.3 mmol) in 18 N sulfuric acid solution was refluxed for 1 h. The mixture was cooled and pH was adjusted to 8 with 30% sodium hydroxide at 10°. Then, methanol (10 mL) was added and the mixture treated portionwise with sodium borohydride (0.9 g, 23.3 mmol) while the temperature was maintained at 10°. After complete addition, stirring was continued for a further 15 min.. The reaction was adjusted to pH 12 with 30% sodium hydroxide and extracted with 2-butanone, dried over anhydrous sodium sulfate and evaporated under reduced pressure to leave the 3-hydroxymethyl quinuclidine (**6**) as a clear oil (2.9 g, 88%). The product was used in subsequent reaction without further purification. An analytical sample was crystallized as its hydrochloride salt from 2-butanone mp. 260°, lit.[2] isolated as a picrate, mp. 188-190°. ^{1}H NMR (400 MHz, DMSO) (free base): δ 4.86 (m, 1H), 3.42 (d, 2H), 3.26 (t, 1H), 3.08-3.17 (m, 4H), 2.67-2.72 (m, 1H), 2.06 (t, 1H), 1.62-1.88 (m, 4H).

Anal. Calcd : $C_8H_{15}NO{\bullet}HCl{\bullet}H_2O$: C, 53.27; H, 8.98; N, 7.86. Found : C, 52.93; H, 9.01; N, 7.78

3-Methanesulfonyloxymethylquinuclidine Hydrochloride (7).- To a stirred solution of (**6**) (50 g, 0.354 mol) in chloroform (760 mL) and pyridine (33.3 g, 34 mL, 0.421 mol) was added dropwise methanesulfonyl chloride (48.8 g, 33 mL, 0.426 mol) while the temperature was kept below 10° in an ice bath. After the end of addition, stirring was continued 6 h at room temperature. The suspension of the resulting hydrochloride was collected from reaction mixture, washed with acetone and diethyl ether then dried at 50° under vacuum to give the hydrochloride salt as white crystals **7** (73 g, 80%), mp. 180°. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.38 (1H, m), 1.48-1.50 (1H, m), 1.57-1.58 (1H, m), 1.79 (1H, s), 2.02-2.05 (1H, m), 2.29-2.34 (1H, dd), 2.70-2.83 (4H, m), 2.95 (3H, s), 2.95-3.02 (1H, m), 4.09-4.17 (2H, m).

Separation of Enantiomers of 3-Methanesulfonyloxymethylquinuclidine (7).- A mixture of 3-methanesulfonyloxymethyl quinuclidine (**7**), as the free base (22 g, 0.1 mol) and L-tartaric acid (15 g, 0.1 mol) were refluxed in a mixture ethanol/water (80:20) (300 mL) to dissolution. The solution was slowly allowed to reach room temperature. The precipitate was collected to afford white crystals (25.9 g) of the L-tartrate salt. Two recrystallizations from the mixture ethanol/water (80:20) yielded L-tartrate salt (14.5 g, 80%). A sample of this salt was treated with a 30% sodium hydroxide and extracted with 2-butanone. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to leave a pure clear oil. ^{1}H NMR is in accordance with its hydrochloride salt. $[\alpha]_D^{24} = -48.3°$ (0.295%, methanol).

Racemic Mequitazine (1).- A solution of phenothiazine (**8**) (60 g, 0.3 mol) in THF (200 mL) was cooled at 0° under nitrogen atmosphere. A solution of *n*-butyllithium in hexane (2.5 M , 100 mL, 0.25 mol) was introduced dropwise over 20 min. at 0°. The reaction mixture was stirred 1 h reaching room temperature. Then, the 3-methanesulfonyloxymethylquinuclidine hydrochloride (**7**) (25.6 g, 0.1 mol)

was added with N-methyl-2-pyrrolidinone (100 mL). The slurry was refluxed for 2 h at 65°, and poured into ice-water (1000 mL) with stirring. The material was extracted with a mixture of ethyl acetate-isopropyl ether (1:1) (2 x 500 mL). The separated organic layers were washed with water (2 x 500 mL), then with 1 N HCl solution (2 x 500 mL). Aqueous acidic layers were again extracted with ethyl acetate-isopropyl ether (1:1). Mequitazine hydrochloride (**1**) precipitated slowly in the aqueous acidic layer. Crystals were collected and washed with isopropyl ether, yielding 31 g (91%) of mequitazine hydrochloride (**1**) as a creamy powder. A pure sample was obtained by crystallization from isopropyl-alcohol, mp. 261°. Mequitazine hydrochloride was converted to the free base as a white powder, mp. 130°, lit[1] 130°. ^{1}H NMR spectrum was identical to that of an authentic sample.[1] MS: m/e = 323 (M^+).

S(-)-Mequitazine.- Following the procedure described for the racemic mequitazine (**1**), the S(-)3-methanesulfonyloxymethylquinuclidine was treated with phenothiazine (**8**) to give S(-)-mequitazine, mp. 140° (free base). $[\alpha]_D^{24}$ = - 40.5° (0.93%, ethanol), lit.[11] mp. 139-140°, $[\alpha]_D^{24}$ = -39.8° (1%, ethanol). Chiral HPLC: enantiomeric purity > 99%.

REFERENCES

1. C. Gueremy, R. Laley, D. Wirth and M. Auclair, *Ger. Offen. Pat.* 2,009,555; *Chem. Abstr.*, **73**, 131017 (1970).

2. C. A. Grob and E. Renk, *Helv. Chim. Acta*, **37**, 1689 (1954).

3. J. Goetz, W. Orth, W. Weiss, B. Rapp and H. W. Kleffner, *EP.* 0354301; *Chem. Abstr.*, **113**, 6167 (1988).

4. F. J. Ricciardi and P. H. Doukas, *Heterocycles*, **24**, 971 (1986).

5. E. J. Corey and M. Chaykovsky, *Org. Synth.* **49**, 78 (1969).

6. G. Nordwall, S. Sundquist, G. Glas, A. Gogoll, L. Nilvebrant and U. Hacksell, *J. Med. Chem.*, **35**, 1541 (1992).

7. A. I. Kuznetsov, T. M. Serova, Tran Nghi, A. Vladimirova and A. S. Moskovkin, *J. Org. Chem. USSR*, **30**, 391 (1994); *Chem. Abstr.* **122**, 105837 (1995).

8. I. Masami and H. Takedo, *JP.* 04,169,583; *Chem. Abstr.*, **118**, 6983 (1990).

9. P. L. Stotter, M. D. Friedman, G. O. Dorsey, R. W. Shiely, R. F. Williams and D. E. Minter, *Heterocycles*, **25**, 251 (1987).

10. G. A. Epling and A. Kumar, *Synlett*, 347 (**1991**).

11. C. Renaut and G. Lefur, *EP.* 0089,860; *Chem. Abstr.*, **100**, 68312 (1982).

****