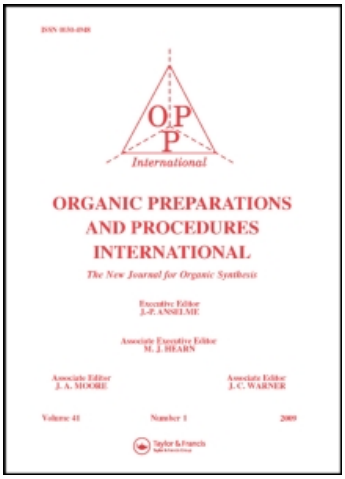


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF THE ANTIHYPERTENSIVE AGENT 1-(1-METHYLETHYL)-2-(2-[4-(3-TRIFLUOROMETHYLPHENYL)-1-PIPERAZINYL]ETHYL)-1H-NAPHTH[1, 2-d] IMIDAZOLE CITRATE

E. Toja[a]; A. Trani[a]
[a] Lepetit Research Center, Merrell-Dow Research Institute, Gerenzano, VA, ITALY

To cite this Article Toja, E. and Trani, A.(1988) 'SYNTHESIS OF THE ANTIHYPERTENSIVE AGENT 1-(1-METHYLETHYL)-2-(2-[4-(3-TRIFLUOROMETHYLPHENYL)-1-PIPERAZINYL]ETHYL)-1H-NAPHTH[1, 2-d] IMIDAZOLE CITRATE', Organic Preparations and Procedures International, 20: 3, 253 — 260
To link to this Article: DOI: 10.1080/00304948809355818
URL: http://dx.doi.org/10.1080/00304948809355818

ORGANIC PREPARATIONS AND PROCEDURES INT. 20(3), 253-260 (1988)

SYNTHESIS OF THE ANTIHYPERTENSIVE AGENT 1-(1-METHYLETHYL)-2-(2-[4-(3-TRIFLUOROMETHYLPHENYL)-1-PIPERAZINYL]ETHYL)-1H-NAPHTH[1,2-d]IMIDAZOLE CITRATE

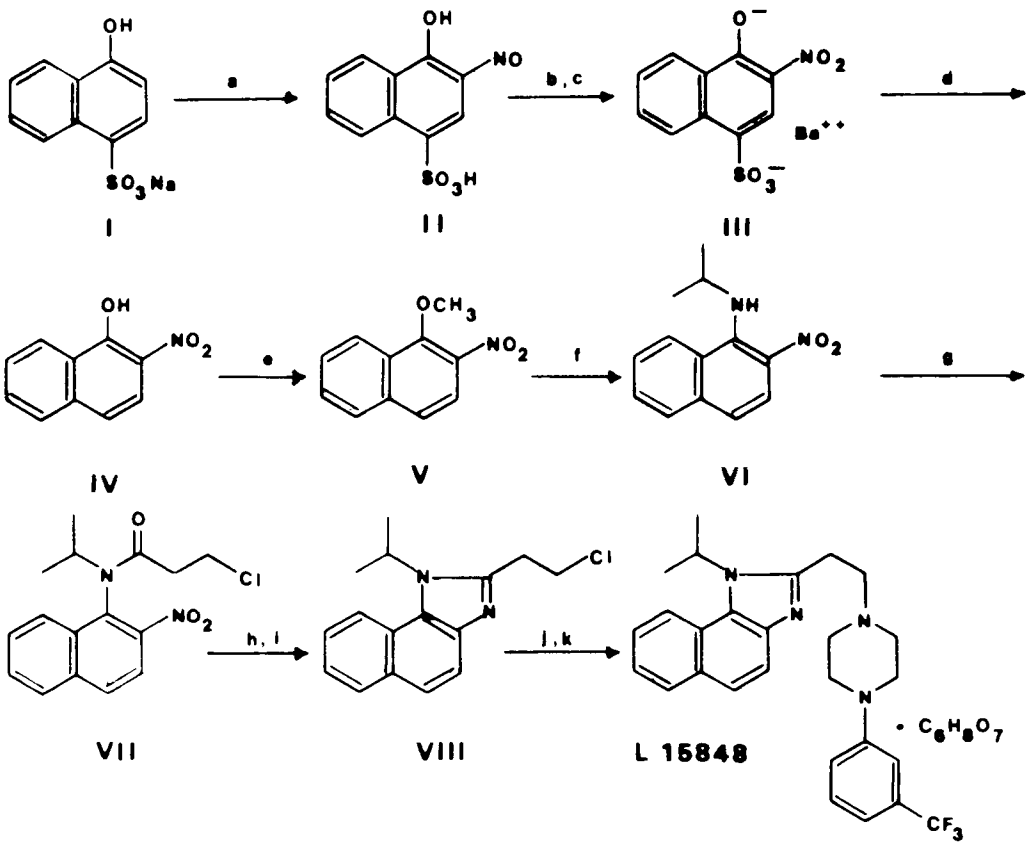
E. Toja† and A. Trani*

Merrell-Dow Research Institute, Lepetit Research Center,
Via R. Lepetit 34 - 21040, Gerenzano (VA) ITALY

The citrate salt of 1-(1-methylethyl)-2-(2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl)-1H-naphth[1,2-d]imidazole, coded L 15848, is a long-lasting antihypertensive agent, orally active in conscious normotensive and renal hypertensive dogs without CNS depressant effects.[1] The synthesis of L 15848 and of other naphth[1,2-d]imidazoles from 1-methoxynaphthalene has been reported.[2] This route works well on a lab scale but is less suitable for large scale production because of low yields in the nitration of the intermediate 4-bromo-1-methoxynaphthalene and the hazardous use of 99% nitric acid in acetic anhydride. This paper describes an alternative procedure for the preparation of L 15848 that is more suitable for larger scale reactions.

Treatment of the sodium salt of 1-hydroxynaphthalene-4-sulfonic acid (I) with nitrous acid gave 2-nitroso-1-hydroxynaphthalene-4-sulfonic acid (II)[3], in nearly quantitative yield; in contrast, treatment of I with aqueous nitric acid afforded 2,4-dinitro-1-hydroxynaphthalene.[3] Complete oxidation of the nitroso group was achieved using a 4:1 molar ratio of 36%

hydrogen peroxide to II in alkaline solution;[4] III was purified via its barium salt obtained by treatment of the reaction mixture with a molar quantity of barium hydroxide.[5] Desulfonation of III was best accomplished by a modification of Bogdanov's procedure[6] with 85% phosphoric acid at 160°. Methylation of IV was best carried out with only a slight excess dimethyl sulfate and potassium carbonate in methyl ethyl ketone (MEK), thus avoiding the use of excess dimethyl sulfate of the original procedure.[7]



a) $NaNO_2$, HCl b) H_2O_2, OH^- c) $Ba(OH)_2$ d) H_3O^+ e) Me_2SO_4, MEK, K_2CO_3 f) i-$PrNH_2$, t-BuOMe g) $ClCH_2CH_2COCl$, $ClCH_2CH_2Cl$ h) H_2, Pt, EtOAc i) HCl, i-PrOH J) N-(3-trifluoromethylphenyl)piperazine, AmOH k) Citric acid.

The replacement of the methoxy group was accomplished by treatment with isopropylamine in t-butyl methyl ether in nearly quantitative yield. Acylation of VI with 3-chloropropionyl chloride did not require any acid acceptor. Catalytic reduction of the nitro group of VII followed by acid-catalyzed cyclization gave 2-chloroethylnaphth[1,2-d]imidazole VIII. During the work-up of the reaction mixture, a partial dehydrohalogenation of the alkyl chain was observed, giving rise to about 5% of the corresponding 2-vinyl derivative. The crude reaction mixture was then finally treated with N-(3-trifluoromethylphenyl)piperazine to yield the final compound as a free base.

Formation of the citrate (L 15848) represents a convenient procedure for eliminating all the by-products of the preceding steps. L 15848 is obtained in a yield of about 60% from V in the form of a non-hygroscopic white crystalline solid, stable to air and light.

EXPERIMENTAL SECTION

Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were measured in nujol mull with a Perkin-Elmer 157 spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker WH 270 or AM 250 spectrophotometer. Microanalyses were performed by the Analytical Department of Gruppo Lepetit. Differential scanning calorimetry curves (DSC) were obtained on a TA 2000 Mettler thermal analyzer, in a normal pan, with Nitrogen flow of 25 mL/min and a heating rate of 5°/min. TLC determinations were carried out on silica gel plates 60 F254:Merck.

2-Nitro-1-hydroxynaphthalene-4-sulfonic Acid Barium Salt Hydrate (III). - To a solution of sodium 1-hydroxynaphthalene-4-sulfonate (Fluka, purity degree 70%) (350 g, 1 mole) in 4 L of water was added sodium nitrite (75.9 g, 1.1 mole) followed by 1N HCl (1.1 L, 1.1 mole) with the temperature

being maintained below 5°. The reaction mixture was allowed to warm slowly to room temperature and the precipitate was redissolved by addition of NaOH pellets (44 g, 1.1 mole). The pH of the solution was brought to 8 by addition of 1N NaOH and 36% w/v hydrogen peroxide (400 mL, 4.2 moles) was added. The reaction mixture was stirred for 18 hrs and during this time the temperature slowly rose to 29°. A solution of $Ba(OH)_2.8H_2O$ (315.5 g, 1 mole) in 5 L of water was added and the resulting yellow precipitate was collected and air-dried at 60° to give 382 g (90%) of the crude III.[5]

2-Nitro-1-hydroxynaphthalene (IV). - A stirred dispersion of 10 g (23.6 mmoles) of III in 1 L of 85% H_3PO_4 was heated at 160° in a flask set up for steam distillation. Compound IV was steam distilled as it was formed . The phosphoric acid was decanted and the reaction flask washed with methylene chloride. The same solvent was used to extract the distillate and the combined extracts were evaporated to afford 3.3 g (74%) of IV, mp. 126-128°, assay by DSC 97%, IR (nujol): 1625, 1585, 1545, 1390, 1380, 980, 810, 770, 735 cm^{-1}; NMR (d_6-DMSO): δ 5.5 (broad band due to exchange with water present in the solvent, 1H), 7.43 (d, 1H), 7.64 (dd, 1H), 7.75 (dd, 1H), 7.94 (d, 2H), 8.39 (d, 1H); R_f: 0.28 (n-hexane:ethyl acetate:dioxane: acetic acid 9:0.5:0.5:0.2).

Larger quantities of IV were prepared through Bogdanov's procedure,[6] without modification.

1-Methoxy-2-nitronaphthalene (V). - Anhydrous potassium carbonate (400 g) was added to a stirred solution of 97% 2-nitro-1-hydroxynaphthalene (IV) (500 g, 2.56 moles) in 5 L of methyl ethyl ketone followed by dropwise addition of dimethyl sulfate (250 mL, 2.64 moles) during 5 min. at room tem-

perature. The mixture was heated to reflux for 5 hrs then the solvent was evaporated under reduced pressure. The residue was taken up with 3.5 L of methylene chloride, filtered and the solution washed with 10% sodium hydroxide, dried (Na_2SO_4) and evaporated. The residue was recrystallized from 2 L of absolute ethanol to yield 437 g (84%) of V, mp. 77-78°, lit.[8] mp. 80°; IR (nujol): 1620, 1585, 1520, 1340, 1210, 980, 815, 792, 760 cm^{-1}; NMR ($CDCl_3$): δ 4.13 (s, 3H), 7.6 (d and dd overlapped, 3H), 7.89 (d, 2H), 8.31 (d, 1H); R_f: 0.25 (n-hexane:acetone 8:2).

N-(1-methylethyl)-2-nitro-1-naphthylamine (VI).- Isopropylamine (92 mL, 0.357 mole) was added to a slowly stirred solution of V (72.6 g, 0.357 mole) in 290 mL of t-butyl methyl ether. The mixture was kept at 40° under nitrogen for three days. The solvent was evaporated and the residue (82 g) was utilized in the next step without purification. An analytical sample melted at 58° after recrystallization from i-PrOH; IR (nujol): 3330, 1615, 1570, 1530, 1395, 1115, 820-660 cm^{-1}; NMR ($CDCl_3$): δ 1.30 (d, 6H), 4.15 (m, 1H), 7.24 (d, 1H), 7.51 (dd, 1H), 7.62 (dd, 1H), 7.95 (d, 1H mobile proton), 8.04 (d, 1H), 8.28 (d, 1H), all the peaks are doubled for the presence of two rotational conformers; R_f: 0.36 (n-hexane:acetone 8:2).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.80; H, 6.13; N, 12.16

Found: C, 68.16; H, 5.69; N, 12.14

3-Chloro-N-(1-methylethyl)-N-(2-nitro-1-naphthyl)propionamide (VII). - A solution of VI (100 g, 0.434 mole) in 600 mL of 1,2-dichloroethane was added to a 1 L flask equipped with a reflux condenser, a Claisen distillator and a mechanical stirrer. About 50 mL of solvent were distilled off to remove traces of water from the reaction mixture. 3-Chloropropionyl chloride

(45 mL, 0.467 mole) was added dropwise at 60° and the mixture was heated again in order to distill off about 400 mL of solvent during 5 hrs. Another portion of the acyl chloride (16.8 mL, 0.174 mole) was added dropwise and the mixture was heated at 120° for an additional hour. After cooling to room temperature, 500 mL of methylene chloride were added followed by 300 mL of 1N sodium hydroxide while the temperature was maintained below 20°. The organic layer was separated, dried over Na_2SO_4 and evaporated to dryness. The residue was triturated twice with 250 mL of hexane to afford after filtration 131 g (about 94%) of VII used as such in the next step. An analytical sample was obtained by crystallization from 2-propanol, mp. 108-109°; IR (nujol): 1655, 1525, 1350, 825, 800, 750 cm^{-1}; NMR ($CDCl_3$): δ 0.9 (d, 3H), 1.04 (d, 3H), 2.24 (m, 1H), 2.71 (m, 1H), 3.71 (m, 1H), 3.82 (m, 1H), 4.91 (m, 1H), 7.7-8.22 (d, and dd, aromatic protons, 6H); R_f: 0.28 (n-hexane:acetone 8:2).

Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73; Cl, 11.05

Found: C, 60.05; H, 5.38; N, 8.57; Cl, 10.86

2-(2-Chloroethyl)-1-(1-methylethyl)-1H-naphth[1,2-d]imidazole (VIII). - A solution of VII (500 g, 1.56 mole) in 3.2 L of ethyl acetate was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (5 g) for 6 hrs. The catalyst was filtered and the solvent was evaporated under reduced pressure yielding the corresponding amino derivative[8] (453 g). To a suspension of this crude material in 2-propanol (2.5 L), 277 mL of 37% HCl was added dropwise with stirring at room temperature and then the mixture was heated to reflux for 3 hrs. The solvent was evaporated under reduced pressure and 2.9 L of methylene chloride was added followed by

dropwise addition of 1.16 L of 20% NaOH to reach pH 8. The organic layer was washed twice with 700 mL of water and evaporated to dryness to yield 419.4 g of VIII used as such in the next step. NMR spectra showed that the mixture contained 85% of VIII, 5% of the corresponding 2-vinyl derivative and 10% of an unknown material. An analytical sample was obtained by column chromatography on silica gel eluting with benzene:acetone 9:1, mp. 126-128°; IR (nujol): 1300, 810, 750 cm^{-1}; NMR ($CDCl_3$): δ 1.7 (d, 6H), 3.46 (t, 2H), 4.15 (t, 2H), 5.44 (broad multiplet, 1H), 7.39-8.42 (d, and dd, aromatic protons, 6H); R_f: 0.41 (benzene:acetone 8:2).

Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27; Cl, 12.99

Found: C, 70.70; H, 6.33; N, 10.30; Cl, 12.71

1-(1-Methylethyl)-2-(2-(4-(3-trifluoromethylphenyl)-1-piperazinyl)ethyl)-1H-naphth[1,2-d]imidazole citrate (L 15848). - A solution of crude VIII (354 g) and N-(3-trifluoromethylphenyl)piperazine (597.2 g, 6.72 moles) in 4.2 L of n-amyl alcohol was heated at reflux under nitrogen for 6 hrs. The solvent was distilled off at reduced pressure and the residue was taken up with 2 L of water and 3 L of methylene chloride. The organic layer was washed twice with 600 mL of water and evaporated to dryness to yield 594 g of the final compound as a free base. To the solution of the base in 1.7 L of methanol, previously decolorized with charcoal at reflux, a solution of citric acid monohydrate (227 g, 1.08 mole) in 650 mL of methanol was added. After cooling to room temperature, the precipitate was collected by filtration and triturated several times with cold methanol till complete decoloration. The product was dried at 50° under vacuum to yield 549 g of L 15848, mp. 141-143°; IR (nujol): 3500, 1730, 1170, 1120, 820, 785, 748, 690

cm^{-1}; NMR (d_6-DMSO): δ 1.77 (d, 6H), 2.62 (d, 2H), 2.73 (d, 2H), 3.02 (unresolved m, 4H), 3.31 (unresolved m, 2H), 3.38 (unresolved m, 4H), 5.44 (broad multiplet, 1H), 7.11 (d, 1H), 7,24 (s, 1H), 7.26 (d, 1H), 7.46 (dd, 2H), 7.68 (dd, 1H), 7.72 (2d, 2H), 8.05 (d, 1H), 8.44 (d, 1H); R_f 0.81 (methanol: chloroform: 15% NH_4OH 97:3:0.5).

Anal. Calcd for $C_{33}H_{37}F_3N_4O_7$: C, 60.17; H, 5.66; N, 8.51

Found: C, 60.06; H, 5.65; N, 8.45

REFERENCES

† Present Address: Roussel Maestretti, Via Gran Sasso 18, 20131 Milano.

1. E. Toja, D. Barone and E. Baldoli, U. S. Patent 4,594,348 (1986); C. A., 104, 75025m (1986).

2. E. Toja, G. Di Francesco, D. Barone, E. Baldoli, N. Corsico, G. Tarzia, Eur. J. Med. Chem., 22,221 (1987).

3. O. N. Witt and H. Kaufmann, Ber., 24, 3157 (1891).

4. Many other oxidizing agents could be used, see H. Feuer, "The Chemistry of the Nitro and Nitroso Groups", CH 3, Part 2, S. Patai, Ed., Interscience Publishers, New York, N. Y., 1970.

5. An excess of barium hydroxide has to be avoided because barium peroxide also precipitates by reaction with excess hydrogen peroxide. To avoid this problem it is profitable to destroy excess hydrogen peroxide by introducing a catalytic amount of Pt black in the reaction mixture and stirring at room temperature till the peroxide test is negative, prior to the addition of $Ba(OH)_2$.

6. S. V. Bogdanov and I. N. Koroleva, Zur. Obsch. Khim., 23, 1761 (1953).

7. G. R. Clemo, J. G. Cockburn and R. Spence, J. Chem. Soc., 1265 (1931).

8. R_f:0.33 (benzene:acetone 8:2), IR (Nujol): 3460, 3340, 1620, 1295, 810, 750 cm^{-1}.

(Received January 27, 1987; in revised form November 16, 1987)