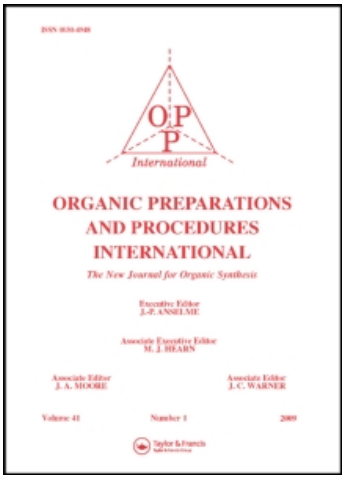

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SYNTHESIS OF ANALOGS OF PROPRANOLOL HYDROCHLORIDE

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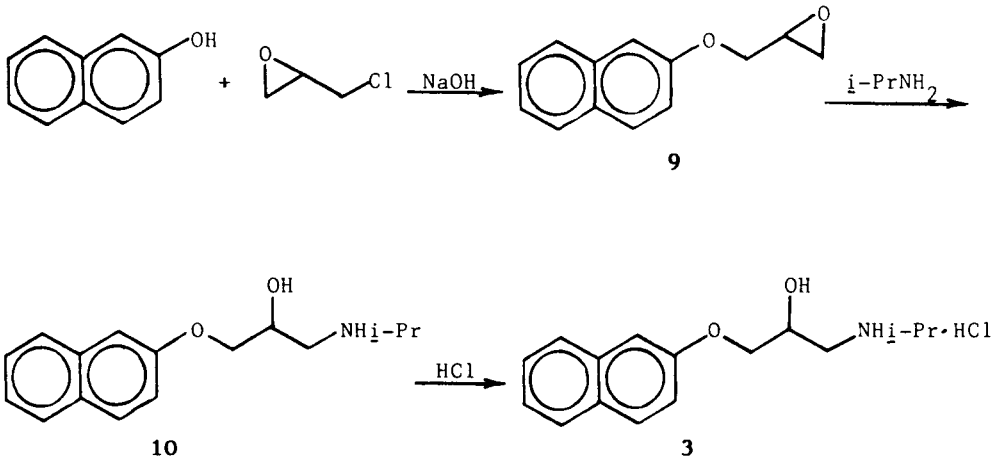
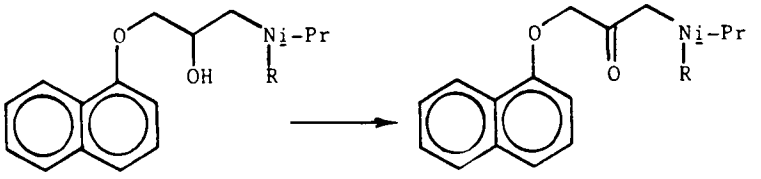
Propranolol hydrochloride (1) is amongst the major β-adrenergic receptor antagonists used in the treatment of certain cardiovascular disorders. Consequently, many analogs[1] and metabolities[2] of propranolol hydrochloride (1) have been prepared for various biological and chemical studies. However, few reports of the synthesis of its regioisomer[3] or ketone derivative[4] have been published. We report herein a synthesis (Table I) of the ketone analog (2) of propranolol hydrochloride and a one-pot route to the 2-isomer (3) of 1 from 2-naphthol.

Scheme I



Initial efforts[5] at synthesizing 1-isopropylamino-3-(1-naphthoxy)-2-propanone (2) focused on oxidizing propranolol base (4) directly. Upon treating 4 with varying amounts of Jones reagent in several solvents, the starting material was consumed, several products were formed, and none of

the desired ketone could be isolated. Similar results were realized with the milder Collins reagent, pyridinium chlorochromate (PCC), and potassium permanganate. Consequently, the oxidation of N-protected derivatives of **4** were examined (Table I).



1, R = H·HCl
4, R = H
5, R = CO_2Me
7, R = CO_2t-Bu

2, R = H·HCl
6, R = CO_2Me
8, R = CO_2t-Bu

Table I

Entry	Carbamate	Oxidant	% Yield
1	5	$KMnO_4$	No Rxn
2	5	PCC	25
3	5	CrO_3·2Pyr	90
4	7	$KMnO_4$	No Rxn
5	7	CrO_3·2Pyr	95

Methyl carbamate **5** was readily prepared in 58% yield by allowing a CH_2Cl_2 solution of propranolol base (**4**) to react with methyl chloroformate in the presence of potassium carbonate. Upon treating carbamate **5** with $KMnO_4$ in acetone, no reaction occurred (entry 1, Table I), while partial oxidation to **6** was observed (entry 2, Table I) when PCC was employed. The protected ketone **6** was isolated in 90% yield (entry 3) when alcohol **5** was treated with freshly prepared CrO_3·2Pyr.

The t-butyl carbamate (**7**) of **4** was synthesized in quantitative yield by reacting a methylene chloride solution of propranolol (**4**) with di-t-butyl dicarbonate in the presence of potassium carbonate. As was the case with methyl carbamate **5**, t-butyl carbamate **7** was unaffected by $KMnO_4$ (entry 4), but was readily oxidized with excess CrO_3·2Pyr to give keto carbamate **8** in 95% yield (entry 5, Table I).

Having successfully oxidized the 2° alcohol of propranolol, it then

remained to remove the N-protecting groups. Treatment of keto methyl carbamate **6** with potassium hydroxide, hydrochloric acid, acetic acid, trifluoroacetic acid, lithium chloride, sodium iodide, or potassium iodide under various conditions of time, temperature, and solvent did not afford any desired ketone **2** or its free base.[6] Equally disappointing results were obtained when keto t-butyl carbamate **8** was treated with trifluoroacetic acetic acid in CH_2Cl_2.[7] However, 1-isopropylamino-3-(1-naphthoxy)-2-propanone hydrochloride (**2**) was isolated in 90.6% yield when the deprotection-protonation sequence was conducted in one pot. Thus, keto t-butyl carbamate **8** was dissolved in n-PrOH and allowed to react at room temperature with 1.5 equivalents of anhydrous hydrogen chloride dissolved in n-PrOH. The product (**2**) was a white solid and gave an NMR and IR spectrum consistent with its structure.

The synthesis of β-propranolol·HCl (**3**), the 2-regioisomer of **1**, was straightforward and could be accomplished without isolation or purification of the intermediates (Scheme I). Thus, 2-naphthol was dissolved in warm epichlorohydrin and treated with 1.5 equivalents of aqueous sodium hydroxide. After the reaction was completed (TLC), the unreacted epichlorohydrin was removed by distillation and the resulting aqueous suspension of epoxide **9** allowed to react with excess isopropylamine. Upon workup and recrystallization, pure β-propranolol (**10**) was obtained in 74% yield. Alternatively, crude **10** was converted directly to its hydrochloride salt (**3**) with anhydrous hydrogen chloride in n-propanol in 86% yield.

In summary, practical processes for synthesizing preparative quantities of 1-isopropylamino-3-(1-naphthoxy)-2-propanone hydrochloride (**2**) and 1-isopropylamino-3-(2-naphthoxy)-2-propanol hydrochloride (**3**), analogs of the β-adrenergic blocking agent propranolol hydrochloride (**1**), have been presented.

EXPERIMENTAL SECTION

1-(N-t-Butoxycarbonyl-N-isopropylamino)-3-(1-naphthoxy)-2-propanol (**7**).- To 15.2 g (58.6 mmoles) of propranolol (**4**) dissolved in methylene chloride (65 ml) was added 4.0 g (28.9 mmoles) of potassium carbonate, followed by dropwise addition of di-t-butyl dicarbonate (14 ml, 60.1 mmoles) in methylene chloride (10 ml). After stirring at 25 ± 5°C for 3.5 hrs, the reaction mixture was diluted with methylene chloride (75 ml), poured into water

(75 ml), extracted with methylene chloride (2 x 35 ml) and washed with water (2 x 30 ml). The combined organic extracts were washed with dilute HCl (2.5%, 40 ml), water (30 ml), and dried over anhydrous sodium sulfate. Filtration and removal of the solvent in vacuo gave 7 in quantitative yield. IR (neat) 3408, 1690 cm^{-1}. This material was used in the next step without purification.

1-(N-t-Butoxycarbonyl-N-isopropylamino)-3-(1-naphthoxy)-2-propanone (8).- To 30.4 g (117.8 mmoles) of chromium trioxide-pyridine complex suspended in methylene chloride (300 ml) at 18 ± 3°C, was added 5.25 g (14.6 mmoles) of alcohol 7 dissolved in methylene chloride (50 ml). The reaction mixture was then diluted with 100 ml of methylene chloride and stirred at 18 ± 3°C. After 1.25 hrs the heterogeneous mixture was filtered through Celite, rinsed with methylene chloride (100 ml), diluted with ether (450 ml), stirred at room temperature, and refiltered through Celite. The clear filtrate was washed with 20% sodium citrate solution (2 x 120 ml), 3% hydrochloric acid (2 x 50 ml), brine, and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave 4.94 g (95%) of product 8. IR (neat) 1743, 1690 cm^{-1}. This material was used in the next step without purification.

1-Isopropylamino-3-(1-naphthoxy)-2-propanone Hydrochloride (2).- To 3.91 g (10.9 mmoles) of carbamate 8 dissolved in n-propanol (25 ml) was added 0.59 g (16.3 mmoles) of anhydrous hydrogen chloride dissolved in n-propanol (3.5 ml). The resulting heterogeneous mixture was stirred at room temperature for 1 hr, filtered, and the crystals washed with cold acetone (25 ml). Upon drying at 45°C in vacuo, 2.04 g (63%) of product 2, mp. 154.7-155.5°C (dec.) was obtained as a white solid. IR (KBr) 2800-2400, 1740 cm^{-1}; NMR (60 MHz, DMSO-d_6) δ 9.22 (bs, 2H), 8.05 (m, 1H), 7.65 (m, 1H), 7.48-7.12 (m, 4H), 6.76 (dd, 1H, J = 6, 2 Hz), 5.05 (s, 2H), 4.18 (bs, 2H), 3.11 (m, 1H), 1.11 (d, 6H, J = 6 Hz).

1-Isopropylamino-3-(2-naphthoxy)-2-propanol (10).- To 376 g (2.61 moles) of 2-naphthol dissolved in 482.8 g (5.22 moles) of epichlorohydrin at 60°C was added, over a period of 30 minutes, 784 g (3.93 moles) of 20% aqueous NaOH. The resulting heterogeneous mixture was stirred for 1 hr at 62 ± 2°C, then cooled to less than 35°C. Vacuum distillation removed the unreacted epichlorohydrin and left a brown, heterogeneous mixture that was diluted with water (135 ml) and treated with 627 g (10.6 moles) of isopro-

pylamine while maintaining the temperature at 34 ± 2°C. After stirring for 2 hrs at 34 ± 2°C, the reaction mixture was cooled to room temperature, stirred overnight, then concentrated via atmospheric distillation. The remaining concentrate was slurried with water (470 ml) and toluene (434 ml), cooled, filtered, and the crystals washed with cold toluene (2 x 200 ml). Upon drying in vacuo at 60°C, 522.4 g (77%) of crude **10** was isolated as a white solid. NMR (60 MHz, $CDCl_3$) δ 7.85-7.0 (m, 7H), 4.05 (bs, 3H), 3.03-2.5 (m, 5H), 1.08 (d, 6H, J = 6Hz). The crude material was used in the next step without purification.

1-Isopropylamino-3-(2-naphthoxy)-2-propanol Hydrochloride (3).- To a suspension of 520 g (2.01 moles) of **10** in 1,658 ml of n-propanol at 33 ± 2°C was added 73.2 g (2.01 moles) of anhydrous hydrogen chloride dissolved in n-propanol (675.4 ml). The reaction mixture was heated to 92 ± 2°C, treated with Norit A (4.2 g), clarified and washed (n-PrOH, 300 ml). The clear, hot filtrate was then cooled to 0°C with vigorous stirring, then stirred at 0°C overnight. Upon isolating the product by suction filtration, washing with acetone (2 x 210 ml), and drying in vacuo at 60°C, 513.1 g (86%) of white **3** was obtained; m.p. 147.7-149°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (bs, 1H), 8.68 (bs, 1H), 7.82 (m, 3H), 7.46 (m, 1H), 7.34 (m, 2H), 7.19 (dd, 1H, J = 8.9, 2.5 Hz), 5.95 (d, 1H, J = 4.9 Hz), 4.3 (m, 1H), 4.1 (d, 2H, J = 5.3 Hz), 3.37 (m, 1H), 3.15 (m, 1H), 3.0 (m, 1H), 1.27 (d, 3H, J = 6.3 Hz), 1.26 (d, 3H, J = 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 134.2, 129.3, 128.6, 127.5, 126.7, 126.4, 123.7, 118.6, 106.9, 69.9, 65.1, 49.8, 46.9, 18.6, 18.2; MS m/e 259, 244, 215, 144, 127, 115, 72 (base).

Anal. Calcd for $C_{12}H_{22}ClNO_2$: C, 64.97; H, 7.50; N, 4.73
Found: C, 64.80; H, 7.58; N, 4.82

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5. The synthesis of keto propranolol **2** from 1-naphthol, 1,3-dichloroacetone, and isopropylamine was not successful in our hands.

6. It is possible that **2**, or its free base, was formed during the hydrolysis step, but may have decomposed during the various workup procedures employed. We subsequently found the free base of **2** to be a labile compound which decomposed to 1-naphthol and several other compounds in the presence of bases and nucleophiles.

7. Carbamate **8** was consumed in less than 30 minutes at room temperature, however, none of the desired product (**2**) was isolated on workup. See reference 6.

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