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The optical isomers of *cis*-*N*-normetazocine are the starting materials for the synthesis of a number of pharmacologically useful compounds. An improved resolution procedure for obtaining these isomers is reported.

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The optical isomers of *cis*-*N*-normetazocine (*cis*-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan [1,2]) are starting materials for the synthesis of a number of *N*-substituted derivatives useful as research tools [3-8]. We have synthesized several optically active *N*-substituted-*cis*-*N*-normetazocines. These preparations have required large amounts of the *cis*-*N*-normetazocine optical isomers. In this paper we report an improved resolution procedure for obtaining the necessary amounts of these isomers. We also provide data on the optically active *N*-substituted-*cis*-*N*-normetazocines prepared from our resolved material.

Discussion.

The initial resolution [3] of (\pm)-*cis*-*N*-normetazocine involved the fractional crystallization of (-)-*cis*-*N*-normetazocine (+)-tartrate from aqueous solution. Crude (+)-*cis*-*N*-normetazocine was recovered from the filtrate and further resolved by crystallization of the (-)-tartrate salt from aqueous solution. Subsequent liberation of the respective bases followed by recrystallization from 95% ethanol provided the pure optical isomers (50% chemical yield). The reported [3] experiment was carried out on a tenth molar scale. A subsequent resolution [9] utilized the original pro-

cedure [3].

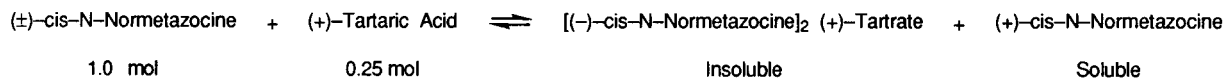
Our synthetic needs required the routine resolution of (\pm)-*cis*-*N*-normetazocine on at least a two molar scale. Upon examining this problem, we found that the initial [3] resolution procedure was difficult to either reproduce or scale up. The inherent difficulty was due to the similar solubilities of the initially formed diastereoisomeric salts. Because of this solubility similarity, (\pm)-*cis*-*N*-normetazocine (+)-tartrate was often the major fractionation product. Modifications of the procedure involving the use of various aqueous alcohol combinations provided some improvement but still failed to separate completely the diastereoisomeric salts. Consequently, resolutions on a two molar scale not only involved a large number of fractionations but also took considerable time to complete. Moreover, the chemical yield of the resultant isomers remained around 50%.

Another approach was suggested by a resolution procedure in which organic bases were reacted with optically active organic acids in a two-phase solvent mixture of water and a water-immiscible organic solvent [10]. This method was said to provide diastereoisomeric salts of the organic bases in high optical purity and good yield. Ef-

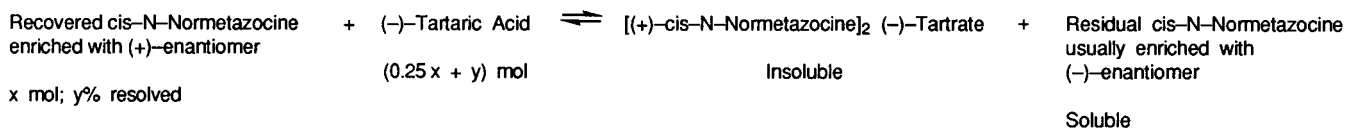
Scheme 1

Improved Resolution of (\pm)-*cis*-*N*-Normetazocine

Initial Step



Second Step



Subsequent fractional steps are carried out in a manner similar to the second step.

forts to apply this procedure to the resolution of (\pm)-*cis*-*N*-normetazocine with tartaric acids were hindered initially by the low solubility of the base in all organic solvents which were not miscible with water. However, this difficulty was overcome by using a ternary system of chloroform, ethanol and water and by carrying out the salt formation at reflux temperature. Our results to date indicated that the following solvent ratios are optimal: chloroform, 6.5-7.0 ml/g of *cis*-*N*-normetazocine; ethanol, 5.0-5.5 ml/g; water, 2.5-3.0 ml/g.

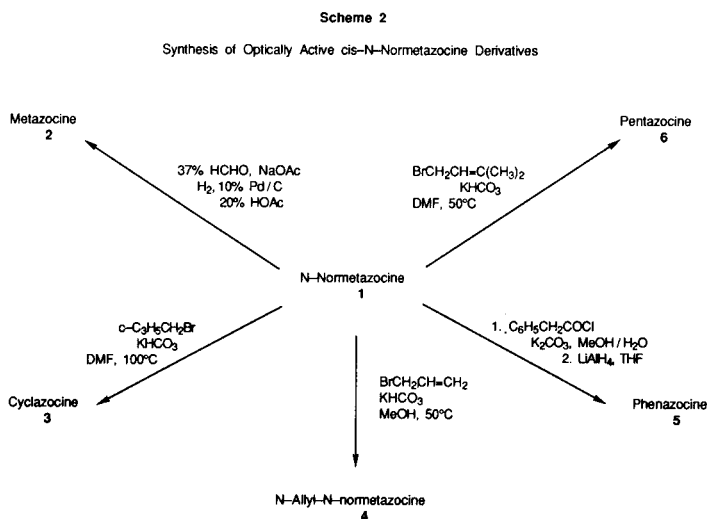
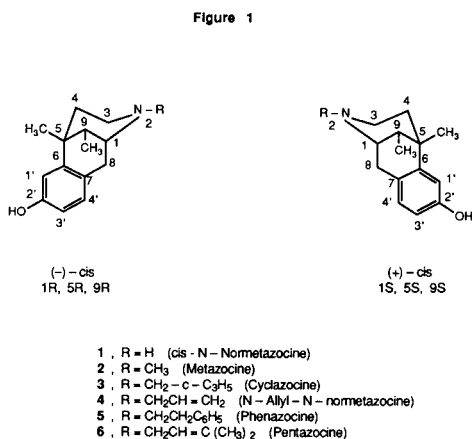
In addition, we discovered that use of a tartaric acid: *cis*-*N*-normetazocine molar ratio of 0.25:1.0 helped to ensure that the major tartrate salt formed was the most insoluble one (*cf.* Scheme 1). This tactic avoided the formation of an equivalent amount of the diastereoisomeric salt and left one of the *cis*-*N*-normetazocine optical isomers in solution primarily as the free base. After the initial fractionation step, the 0.25:1.0 molar ratio was adjusted further depending on the degree of resolution (estimated from the optical rotation) of the *cis*-*N*-normetazocine recovered from the neutralized filtrates.

Use of the ternary solvent system, the reflux conditions, and the 0.25:1.0 acid:base ratio enabled us to obtain good yields of diastereoisomeric salts of >90% optical purity (estimated from the optical rotation of the corresponding free bases). Subsequent fractionation steps provided the balance of each salt with no loss of optical purity. Similar salts were combined and converted to the free bases. Because of the high optical purity of the free bases, final purification was achieved by crystallization. The physical properties of the resultant *cis*-*N*-normetazocine optical isomers were in excellent agreement with reported values [3].

After several small scale experiments, we successfully scaled up the new procedure. In the two molar scale experiments we isolated 75-80% of the total (-)-*cis*-*N*-normetazocine (+)-tartrate in the initial fractionation step and 79-94% of the total (+)-*cis*-*N*-normetazocine (-)-tartrate in the second step (*cf.* Scheme 1). From the larger scale experiments to date we have obtained the purified optical isomers in 72-73% chemical yield. Moreover, we have accomplished the larger scale resolutions in about one-third the time required by the older procedure [3]. Hence, our new resolution procedure constituted a significant improvement in terms of yield and time.

The absolute configuration of (-)-*cis*-metazocine has been determined to be 1*R*,5*R*,9*R* by Casy and Parulkar [11]. Therefore, the absolute configurations of (-)-*cis*-*N*-normetazocine and (+)-*cis*-*N*-normetazocine are 1*R*,5*R*,9*R* and 1*S*,5*S*,9*S*, respectively. The absolute configurations as depicted by Palmer and Strauss [2] are shown in Figure 1.

Starting with the optical isomers of *cis*-*N*-normetazocine (**1**) obtained by our resolution procedure, we have prepared the optical isomers of metazocine (**2**) [12], cyclazocine (**3**) [3], *N*-allyl-*N*-normetazocine (**4**) [7], phenazocine (**5**) [12] and pentazocine (**6**) [3] (*cf.* Figure 1)



using slight modifications of reported procedures (*cf.* Scheme 2 and Experimental). Our choice of salts was dictated by shelf life as well as by ease of preparation. Repeat syntheses have yielded compounds of comparable purity.

EXPERIMENTAL

Melting points were determined on either a Thomas Hoover apparatus or a Kolfer hot stage and are uncorrected. Optical rotations were taken on either a Perkin-Elmer 141 or a Rudolph Research Autopol III Polarimeter. Proton nmr spectra were recorded on a Bruker WM-250 nmr spectrometer using tetramethylsilane as the internal standard. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Technical grade (\pm)-*cis*-*N*-normetazocine [13] was manufactured by Fabbria Italiana Sintetici, SPA, Vicenza, Italy. Sodium sulfate was used routinely to dry organic solutions.

Resolution of (\pm)-*cis*-*N*-Normetazocine.

(\pm)-*cis*-*N*-Normetazocine (500.00 g, 2.30 moles) was dissolved in chloroform (3,300 ml) and ethanol (2,600 ml) with heating and vigorous stirring. Under nitrogen a solution of (+)-tartaric acid (84.34 g, 0.58 mole) in water (1,300 ml) was added all at once. The resultant two-phase mixture was refluxed 21 hours. Crystallization of the tartrate salt began almost immediately after the addition of the acid. After the reflux period, the mixture was kept at 45° for 6 hours, then cooled to room temperature overnight. Vigorous stirring under nitrogen was maintained the entire time. The crystallized (-)-*cis*-*N*-normetazocine (+)-tartrate was collected by filtration, washed with several portions of cold ethanol, air dried and then vacuum dried overnight. Afterwards, the salt was a powdery white solid weighing 212.46 g and melting at 305.5° (lit 305-308° [3]). A 0.25 g sample was converted to the free base by partitioning between chloroform containing a small amount of methanol and dilute ammonium hydroxide. The layers were separated, and the organic layer was dried and evaporated to a glass. Stirring the glass with tetrahydrofuran gave the free base as an off-white solid, $[\alpha]_D^{23}$ -62.2° (c 0.88, ethanol) (lit -69.3° [3]). To confirm the 2:1 structure of the tartrate salt, a sample was submitted for elemental analysis.

Anal. Calcd. for $C_{32}H_{44}N_2O_8$: C, 65.73; H, 7.58; N, 4.79. Found: C, 65.56; H, 7.52; N, 4.72.

The biphasic mother liquor was treated with sufficient ammonium hydroxide to adjust the aqueous layer to pH 11. The organic layer was separated, dried and concentrated to approximately 1,000 ml. Crystallization of the free base began during the concentration process. The mixture was diluted with 2-propanol, the concentrated again to approximately 1,000 ml and left overnight. The crystalline solid was collected by filtration, washed several times with cold 2-propanol, air dried and then vacuum dried overnight. Two additional crops were collected from the filtrate and combined with the first, yielding 292.23 g of partially resolved (+)-*cis*-*N*-normetazocine, $[\alpha]_D^{23}$ +33.0° (c 1.0, ethanol) (lit +70.1° [3]). Based on the optical rotation, the enantiomeric excess (ee) was estimated to be 47%.

The recovered base (1.34 mole) was dissolved in a mixture of chloroform (1,900 ml) and ethanol (1,450 ml) with heating and stirring. A solution of (-)-tartaric acid (73.91 g, 0.49 mole; 0.25 molar equivalent plus 47% excess) in water (750 ml) was added all at once. A precipitate appeared immediately. Under a nitrogen atmosphere the resultant mixture was stirred vigorously

at reflux temperature for 22 hours, then at 45° for 6 hours, then at room temperature overnight. The crystalline salt was collected by filtration, washed with several portions of cold ethanol, air dried and then vacuum dried overnight to obtain 254.17 g of (+)-*cis*-*N*-normetazocine (-)-tartrate as a white powder, mp 306° (lit 305-308° [3]). A small sample of the corresponding free base, generated as described above, had $[\alpha]_D^{23}$ +65° (c 1.02, ethanol). A sample of the tartrate salt was submitted for elemental analysis.

Anal. Calcd. for $C_{32}H_{44}N_2O_8$: C, 65.73; H, 7.58; N, 4.79. Found: C, 65.56; H, 7.62; N, 4.76.

The biphasic mother liquor was treated as described above to recover 89.21 g of free base as an off-white powder, $[\alpha]_D^{23}$ -25.0° (c 1.0, ethanol) (36% ee). This material was later combined with other recovered base samples for further processing.

The (-)-*cis*-*N*-normetazocine (+)-tartrate (212.21 g, 0.36 mole) was partitioned between chloroform (2,000 ml), methanol (1,000 ml) and 20% aqueous ammonium hydroxide (1,500 ml). The resultant aqueous layer was extracted with several portions of chloroform, which extracts were combined with the original organic layer. The combined organic extracts were washed with water (500 ml), dried, and concentrated on a steam bath under a stream of nitrogen to approximately 500 ml, at which point the base began to crystallize. The mixture was diluted with 2-propanol (500 ml) and concentrated again. The dilution process was repeated and the mixture was concentrated to a final volume of 500 ml. After overnight cooling, the solid was collected by filtration, washed with several portions of 2-propanol, and vacuum dried to obtain 131.05 g of (-)-*cis*-*N*-normetazocine as a powdery white solid, mp 261-264° (lit 260-262° [3]); $[\alpha]_D^{23}$ -69.7° (c 0.97, ethanol) (lit -69.3° [3]). Two additional crops were collected and combined to give 17.70 g of partially resolved base, $[\alpha]_D^{23}$ -27° (c 1.0, ethanol) (39% ee). The (+)-*cis*-*N*-normetazocine (-)-tartrate (253.92 g, 0.43 mole) was treated in a similar manner to get 149.27 g of (+)-*cis*-*N*-normetazocine as a white powder, mp 261-264° (lit 260-262° [3]); $[\alpha]_D^{23}$ +68.9° (c 0.99, ethanol) (lit +70.1° [3]). A 10.52 g second crop was also obtained which had $[\alpha]_D^{23}$ +36.5° (c 1.0, ethanol) (52% ee).

The partially resolved samples of *cis*-*N*-normetazocine base recovered from the (-)-tartaric acid treatment and the above conversions to the free bases were taken through the resolution process again. Three additional tartaric acid treatments were performed. The additional processing afforded 48.16 g of (-)-*cis*-*N*-normetazocine with mp 262-264° and $[\alpha]_D^{23}$ -68.7° (c 1.0, ethanol), 20.97 g of (+)-*cis*-*N*-normetazocine with mp 262-264° and $[\alpha]_D^{23}$ +68.5° (c 1.0, ethanol), and 8.95 g of (+)-*cis*-*N*-normetazocine with mp 262-264° and $[\alpha]_D^{23}$ +68.3° (c 1.0, ethanol). The total amount of (-)-*cis*-*N*-normetazocine produced was 179.21 g (72%). The total amount of (+)-*cis*-*N*-normetazocine produced was 179.19 g (72%).

(-)-Metazocine (2) Fumarate (2:1).

A solution of (-)-*cis*-*N*-normetazocine (5.0 g, 0.023 mole) in 20% acetic acid (135 ml) was treated with 37% formaldehyde (1.9 ml), sodium acetate trihydrate (5.0 g) and 10% palladium/carbon (0.5 g). The resultant mixture was hydrogenated on a Parr shaker at 50 psi for 44 hours. Additional portions of 37% formaldehyde (0.6 ml) and 10% palladium/carbon (0.1 g) were added after the initial 22 hours. The mixture was filtered, and the filtrate was cooled and basified using concentrated ammonium hydroxide. The resultant suspension was extracted with three portions of chloroform. The combined organic layers were dried and

evaporated to obtain 5.49 g (103%) of (-)-metazocine as a white foam. This was combined with product from another run and the combined sample (8.10 g, 0.035 mole) was dissolved in a mixture of ethanol (50 ml) and ethyl acetate (40 ml). To this solution was added a solution of fumaric acid (2.7 g, 0.023 mole) in ethanol (80 ml). Subsequent dilution with 100 ml of 1:2.5 tetrahydrofuran:ether followed by overnight standing at 5° resulted in crystallization. Collection and drying provided 9.0 g (8.9%) of (-)-metazocine (2) fumarate (2:1) as off-white crystals, mp 258-260° dec; $[\alpha]_D^{25}$ -63.6° (c 1.0, 95% ethanol); ¹H nmr (deuteriomethanol containing several drops of deuteriochloroform): δ 0.93 (d, two x 3H), 1.40 (s, two x 3H), 2.84 (s, two x 3H), 6.70 (s, 2H, fumarate).

Anal. Calcd. for (C₁₅H₂₁NO)₂·C₄H₄O₄: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.46; H, 8.10; N, 4.82.

(+)-Metazocine (2) Fumarate (2:1).

A sample of (+)-*cis*-*N*-normetazocine (7.0 g, 0.032 mole) was converted to (+)-metazocine base (7.23 g, 97%) using the hydrogenation procedure described for the (-)-isomer. A 7.0 g sample (0.030 mole) of the (+)-base was carried on to the fumarate salt, yielding 7.6 g (87%) of (+)-metazocine (2) fumarate (2:1) as off-white crystals, mp 260-262° dec; $[\alpha]_D^{25}$ +64.3° (c 1.0, 95% ethanol); ¹H nmr (deuteriomethanol containing several drops of deuteriochloroform): δ 0.93 (d, two x 3H), 1.40 (s, two x 3H), 2.84 (s, two x 3H), 6.70 (s, 2H, fumarate).

Anal. Calcd. for (C₁₅H₂₁NO)₂·C₄H₄O₄: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.52; H, 8.06; N, 4.85.

(-)-Cyclazocine (3).

Under nitrogen a mixture of (-)-*cis*-*N*-normetazocine (25.0 g, 0.115 mole) and potassium bicarbonate (16.0 g, 0.16 mole) in *N,N*-dimethylformamide (300 ml) was heated to 100°. Cyclopropylmethyl bromide (16.31 g, 0.121 mole) was added dropwise, and the resultant mixture was stirred 24 hours at 100° with additional cyclopropylmethyl bromide (1.63 g) being added after the first 18 hours. The reaction mixture was filtered, and the filtrate was evaporated at a bath temperature of 50° with the aid of a vacuum pump. The brown residue was partitioned between chloroform (500 ml) and water (250 ml). The aqueous phase was extracted with chloroform (2 x 100 ml). The combined organic extracts were washed with water (200 ml), dried, treated with Norit, filtered and evaporated to obtain crude (-)-cyclazocine as a brown solid. Chromatography on silica gel (590 g) using a 1% → 20% methanol/methylene chloride gradient provided essentially pure material. Subsequent recrystallization from methanol/chloroform/ethyl acetate afforded 11.2 g (36%) of (-)-cyclazocine as a white solid, mp 194.5-196° (lit 195-196.8° [3]); $[\alpha]_D^{25}$ -117.7° (c 1.0, ethanol) (lit -117.2° [3]).

(+)-Cyclazocine (3).

The alkylation of (+)-*cis*-*N*-normetazocine (25.0 g, 0.115 mole) with cyclopropylmethyl bromide was carried out using the same conditions described for the (-)-isomer. Purification of the crude product was accomplished by column chromatography on silica gel followed by recrystallization to obtain 10.0 g (32%) of (+)-cyclazocine as a white solid, mp 195-196° (lit 195-196.4° [3]); $[\alpha]_D^{25}$ +117.9° (c 0.5, ethanol) (lit +118.2° [3]).

(-)-*N*-Allyl-*N*-normetazocine (4) Hydrochloride.

Under nitrogen a mixture of (-)-*cis*-*N*-normetazocine (65.0 g, 0.30 mole) and potassium bicarbonate (81.1 g, 0.81 mole) in

methanol (1,300 ml) at 45° was treated with allyl bromide (39.0 g, 0.32 mole), added dropwise. After addition, the reaction mixture was stirred overnight at 45-50°. Additional allyl bromide (4 g) was then added and stirring at 45-50° was continued for 4-5 hours. The reaction mixture was then filtered, the filtrate evaporated, and the residue partitioned between chloroform (1,000 ml) and water (500 ml). The resultant aqueous layer was extracted with chloroform (2 x 100 ml). The combined organic layers were washed with water (100 ml), dried and evaporated. The residue was dissolved in methylene chloride and flushed through a short silica gel column using a methylene chloride → 20% methanol/methylene chloride gradient to obtain 62.8 g (82%) of chromatographically pure (-)-*N*-allyl-*N*-normetazocine base. A suspension of the base in methanol (200 ml) was treated with 100 ml of 10% hydrogen chloride in ethanol, and the resultant solution was evaporated to dryness. Recrystallization of the crude hydrochloride salt from 2-propanol/ethyl acetate provided 56.8 g (77%) of the title compound as a white solid, mp 200-202°; $[\alpha]_D^{23}$ -90.5° (c 0.95, ethanol).

Anal. Calcd. for C₁₇H₂₄ClNO·0.5 H₂O: C, 67.42; H, 8.32; Cl, 11.71; N, 4.63. Found: C, 67.17; H, 8.09; Cl, 11.65; N, 4.52.

A sample of the free base from another preparation had mp 130-132° (lit 138-139° [7]) and $[\alpha]_D^{25}$ -121.3° (c 2.0, ethanol) (lit -121.6° at 22° and c 0.92, methanol [7]). A batch of the hydrochloride salt which by elemental analysis was anhydrous had mp 198-200° and $[\alpha]_D^{23}$ -91.4° (c 1.0, ethanol). Prolonged vacuum drying at 50-60° was necessary to obtain anhydrous material, especially on larger scale runs.

(+)-*N*-Allyl-*N*-normetazocine (4) Hydrochloride.

Starting with 55.0 g (0.025 mole) of (+)-*cis*-*N*-normetazocine and with all reagents scaled down proportionately, (+)-*N*-allyl-*N*-normetazocine base (47.5 g, 73%) was prepared using the same procedure described for the (-)-isomer. Preparation and recrystallization of the hydrochloride salt afforded 41.8 g (75%) of the title compound as a white solid, mp 201-203°; $[\alpha]_D^{25}$ +90.6° (c 1.0, ethanol).

Anal. Calcd. for C₁₇H₂₄ClNO·0.5H₂O: C, 67.42; H, 8.32; Cl, 11.71; N, 4.63. Found: C, 67.33; H, 8.00; Cl, 11.73; N, 4.51.

A sample of the free base from another preparation had mp 129-131° (lit 138-139° [7]) and $[\alpha]_D^{25}$ +119.8° (c 1.0, ethanol) (lit +121.3° at 22° and c 1.02, methanol [7]). A batch of the hydrochloride salt which by elemental analysis was anhydrous had mp 198-200° and $[\alpha]_D^{23}$ +91.1° (c 1.0, ethanol). Prolonged vacuum drying at 50-60° was necessary to obtain anhydrous material, especially on larger scale runs.

(-)-Phenazocine (5) Hydrobromide.

A 3.0 g (0.014 mole) sample of (-)-*cis*-*N*-normetazocine was converted to (-)-phenazocine hydrobromide using the reported sequence involving alkylation with phenylacetyl chloride followed by lithium aluminum hydride reduction of the intermediate amide [12]. Subsequent recrystallization from 2-propanol/tetrahydrofuran afforded 2.60 g (47%) of the title compound as white crystals, mp 283-285° (lit 284-287° [12]); $[\alpha]_D^{20}$ -84.5° (c 0.5, ethanol) (lit -84.1° at c 1.12, 95% ethanol [12]).

Anal. Calcd. for C₂₂H₂₈BrNO: C, 65.67; H, 7.01; N, 3.48. Found: C, 65.84; H, 7.33; N, 3.38.

(+)-Phenazocine (5) Hydrobromide.

A 3.0 g, (0.014 mole) sample of (+)-*cis*-*N*-normetazocine was

converted to (+)-phenazocine hydrobromide utilizing the same procedure described for the (-)-isomer. Recrystallization provided 2.35 g (42%) of the title compound as white crystals, mp 282-284° (lit 284-287° [12]); $[\alpha]_D^{25} +84.3^\circ$ (c 0.5, ethanol) lit +84.4° at c 1.47, 95% ethanol [12].

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.67; H, 7.01; N, 3.48. Found: C, 65.90; H, 6.86; N, 3.37.

(-)-Pentazocine (6) Succinate.

Under nitrogen a mixture of (-)-*cis*-*N*-normetazocine (21.7 g, 0.10 mole) and potassium bicarbonate (15.0 g, 0.15 mole) in *N,N*-dimethylformamide (300 ml) was heated to 45-50°. 4-Bromo-2-methyl-2-butene (26.8 g, 0.15 mole; 97%) was added dropwise, and the resultant mixture was stirred at 45-50° overnight. Afterwards, the mixture was filtered, the filtrate was evaporated, and the glassy residue partitioned between chloroform (300 ml) and water (150 ml). The aqueous phase was extracted with chloroform (2 x 50 ml). The combined organic extracts were dried and evaporated to obtain a brown residue. This was chromatographed on silica gel (700 g) using a chloroform - 15% methanol/chloroform gradient to get 17.7 g (62%) of (-)-pentazocine as an off-white glass. A solution of the base (0.062 mole) in methanol was treated with a solution of succinic acid (7.31 g 0.062 mole) in methanol. Concentration and dilution with tetrahydrofuran induced crystallization of the succinate salt (12.2 g, 49%) as white crystals, mp 163-165°; $[\alpha]_D^{25} -84.2^\circ$ (c 1.0, ethanol); 1H nmr (deuteriomethanol): δ 0.93 (d, 3H), 1.41 (s, 3H), 1.79 (s, 3H), 1.84 (s, 3H), 2.51 (s, 4H, succinate).

Anal. Calcd. for $C_{19}H_{27}NO \cdot C_4H_6O_4$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.59; H, 8.15; N, 3.66.

Several initially prepared batches of (-)-pentazocine were isolated and characterized as the hydrochloride salt hemihydrate, mp 127-130°; $[\alpha]_D^{25} -104.8^\circ$ (c 1.0, ethanol). However, this salt was too hygroscopic for storage purposes.

(+)-Pentazocine (6) Succinate.

Starting with 13.0 g (0.060 mole) of (+)-*cis*-*N*-normetazocine and with all reagents scaled down proportionately, (+)-pentazocine succinate (14.5 g, 60% overall) was prepared using the same

procedure described for the (-)-isomer. The title compound was obtained as white crystals, mp 163.5-165.5°; $[\alpha]_D^{25} +84.4^\circ$ (c 1.0, ethanol); 1H nmr (deuteriomethanol): δ 0.93 (d, 3H), 1.41 (s, 3H), 1.79 (s, 3H), 1.84 (s, 3H), 2.51 (s, 4H, succinate).

Anal. Calcd. for $C_{19}H_{27}NO \cdot C_4H_6O_4$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.29; H, 7.92; N, 3.40.

Several initially prepared batches of (+)-pentazocine were isolated and characterized as the hydrochloride salt hemihydrate, mp 129-132°; $[\alpha]_D^{25} +105.5^\circ$ (c 1.0, ethanol). However, this salt was too hygroscopic for storage purposes.

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