First Synthesis and Utilization of Oripavidine – A Concise and Efficient Route to Important Morphinans and Apomorphines

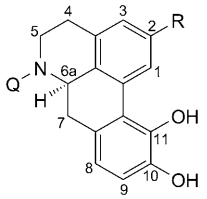
by **Attila Sipos***[a]), **Sándor Berényi**[a]), and **Sándor Antus**[a])[b])

[a]) Department of Organic Chemistry, University of Debrecen, P.O. Box 20, HU-4010 Debrecen (fax: +36-52-512836, e-mail: asipos@puma.unideb.hu)

[b]) Research Group for Carbohydrates of the Hungarian Academy of Sciences, P.O. Box 55, HU-4010 Debrecen

The synthesis and transformation of oripavidine (**8**) offer an efficient and simple route to highly active dopamine agonist apomorphines and a variety of important 14β-hydroxy-morphinan derivatives. Natural origin thebaine (**6**), the starting compound of the procedure, was converted into its *N*-{[1,2-bis(ethoxycarbonyl)hydrazinyl]methyl} counterpart. L-*Selectride* was found to be an efficient agent to perform a one-pot *O*- and *N*-deprotection at positions 3 and 17, respectively.

Introduction. – The synthesis of high affinity dopamine agonists is one of the main directions of the chemistry of aporphines. It is a general observation that the *N*-substitution of potent compounds could further improve their binding affinities and selectivities to D_1 or D_2 receptor subtypes[1]). In the *Figure*, the structure and D_2 affinity of some important apomorphines, **1**–**5**, are presented.



	R	Q	D_2 Binding affinity [nM]
1	H	Me	11.1
2	H	Pr	0.80
3	OH	Pr	0.05
4	MeO	Pr	0.17
5	MeS	Pr	3.7

Figure. *Some important D_2 agonists*

Apomorphine hydrochloride (**1**·HCl) is the active drug substance of some pharmaceutical products acting *via* its dopaminergic potency. Compounds **2**–**4** are frequently used in the pharmacological studies associated with the activation of the dopamine system.

These *N*-substituted derivatives are traditionally prepared with the acid-catalyzed rearrangement of previously *N*-substituted morphinans. Our research group explored the opportunities of a one-step synthesis of 2-*O*- and 2-*S*-substituted aporphines from appropriate morphinandienes [2]. This shortened methodology still comprises at least five steps from natural thebaine (**6**), and 19–23% of overall yields were achieved. In

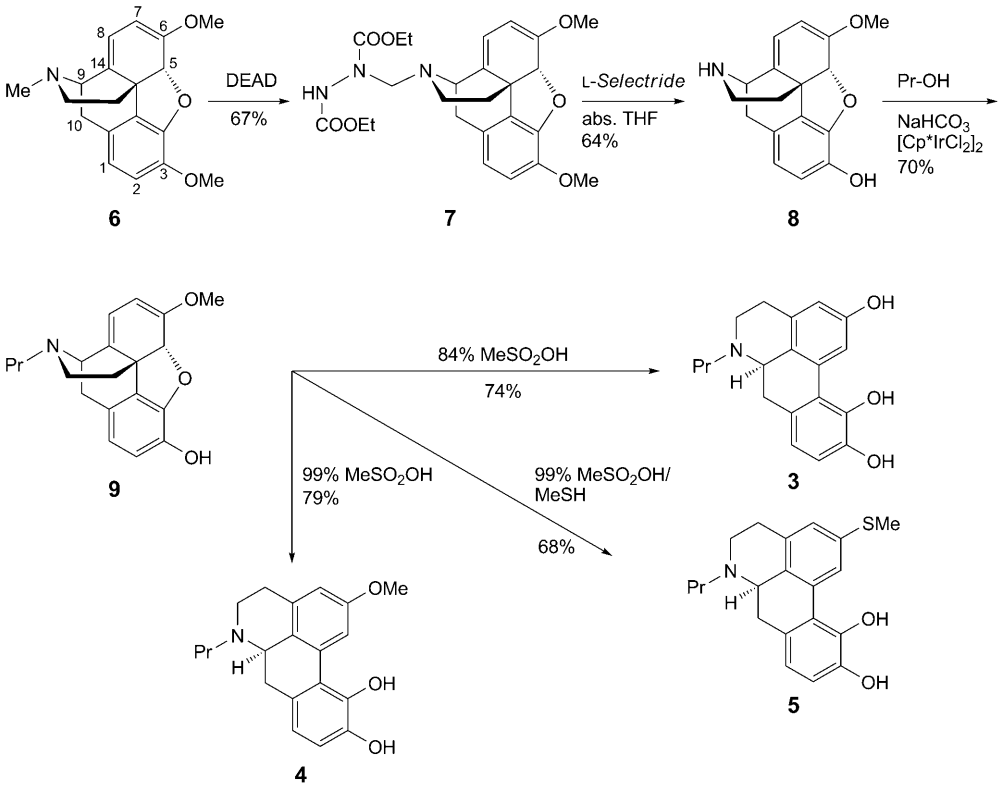
[1]) For recent reviews, see [1].

comparison, the traditional synthesis of *N*-Pr-2-MeO-norapomorphine (**4**) consists of seven steps with an overall yield of 10% [3].

Results. – In this work, we present a novel strategy for the synthesis of several important dopamine D_2 agonists and the successful extension of the method for the preparation of 14β-hydroxy-6-ketomorphinan derivatives. *Coop* and *Rice* developed the first one-pot *O*- and *N*-deprotection procedure applying the previously formed *N*-(carbomethoxy)normorphinans [4]. The only restriction of this method is that in morphinans having a C(8)=C(14) bond the formation of corresponding *N*-methoxycarbonyl derivative is always accompanied with the cleavage of the C(9)–N(17) bond [5].

In order to circumvent this issue in the case of thebaine (**6**), we applied the formation of a *N*-nor-*N*-{[1,2-bis(ethoxycarbonyl)hydrazinyl]methyl} derivative [3a] and tried the L-*Selectride*-mediated *O*- and *N*-deprotection to obtain oripavidine (**8**, *Scheme 1*).

Scheme 1. *Novel Synthesis of Highly Potent Dopamine D_2 Agonists*



We found that, with the application of the method described by *Coop* and *Rice*, compound **8** was isolated in 44% yield as a HCl salt [4]. However, the optimization of

the reaction time and cooling period had a significant effect on the conversion (*Table 1*).

Table 1. *Time Optimization of One-Pot* O- *and* N-*Deprotection*

Run	Reflux period [h]	Cooling period [h]	Yield after isolation[a]) [%]
1	4.5	0.5	44
2	6.0	0.5	49
3	9.0	0.5	59
4	9.0	2.0	64

[a]) Reported yields are averages of 3 runs.

Analytical data for oripavidine (**8**) were found to be in accordance with previously published data of the natural origin compound [6]. The regioselective propylation of compound **8** was found to be an unpredicted issue in the synthesis route as it was realized that the usual propylation procedure with PrI and K_2CO_3 in refluxing EtOH yielded a mixture of *N*- and *O*-alkylated products (*Table 2*).

Table 2. *Selective* N-*Alkylation of Oripavidine* **8**

Reagents/Conditions	Time [h]	Temp. [°]	Yields after isolation[a]) [%]	
			N-Pr product **9**	*N*- and *O*-Pr product
PrI/K_2CO_3/thermal	20	77	47	12
PrI/K_2CO_3/thermal	5	77	29	4
PrOH/[Cp*$IrCl_2$]$_2$/$NaHCO_3$/thermal[b])	17	110	75	0
PrOH/[Cp*$IrCl_2$]$_2$/$NaHCO_3$/MW[b])	0.5	140	70	0

[a]) Reported yields are averages of 3 runs. [b]) 1 Equiv. of amine, 1 equiv. of PrOH, 1 mol-% of catalyst, and 2 mol-% base in toluene.

To perform the selective *N*-alkylation of the valuable oripavidine **8** in the highest possible yield in a mild procedure, our attention turned to the catalytic method of *Fujita et al.* applying a pentamethylcyclopentadienyliridium(III) chloride/sodium hydrogencarbonate {[Cp*$IrCl_2$]$_2$/$NaHCO_3$} reagent combination and PrOH as alkylating agent [7a][2]). To reduce the reaction time and the applied temperature, the conventional thermal activation was replaced with microwave-activation also providing high conversion (*Table 2*).

The acid-catalyzed rearrangement was performed with and without the presence of nucleophiles in line with literature methods [2][3c], giving rise to the aimed apomorphines **3**–**5** in high yield (*Scheme 1*).

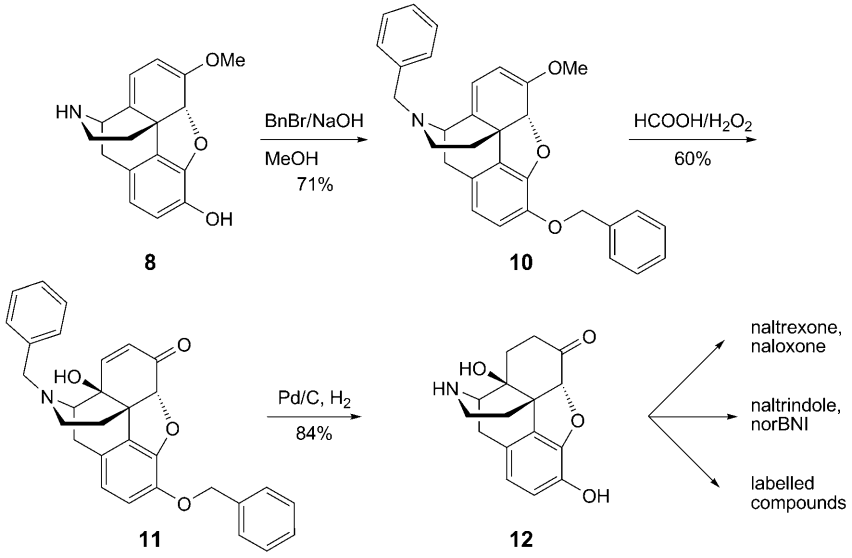
Due to the fact that the structure of compound **8** includes the same ring *C* motif as thebaine (**6**), we studied the transformation of this skeleton into pharmaceutically determining 14β-hydroxy-6-ketomorphinans. There are two well-established methods for the conversion of thebaine-like ring *C* into this substitution pattern; one of them

[2]) The applied catalyst, [Cp*$IrCl_2$]$_2$, was prepared in accordance with the procedure described in [7b].

utilizes a $HCOOH/H_2O_2$ reagent combination, the other uses MCPBA and oxalic acid in glacial AcOH [8].

After testing both procedures, it was realized that the unprotected phenolic OH group is a major concern according to the obtained analytical data of the crude product mixtures. Therefore, N(17) and the phenolic OH group were protected with an easily removable benzyl group prior to the oxidative transformation of ring *C* (*Scheme 2*). The $MeOH/H_2O$ solution of compound **8**, 2.5 equiv. of BnBr, and 3 equiv. of NaOH was stirred for 4 h. The benzylation product was removed by CH_2Cl_2 extraction and chromatographed on silica gel.

Scheme 2. *Concise and Efficient Route to 14β-Hydroxy Derivatives*



The reaction of 3,17-dibenzylnormorphinandiene **10** with a $HCOOH/H_2O_2$ reagent mixture gave rise to the desired diprotected 14β-hydroxy derivative **11** in average yield. The catalytic hydrogenation to **12** was carried out in a *Parr* hydrogenator at room temperature in the presence of acid for 50 h and was found to be appropriate for both the saturation of the C=C bond in ring *C* and the removal of benzyl protecting groups [9]. The structure of the hydrochloride salt of noroxymorphone (**12**) offers the chance of easy transformation into important pharmaceutical compounds (naltrexone, naloxone, oxycodone, *etc.*) [8] or into frequently used diagnostic and experimental derivatives (naltrindole, norBNI, IOXY, and other *N*-labelled PET or SPECT radiotracers) [10].

Discussion. – The first synthesis of oripavidine (**8**) opened up new transformation possibilities to both pharmacologically useful, highly active, and selective apomorphines and medically and diagnostically important 14β-hydroxymorphinan derivatives on the basis of the diene motif in its ring *C*. Among the applied methods, there are two novel methodologies besides well-established morphinan transformations. One of them

is the L-*Selectride*-mediated *O*- and *N*-deprotection of a *N*-nor-*N*-{[1,2-bis(ethoxycarbonyl)hydrazinyl]methyl} derivative, and the other one is the catalytic, chemoselective alkylation of a secondary amine in the presence of a free phenolic OH moiety.

Experimental Part

M.p.: *Kofler* hot-stage apparatus. Thin layer chromatography (TLC): pre-coated *Merck 5554 Kieselgel 60 F_{254}* foils using $CHCl_3$/MeOH 8:2 as the mobile phase. The spots were visualized with *Dragendorff*'s reagent. $[\alpha]_D$: *Perkin-Elmer Model 241* polarimeter. ^{1}H- and ^{13}C-NMR spectra: *Bruker DMX 400* spectrometer, chemical shifts are reported in ppm [δ] from internal TMS, and coupling constants *J* are measured in Hz. HR-MS: *Bruker micrOTOF-Q* instrument in the ESI mode.

17-{[1,2-bis(ethoxycarbonyl)hydrazino]methyl}northebaine (= *Diethyl 1-{[(5α)-6,7,8,14-Tetradehydro-3,6-dimethoxy-4,5-epoxymorphinan-17-yl]methyl}hydrazine-1,2-dicarboxylate*; **7**). Despite several references to the preparation of compound **7**, its detailed characterization has not been presented. The title compound was prepared from thebaine (**6**, 1000 mg, 3.21 mmol) according to the procedure described in [4] with 9 h of refluxing and 2 h of cooling periods (*Table 1*). Pale yellow solid. Yield: 1011 mg (67%). M.p. 168–170°. R_f ($CHCl_3$/MeOH 8:2): 0.43. $[\alpha]_D^{25} = 321$ ($c = 0.1$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 11.23 (br. *s*, NH); 6.69, 6.58 (2*d*, *J*(1,2) = 8.0, H–C(1), H–C(2)); 5.80 (*d*, *J*(7,8) = 5.1, H–C(8)); 4.94 (*d*, *J*(7,8) = 5.2, H–C(7)); 4.71 (*s*, H_b–C(5)); 4.29–4.21 (*m*, 2 $COOCH_2Me$); 4.08 (*s*, N–CH_2–N); 3.87 (*s*, MeO–C(3)); 3.62–3.58 (*m*, H_a–C(9), MeO–C(6)); 2.87–2.09 (*m*, H_a–C(10), H_b–C(10), H_b–C(15), H_a–C(16), H_b–C(16)); 1.98 (*td*, *J*(15,16) = 11.4, *J*(15a,15b) = 4.5, H_a–C(15)); 1.24–1.17 (*m*, 2 $COOCH_2Me$). ^{13}C-NMR (100 MHz $CDCl_3$): 157.12, 156.89 (2 $COOCH_2$); 151.12 (C(6)); 145.01 (C(4)); 143.76 (C(3)); 135.40 (C(14)); 131.31 (C(12)); 126.39 (C(11)); 120.44 (C(1)); 115.07 (C(2)); 110.62 (C(8)); 96.73 (C(7)); 90.42 (C(5)); 71.18 (N–CH_2–N); 62.69, 62.14 (2 $COOCH_2Me$); 57.94 (MeO–C(6)); 55.46 (MeO–C(3)); 54.04 (C(9)); 49.93 (C(16)); 43.99 (C(13)); 35.61 (C(15)); 32.11 (C(10)). ESI-HR-MS: 486.2266 ($[M+H]^+$, $C_{25}H_{32}N_3O_7^+$; calc. 486.2240).

Oripavidine Hydrochloride (= *(5α)-6,7,8,14-Tetradehydro-6-methoxy-4,5-epoxymorphinan-17-ium-3-ol Chloride*; **8**·HCl). The title compound was prepared from compound **7** (1000 mg, 2.06 mmol) in line with the previously described procedure [4], however, the reflux period was 9 h, and the cooling period was 2 h (*Table 1*). The yield for the HCl salt was found to be 64% (422 mg). All the physical and spectral data of this semi-synthetic product were in accordance with those reported for natural origin oripavidine (**8**) [6].

N-*Propylnororipavine Hydrochloride* (= *(5α,17S)-6,7,8,14-Tetradehydro-6-methoxy-17-propyl-4,5-epoxymorphinan-17-ium-3-ol Chloride*; **9**·HCl). In a pressurized glass vial under an atmosphere of N_2 were suspended oripavidine base (**8**, 566 mg, 2 mmol), PrOH (120 mg, 2 mmol), $[Cp^*IrCl_2]_2$ (8 mg, 0.01 mmol), and $NaHCO_3$ (2 mg, 0.02 mmol) in toluene (2 ml). The vial was inserted into the microwave cavity of the *CEM Discover* microwave reactor, irradiated at the 130° target temp. for 30 min hold time and subsequently cooled by rapid gas-jet cooling (*Table 2*). The product mixture was allowed to cool to r.t. in the microwave cavity. After cooling, the pH of the mixture was set to 10 by concentrated NH_3 soln. and extracted with $CHCl_3$ (3 × 15 ml). The org. layers were collected, washed with sat. NaCl soln., dried over anh. $MgSO_4$, and evaporated. The residue was subjected to SiO_2 CC. Elution with $CHCl_3$/MeOH 1:1 gave morphinan **9**. The crystalline product was precipitated by addition of abs. Et_2O and converted into the hydrochloride salt with 1M HCl in EtOH. 456 mg (70%). Yellow, cubic crystals. M.p. 212–214°. $[\alpha]_D^{25} = -199$ ($c = 0.1$, DMSO). R_f of the free base ($CHCl_3$/MeOH 8:2) 0.63. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.63, 6.54 (2*d*, *J*(1,2) = 8.1, H–C(1), H–C(2)); 5.83 (*d*, *J*(7,8) = 6.0, H–C(8)); 4.80 (*d*, *J*(7,8) = 6.1, H–C(7)); 4.66 (*s*, H_b–C(5)); 3.61–3.58 (*m*, H_a–C(9), MeO–C(6)); 2.69–2.12 (*m*, H_a–C(10), H_b–C(10), H_b–C(15), H_a–C(16), H_b–C(16), N–CH_2); 1.81–1.74 (*m*, H_a–C(15), N–CH_2–CH_2); 0.92 (*t*, *J* = 7.5, CH_2–Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 154.42 (C(6)); 148.62 (C(4)); 144.26 (C(3)); 133.11 (C(14)); 130.52 (C(12)); 123.90 (C(11)); 118.34 (C(1)); 114.57 (C(2)); 113.61 (C(8)); 95.54 (C(7)); 88.15 (C(5)); 59.09 (C(9)); 54.76 (N–CH_2); 53.43 (MeO–C(6)); 49.38 (C(16)); 43.72 (C(13)); 35.61 (C(15)); 30.19 (C(10)); 24.61 (N–CH_2–CH_2); 18.67 (CH_2–Me). ESI-HR-MS: 326.1777 ($[M+H]^+$, $C_{20}H_{24}NO_3^+$; calc. 326.1751).

N-*Propyl-2-hydroxynorapomorphine Hydrochloride* (=*(6a*R*)-5,6,6a,7-Tetrahydro-2,10,11-trihydroxy-6-propyl-4*H*-dibenzo[*de,g*]quinolinium Chloride*; **3**·HCl). The title compound was prepared in accordance with the procedure described earlier for its *N*-methyl derivative [2a]. The synthesis was started from the HCl salt of compound **9** (500 mg, 1.38 mmol). The yield for the HCl salt was found to be 74% (356 mg). All the physical and spectral data were in line with the previously reported results [3c].

N-*Propyl-2-methoxynorapomorphine Hydrochloride* (=*(6a*R*)-5,6,6a,7-Tetrahydro-10,11-dihydroxy-2-methoxy-6-propyl-4*H*-dibenzo[*de,g*]quinolinium Chloride*; **4**·HCl). The title compound was prepared in accordance with the procedure described earlier for its *N*-methyl derivative [2c]. The synthesis was started from the HCl salt of compound **9** (500 mg, 1.38 mmol). The yield for the HCl salt was found to be 79% (395 mg). All the physical and spectral data were in line with the previously reported results [3c].

N-*Propyl-2-methylthionorapomorphine Hydrochloride* (=*(6a*R*)-5,6,6a,7-Tetrahydro-10,11-dihydroxy-2-(methylsulfanyl)-6-propyl-4*H*-dibenzo[*de,g*]quinolinium Chloride*; **5**·HCl). The title compound was prepared in accordance with the procedure described earlier [2b]. The synthesis was started from the HCl salt of compound **9** (500 mg, 1.38 mmol). The yield for the HCl salt was found to be 68% (356 mg). All the physical and spectral data were in line with the previously reported results [2b].

3,17-Dibenzylnororipavine (=*(5α)-17-Benzyl-3-(benzyloxy)-6,7,8,14-tetradehydro-6-methoxy-4,5-epoxymorphinan*; **10**). The MeOH/H_2O soln. of compound **8**·HCl (639 mg, 2 mmol), 2.5 equiv. of benzylbromide, and 3 equiv. of NaOH was stirred for 4 h. The volatile org. part of the soln. was removed *in vacuo*, and the residual slurry was extracted with AcOEt (3 × 15 ml). The org. layers were collected, washed with sat. NaCl soln., dried over anh. $MgSO_4$, and evaporated. The residue was subjected to SiO_2 CC in order to separate the diprotected product from monoprotected by-products (eluent: $CHCl_3$/MeOH 8:2). Yield: 71% (619 mg). Yellow solid. M.p. 110–112°. $[\alpha]_D^{25} = -68$ ($c = 0.1$, $CHCl_3$). R_f ($CHCl_3$/MeOH = 8/2) 0.54. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.18–7.04 (*m*, 10 arom. H); 6.51, 6.43 (2*d*, *J*(1,2) = 8.3, H–C(1), H–C(2)); 5.78 (*d*, *J*(7,8) = 5.8, H–C(8)); 5.11 (*s*, CH_2–O); 4.85 (*d*, *J*(7,8) = 5.9, H–C(7)); 4.62 (*s*, H_b–C(5)); 3.64–3.51 (*m*, H_a–C(9), CH_2–N(17), MeO–C(6)); 2.77–2.05 (*m*, H_a–C(10), H_b–C(10), H_b–C(15), H_a–C(16), H_b–C(16)); 1.90 (*td*, *J*(15,16) = 11.1, *J*(15a,15b) = 4.6, H_a–C(15)). ^{13}C-NMR (100 MHz, $CDCl_3$): 156.72 (C(6)); 147.11 (C(3)); 146.59 (C(4)); 140.39, 138.21 (C(1′), C(1″)); 134.72 (C(14)); 129.52–112.47 (14 arom. C, C(8)); 95.10 (C(7)); 89.82 (C(5)); 72.06 (CH_2–O); 59.91 (C(9)); 57.32 (CH_2–N(17)); 53.15 (*Me*O–C(6)); 49.27 (C(16)); 44.16 (C(13)); 36.92 (C(15)); 27.06 (C(10)). ESI-HR-MS: 464.2231 ($[M+H]^+$, $C_{31}H_{30}NO_3^+$; calc. 464.2220).

3,17-Dibenzyl-14-hydroxynormorphinone (=*(5α)-17-Benzyl-3-(benzyloxy)-7,8-didehydro-14-hydroxy-4,5-epoxymorphinan-6-one*; **11**). A soln. of compound **10** (500 mg, 1.08 mmol), HCOOH (0.5 ml), H_2O_2 (350 mg, 30%, 3.24 mmol), and H_2O (1.2 ml) was heated at 45° for 6 h and cooled to r.t. for 2 h. The pH of the soln. was adjusted to 9 with conc. NH_4Cl and extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The remaining brown gum was subjected to CC to give the title compound. Yield: 60% (301 mg). All the physical and spectral data were in line with the previously reported results [8].

14-Hydroxydihydronormorphinone Hydrochloride (=*(5α)-3,14-Dihydroxy-4,5-epoxymorphinan-17-ium-6-one Chloride*; **12**·HCl). A mixture of compound **11** (300 mg, 0.65 mmol), glacial AcOH (60 mg, 1 mmol), and Pd/C (5%, 560 mg) in EtOH (35 ml) was hydrogenated in a *Parr* hydrogenator with H_2 gas at r.t. for 50 h. The mixture was filtered through *Celite*. The filtrate was evaporated *in vacuo*, and the residual slurry was dissolved in H_2O (20 ml). The pH of the soln. was adjusted to 9 with conc. NH_4Cl and extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude **12** was converted into the hydrochloride salt with 1M HCl/EtOH and recrystallized from AcOEt/MeOH 9:1. The yield for the HCl salt was found to be 84% (175 mg). All the physical and spectral data were in line with the previously reported results [8].

Naltrexone Hydrochloride (=*(5α,17*S*)-17-(Cyclopropylmethyl)-3,14-dihydroxy-4,5-epoxymorphinan-17-ium-6-one Chloride*). Title compound was synthesized in line with the procedure presented for the preparation of *N*-propylnororipavine hydrochloride (**9**·HCl). The synthesis was started from the HCl salt of compound **12** (200 mg, 0.62 mmol), cyclopropylmethanol (45 mg, 0.62 mmol), and $NaHCO_3$ (53 mg, 0.63 mmol). The yield for the HCl salt of the title compound was 52% (117 mg). The physical and spectral data were identical with that of the authentic sample of naltrexone·HCl.

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