97. Synthesis of *rel*-(3*RS*,3a*SR*,7a*SR*)-3-(4-Chlorophenyl)-3a,4,5,6,7,7a-hexahydro-1-methylindolin-6-one, the Main Metabolite of the Analgesic *Ro 15-8081*: A Potent Amine-Uptake Inhibitor

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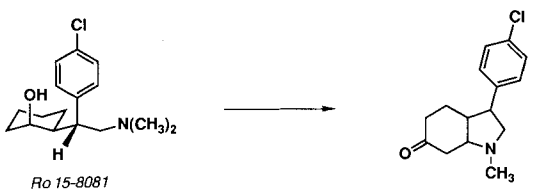
Dedicated to Dr. *O. Isler* on the occasion of his 80th birthday

(29.III.90)

The synthesis of the title compound **2** and its diastereoisomer **3** was accomplished using tricarbonyl[1–5-η-(4-methoxycyclohexa-2,4-dien-1-yl)]iron tetrafluoroborate (**4**) as a precursor to the cyclohexanone ring. The assignments of the relative configurations of **2** and **3** are based on the X-ray analysis of compound **3**. Both compounds **2** and **3** are potent inhibitors of neuronal noradrenaline uptake in rats with similar potencies *in vitro* as compared to amitriptyline and desipramine. Compounds **2** and **3** are less potent as serotonin-uptake inhibitors, very weak inhibitors of dopamine uptake, and virtually devoid of antinociceptive activity.

1. Introduction. – The racemic amino alcohol *Ro 15-8081* (**1**) was found to be a potent dual analgesic-antidepressant [1]. During preclinical metabolic studies, **2** (*Scheme 1*) was identified as the main metabolite of **1**, and the bicyclic structure was elucidated by means of ^{1}H-NMR and mass spectroscopy [2]. This spectral information was insufficient for a configurational assignment of the chiral centers. However, it has been demonstrated in

Scheme 1



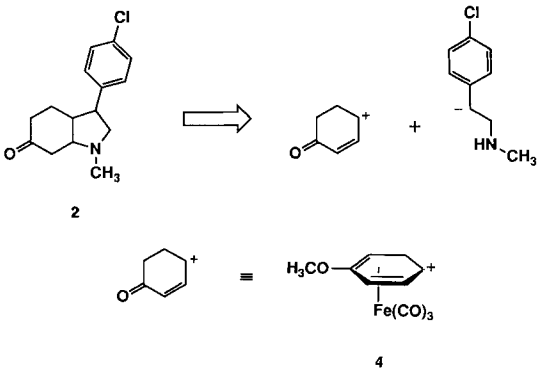
Ro 15-8081

1 **2**

substituted hydrindanes, hydrindanones, and analogous heterocycles [3] that *cis*-fused six- and five-membered ring systems are thermodynamically more stable than the corresponding *trans*-fused systems. Therefore, it was initially assumed that the bicyclic ring system of **2** was *cis*-fused. In the parent compound, the configuration along the C(2)–C(2′) bond was assigned to be *unlike*[1]) [1] [4], and, unless the biotransformation does not invert one of these stereocenters, the same relation should be found in compound **2**.

[1]) For the use of the configuration notations *like* (*l*) and *unlike* (*u*), see [5].

Scheme 2

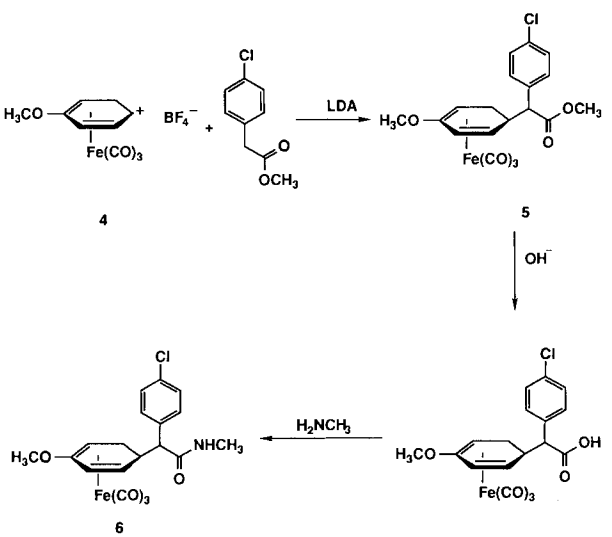


In preliminary *in vitro* studies, the metabolite **2** proved to be an even more potent inhibitor of noradrenaline uptake than the parent compound **1**, but the small amount of material isolated from biological sources did not allow a pharmacological assessment.

The following results describe the synthesis of **2** and its diastereoisomer **3** starting from the organometallic building block **4**. The assignments of the relative configuration of **2** and **3** are based on the X-ray analysis of **3** *(cf. Scheme 6)*. The pharmacological properties of these compounds are demonstrated by their action on the high-affinity amine-uptake in the rat brain and their analgesic activity in the hot-plate test.

2. Synthesis. – 2.1. *Strategy.* A synthetic approach to **2** based on the chosen disconnections in *Scheme 2* would require an 'Umpolung' at the γ-position of the cyclohexenone ring. This corresponds to the known reactivity of the $Fe(CO)_3$ complex of the 2-methoxycyclohexadiene cation **4** [6].

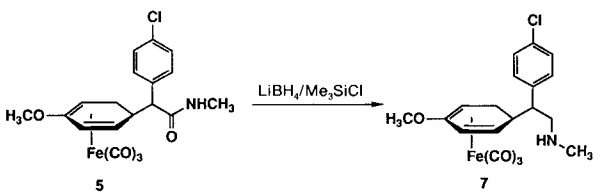
Scheme 3



2.2. *Synthetic Procedure.* Reaction of the lithium enolate of methyl (4-chlorophenyl)acetate with the tetrafluoroborate salt of **4** at – 78° afforded a diastereoisomeric mixture of **5** (1:1 by ^{1}H-NMR). Subsequent hydrolysis led to the corresponding acids, which were transformed to the diastereoisomeric methylamides **6** *(Scheme 3)*.

It was next necessary to reduce the amide function to a secondary amine. This transformation could not be accomplished with $LiAlH_4$ due to the instability of the $Fe(CO)_3$ moiety. However, the reduction was smoothly effected using $LiBH_4/Me_3SiCl$ [7] to give a mixture of diastereoisomeric amines **7** *(Scheme 4)*.

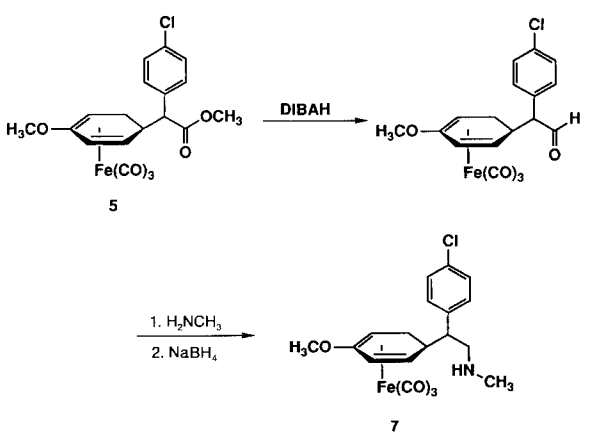
Scheme 4



5 7

An alternative route to **7** is outlined in *Scheme 5*. Reduction of **5** with DIBAH at – 78° gave the corresponding aldehyde which was converted to the amine **7** by *in situ* imine formation and subsequent reduction with $NaBH_4$.

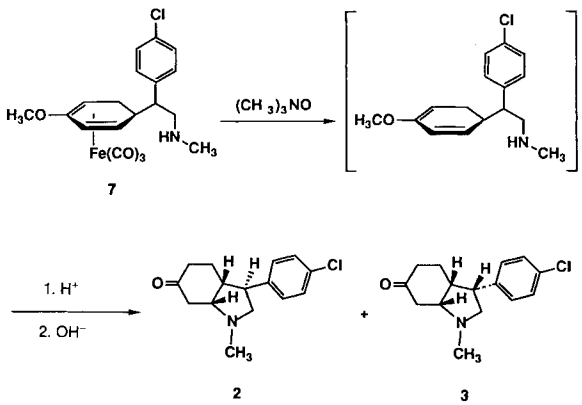
Scheme 5



5 7

Removal of the $Fe(CO)_3$ group was accomplished with anhydrous Me_3N *N*-oxide [8] in AcOEt. The resulting dienol ethers were hydrolyzed and cyclized under basic conditions to give metabolite **2** (14%) and the diastereoisomer **3** (10%), together with 2-(4-chlorophenyl)-2-(4-methoxyphenyl)-*N*-methylethylamine (18%), which were separated by column chromatography *(Scheme 6)*.

Scheme 6



3. X-Ray Analysis. – Suitable crystals for X-ray analysis could be obtained from the hydrochloride salt of **3**. The structure is shown in the *Figure*. From the results of this analysis, the anticipated *cis*-configuration of the bridgehead atoms was established. Since the configuration of the chiral centers of **3** turned out to be 3*R**,3a*R**,7a*R**, and since the ring closure occurs in a *cis*-fashion, the configuration of the metabolite **2** is 3*S**,3a*R**,7a*R**. Therefore, the C(3)–C(3a) bond is not affected in the course of the biotransformation.

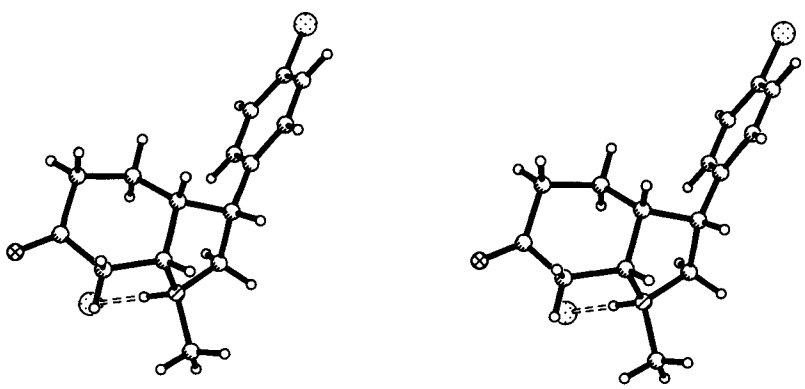


Figure. *Stereoprojection of* **3**

4. Pharmacology. – The neuronal high-affinity amine-uptake inhibition in rats exhibited by the parent compound, its metabolite **2**, and diastereoisomer **3** was measured as described earlier [9] and compared with that of amitriptyline and desipramine *(Table 1)*.

The metabolite **2** and the isomer **3** are 3.5 fold more potent than the parent compound *Ro 15-8081* (**1**) as noradrenaline uptake inhibitors, but they differ neither *in vitro* nor in *ex vivo* experiments. The potencies *in vitro* of the new compounds are between that of amitriptyline and that of desipramine but they are 3–20 fold less potent after *i.p.* adminis-

Table 1. *Effect of Compounds* **1**, **2**, **3**, *and Two Reference Compounds on Amine Uptake into Rat Brain Synaptosomes*[a])

Compound	*In vitro* IC_{50} [nM]			*Ex vivo* ED_{50} [mg/kg]
	Serotonin	Dopamine	Noradrenaline	Noradrenaline
1	110 (83–140)	2230 (1530–3220)	56 (32–96)	24 (17–34)
2	380 (210–660)	4530 (3830–5360)	16 (13–21)	18 (13–27)
3	190 (130–270)	2680 (1890–3790)	16 (13–18)	18 (12–27)
Amitriptyline	100 (53–190)	36000	110 (40–340)	5.8 (4–8.5)
Desipramine	50000	42000	5.5 (2.8–10.5)	0.9 (0.2–3.5)

[a]) *In vitro* results are expressed as IC_{50} values (nM, 95% confidence limits). For *ex vivo* determination, rats (at least four per dose) were injected *i.p.* with the drugs and decapitated 1 h later. These results are expressed as ED_{50} values (mg/kg, 95% confidence limits). Control uptake activity (picomoles per min per g of fresh tissue ± SEM): serotonin, 3.7 ± 0.1; dopamine, 18 ± 1; noradrenaline, 9 ± 0.3.

tration. Compounds **1**, **2**, and **3** were about equally potent as serotonin uptake inhibitors. Compound **1** was 2 fold less potent, **2** and **3** 10–25 fold less potent in serotonin-uptake inhibition than in noradrenaline-uptake inhibition *in vitro*. These observations indicate that there is a certain specificity associated with **2** and **3** concerning noradrenaline and serotonin-uptake inhibition. As inhibitors of dopamine uptake, all compounds tested were very weak with IC_{50} values in the micromolar range.

The parent compound **1**, its metabolite **2**, and the diastereoisomer **3** were also tested in mice for an antinociceptive effect in the hot-plate test and the results compared with that of morphine *(Table 2)*. Compound **1** exhibited a clear antinociceptive activity (with ED_{50} values of 64 and 77 mg/kg, *p.o.* at 30 min and 60 min after drug administration, respectively), being about 2 fold less potent than morphine as an analgesic. The metabolite **2** exhibited only a weak activity 30 min after administration, whereas the isomer **3** was virtually devoid of antinociceptive activity.

Table 2. *Antinociceptive Effects of* **1**, **2**, **3**, *and Morphine in the Hot-Plate Test in Mice*[a])

Compound	Dose [mg/kg *p.o.*]	ED_{50} [mg/kg] or percentage of mice protected	
		30 min	60 min
1		ED_{50} = 64 (17–186)	ED_{50} = 77 (22–300)
2	300	50%	37.5%
3	300	25%	25%
Morphine		ED_{50} = 35 (14–86)	ED_{50} = 32.5 (20–51)
Vehicle	–	0%	0%

[a]) Results are expressed as percentages of animals protected 30 min and 60 min after oral administration of various doses of each experimental compound. If possible, ED_{50} values (mg/kg, 95% confidence limits) were determined. The values in percentage are derived of 8 animals.

From the present results, it can be concluded that the new compounds **2** and **3** might have antidepressant activity, but, unlike **1**, might lack analgesic activity.

The skillful assistance in chemical synthesis by Mr. *R. Canesso* is acknowledged. The authors also thank Drs. *W. Arnold*, *A. Dirscherl* †, *M. Grosjean*, and *W. Meister* for spectroscopic determinations and microanalyses as well as Dr. *U. Widmer* for his careful reading of the manuscript.

Experimental Part

General. All laboratory glassware was flame-dried under vacuum and purged with dry Ar. THF was distilled from sodium benzophenone ketyl and was then transferred *via* a syringe. Column chromatography was carried out by using silica gel (230–400 mesh; *Merck*) and 0.3–1.0 bar pressure. Spectra were recorded with the following instruments. IR (cm^{-1}): *Nicolet-7199-FT-IR*. ^{1}H-NMR (δ values in ppm relative to internal or external TMS, coupling constants J in Hz): *Bruker AS-250* (250 MHz) and *WM-400* (400 MHz). MS: *MS 9* updated with a *Finnigan ZAB* data system *SS 200*.

1. *Tricarbonyl{1–4-η-{5-[4-chloro-α-(methoxycarbonyl)benzyl]-2-methoxycyclohexa-1,3-diene}}iron* (1:1 mixture of diastereoisomers; **5**). To a soln. of freshly prepared LDA (198 mmol) in THF/hexane 9:1 (1000 ml) was added a soln. of methyl (4-chlorophenyl)acetate (33.2 g, 180 mmol) in THF (360 ml) at $-75°$. After stirring for 1 h at $-75°$, *tricarbonyl[1–5-η-(4-methoxycyclohexa-2,4-dien-1-yl)]iron tetrafluoroborate* (**4**) [6] (60.5 g, 180 mmol) was added at once. The mixture was stirred at $-75°$ for 1 h and quenched with AcOH (36 ml). The suspension was diluted with Et_2O (4500 ml) and washed with H_2O (1800 ml), 5% $NaHCO_3$ (1800 ml), and brine (900 ml). The org. layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (1 kg) by gradient elution using hexane/AcOEt 19:1 (4000 ml) and 9:1 (7000 ml) to give **5** (70.4 g, 90%) as a yellow oil. IR (film): 3008, 2955, 2859, 2040, 1969, 1734, 1599. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.14–1.78 (*m*, 1 H); 2.17 (*m*, 1 H); 2.53–2.68 (*m*, 2 H); 2.97 (*d*, J = 11.0, 1 H); 3.19, 3.29 (*m*, 1 H); 3.59, 3.62 (*s*, 3 H); 3.64, 3.67 (*s*, 3 H); 4.92, 5.10 (*dd*, J = 6.6, 2.2, 1 H); 7.24 (*m*, 4 H). MS: 404 ($[M - CO]^+$), 376 ($[M - 2CO]^+$), 348 ($[M - 3CO]^+$), 240 ($[348 - C_6H_5OCH_3]$).

2. *Tricarbonyl{1–4-η-{5-[4-chloro-α-(methylcarbamoyl)benzyl]-2-methoxycyclohexa-1,3-dienyl}}iron* (1:1 mixture of diastereoisomers; **6**). A mixture of **5** (12.4 g, 28.7 mmol), MeOH (290 ml), and 1N NaOH (57 ml) were refluxed for 10 h. The soln. was filtered. After removing MeOH *in vacuo*, the mixture was diluted with H_2O (290 ml) and acidified with 1N HCl (72 ml). The precipitate was collected, washed, and dried to give white crystals (11 g, 92%, m.p. 65–80°). The carboxylic acid (3.45 g, 8.24 mmol) was dissolved in THF (82 ml) and refluxed for 1 h with *N,N'*-carbonyldiimidazole (1.47 g, 9.07 mmol). The soln. was saturated at 5–10° with $MeNH_2$. The mixture was stirred for 2 h at 20° and evaporated *in vacuo*. The crude material was purified by chromatography on silica gel (110 g) with toluene/AcOEt 4:1 to give **6** (33 g, 93%) as yellowish crystals. M.p. 225–230° (dec.). IR (KBr): 3294, 2042, 1972, 1642, 1571, 1486. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.14–2.27 (*m*, 3 H); 2.64 (*m*, 2 H); 2.69, 2.77 (*d*, J = 4.8, 3 H); 3.19, 3.29 (*m*, 1 H); 3.61, 3.62 (*s*, 3 H); 4.92, 5.09 (*dd*, J = 6.5, 2.2, 1 H); 5.31, 5.49 (br., 1 H); 7.15–7.35 (*m*, 4 H). MS: 375 ($[M - 2CO]^+$), 347 ($[M - 3CO]^+$), 239 ($[347 - C_6H_5OCH_3]$). Anal. calc. for $C_{19}H_{18}ClFeNO_5$ (431.656): C 52.87, H 4.20, N 3.24; found: C 52.74, H 4.28, N 3.20.

3. *Tricarbonyl{1–4-η-{5-{4-chloro-α-[(methylamino)methyl]benzyl}-2-methoxycyclohexa-1,3-dienyl}}iron* (1:1 mixture of diastereoisomers; **7**). *a*) To a 1M soln. of $LiBH_4$ in THF (26 ml) was added Me_3SiCl (6.6 ml, 52 mmol) and a soln. of **6** (5.58 g, 12.9 mmol) in THF (39 ml). The mixture was refluxed for 7 h. After 3 h, a second addition of $LiBH_4$ soln. (26 ml) and Me_3SiCl (6.6 ml, 52 mmol) was carried out. The soln. was quenched with MeOH (12.9 ml) at 20–25° and evaporated *in vacuo*. The residue was taken up in ice/H_2O (130 ml) and 1N aq. NaOH (130 ml), and extracted with Et_2O (3 × 130 ml). The combined org. layers were washed with brine (65 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (100 g) by gradient elution using AcOEt (500 ml) and AcOEt/Et_3N 19:1 (800 ml) to give **7** (2.7 g, 50%) as a yellow oil.

b) To a soln. of **5** (103.4 g, 239 mmol) in CH_2Cl_2 (1200 ml) was added diisobutylaluminium hydride (20% in hexane, 240 ml, 240 mmol) at $-75°$. The mixture was stirred at $-75°$ for 1 h, quenched with sat. NH_4Cl (240 ml) and extracted with Et_2O (1 × 3600 ml, 1 × 1200 ml). The combined org. layers were washed (1200 ml sat. NH_4Cl, 600 ml H_2O, 600 ml brine) dried (Na_2SO_4), and evaporated *in vacuo* to give crude tricarbonyl{1–4-η-[5-(4-chloro-α-formylbenzyl)-2-methoxycyclohexa-1,3-dienyl]}iron (96 g) as a yellow oil. A mixture of the aldehyde (96 g, 240 mmol), benzene (2400 ml), 3-Å molecular sieve (240 g), and CF_3COOH (2.4 ml) was saturated at 18–22° with $MeNH_2$ and stirred for 15 h. The sieve was filtered off, and the solvent was removed *in vacuo*. The residue was dissolved in EtOH (2400 ml), and $NaBH_4$ (18.1 g, 480 mmol) was added at 5°. The mixture was stirred for 1 h at 15–20°, quenched with HCl (25%, 120 ml), and evaporated *in vacuo*. The residue was taken up in ice/H_2O (1200 ml) and 1N NaOH (1200 ml), and extracted with Et_2O (1 × 2400 ml, 2 × 1200 ml). The combined org. layers were washed (1200 ml H_2O, 600 ml brine), dried (Na_2SO_4), and evaporated *in vacuo*. The crude material was purified by chromatography on silica gel (900 g) by gradient elution using AcOEt (5000 ml) and AcOEt/Et_3N 19:1 (8000 ml) to give **7** (49 g, 49%) as a yellow oil. IR (film): 2934, 2041, 1960, 1486, 1226. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.21–1.36 (*m*, 1 H); 1.60–1.79 (*m*, 1 H); 2.28, 2.34 (*s*, 3 H); 2.02–2.36 (*m*, 3 H); 3.19, 3.27 (*m*, 1 H); 3.59, 3.60 (*s*, 3 H); 4.88, 5.09 (*dd*, J = 6.5, 2.2, 1 H); 7.02, 7.10 (*d*, J = 8.4, 2 H); 7.25, 7.32 (*d*, J = 8.4, 2 H). MS: 389 ($[M - CO]^+$), 361 ($[M - 2CO]^+$), 333 ($[M - 3CO]^+$), 331 ($[361 - CH_2NH_2]$).

4. rel-*(3*RS,*3a*SR,*7a*SR*)-3-(4-Chlorophenyl)-3a,4,5,6,7,7a-hexahydro-1-methylindolin-6-one* (**2**) *and* rel-*(3*RS,*3a*RS,*7a*RS*)-3-(4-Chlorophenyl)-3a,4,5,6,7,7a-hexahydro-1-methyl-indolin-6-one* (**3**). To a soln. of **7** (48.9 g, 117 mmol) in AcOEt (1170 ml) was added anh. Me_3NO [7] (87.8 g, 1170 mmol). The mixture was stirred for 16 h. The dark suspension was filtered off, and the mother liquor was extracted (3 × 600 ml 2% $NaHCO_3$, 1 × 300 ml brine), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was taken up in MeOH (930 ml) and H_2O (230 ml), oxalic acid dihydrate (29.5 g, 234 mmol) was added, and the soln. was stirred for 5 h. $NaHCO_3$ (58.9 g, 700 mmol) was added, and the mixture was stirred for 15 h. The solvent was removed *in vacuo*, and the residue was taken up in H_2O (1200 ml) and extracted with Et_2O (1 × 1200 ml, 2 × 600 ml). The combined org. layers were dried (Na_2SO_4) and evaporated *in vacuo*.

The residue was chromatographed on silica gel (1.3 kg) with AcOEt containing 1% Et_3N to give 3.1 g (10%) of **3** and 4.4 g (14%) of **2**, and subsequently with AcOEt containing 5% Et_3N to give 5.7 g (18%) of 2-(4-chlorophenyl)-2-(4-methoxyphenyl)-*N*-methylethylamine as brown oil. ^{1}H-NMR (90 MHz, $CDCl_3$): 2.38 (*s*, CH_3NH); 3.11 (*d*, *J* = 5.4, 2 H–C(1)); 3.73 (*s*, CH_3O); 4.07 (*dd*, *J* = 6.0, 5.4, H–C(2)); 6.70–6.96 (*m*, 2 arom. H); 7.00–7.35 (*m*, 6 arom. H). CI-MS: 276 ($[M + 1]^+$).

Compound **2** was further purified by chromatography with AcOEt/MeOH 19:1 and recrystallization from hexane. M.p. 70–74°. IR (KBr): 2916, 1719, 1482. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.79 (*m*, 1 H); 1.95 (*m*, 1 H); 2.31 (*s*, 3 H); 2.35 (*dd*, *J* = 10.8, 9.1, 1 H); 2.48 (*m*, 2 H); 2.55 (*d*, *J* = 4.8, 2 H); 2.81 (*dt*, *J* = 9.7, 4.8, 1 H); 3.04 (*m*, 1 H); 3.27 (*dd*, *J* = 9.1, 6.6, 1 H); 7.20, 7.29 (*AB*, *J* = 10.9, 4 H). MS: 263 (M^+), 206 ($[M - (CH_3)_2CO]$). Anal. calc. for $C_{15}H_{18}ClNO$ (263.768): C 68.30, H 6.88, N 5.31; found: C 68.32, H 6.84, N 5.22.

Compound **2**·HCl was prepared from the Et_2O soln. by treatment with ethereal HCl. M.p. 227–229° (dec.). Anal. calc. for $C_{15}H_{19}Cl_2NO$ (300.229): C 60.01, H 6.38, N 4.67; found: C 60.22, H 6.33, N 4.55.

Compound **3** was further purified by chromatography with AcOEt containing 2% MeOH. IR (CCl_4): 2764, 1720, 1485. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.33 (*m*, 1 H); 1.46 (*m*, 1 H); 2.05 (*m*, 1 H); 2.20 (*dt*, *J* = 17.2, 4.4, 1 H); 2.35 (*s*, 3 H); 2.47 (*dd*, *J* = 15, 6.1, 1 H); 2.57 (*dd*, *J* = 15, 5.2, 1 H); 2.62 (*m*, 1 H); 2.69 (*dd*, *J* = 9.9, 8.3, 1 H); 2.78 (*m*, 1 H); 3,30 (*dd*, *J* = 9.9, 6.0, 1 H); 3.49 (*m*, 1 H); 7.25, 7.28 (*AB*, *J* = 8.3, 4 H). MS: 263 (M^+), 206 ($[M - (CH_3)_2CO]$).

Compound **3**·HCl was prepared from the Et_2O soln. by treatment with ethereal HCl. M.p. 200–202° (dec.). Anal. calc. for $C_{15}H_{19}Cl_2NO$ (300.229): C 60.01, H 6.38, N 4.67; found: C 59.78, H 6.53, N 4.50.

5. *Amine Uptake.* Male albino rats (*SPF*, Fü-albino, 150–200 g) were used for the measurement of neuronal uptake according to *Kuhar et al.* [10]. For *in vitro* studies, synaptosomes were prepared from forebrain (serotonin uptake), striatum (dopamine uptake), and hippocampus (noradrenaline uptake) of untreated rats and incubated at 37° for 10 min with corresponding amine in the absence or presence of various concentrations of the compounds to be tested [9]. For *ex vivo* experiments, the drugs were administered *i.p.* to rats 1 h prior to decapitation and the corresponding brain parts homogenized and incubated with the ^{3}H-amines as mentioned above.

6. *Antinociceptive Activity.* The method used was a modification of that described by *Woolfe* and *MacDonald* [11]. Eight male mice (*SPF*, Fü-albino, 17–25 g) were used per dose. Animals were placed on a hot plate 30 and 60 min after *p.o.* administation. The hot plate was set at a temp. of 60 ± 1°. Control animals characteristically respond to the noxious stimulus by licking their forepaws within 10 s. Animals not responding to the heat were removed after 12 s. The percentage of mice not reacting to the noxious stimulus was determined and, if possible, an ED_{50} value was calculated together with the 95% confidence interval by probit analysis.

7. *X-Ray Analysis of* **3**·*HCl.* $C_{15}H_{19}Cl_2NO$ (300.229); $F(000) = 1264$. *Space Group and Cell Dimensions.* Monoclinic: $P2_1/n$; $a = 13.168$ (5), $b = 10.744$ (6), $c = 21.069$ (10) Å; $D_c = 1.342$ Mgm^{-3}, $Z = 8$; $m(MoK_\alpha/H$ mm$^{-1}) = 0.429$, absorption effects ignored. *Data Collection.* Crystal size 0.15 × 0.35 × 0.5 mm^3; temp. 193 K; wavelength: 0.71069 Å; scan mode: ω; scan speed: variable; 1.72 to 14.65°/min. in ω; scan width 1.00° (ω); q_{min}/q_{max}:0/50° total data measured: 5468 excluding standards; total data observed: 4396. Data were collected on a *Nicolet R3m/V* four-circle diffractometer fitted with a graphite monochromator and the *LT1* cooling apparatus. H-Atom coordinates were calculated using known geometries. All calculations were carried out with the SHELXTL PLUS (*Micro VAX II*)-system.

Coordinates and thermal parameters have been deposited with the *Crystallographic Data Center*, Cambridge, University Chemical Lab., Cambridge CB2 1EW, England.

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