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Synthesis of Tramadol and Analogous

Cuauhtémoc Alvarado,* Ángel Guzmán*, Eduardo Díaz, and Rocío Patiño

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior Ciudad Universitaria, Delegación Coyoacán 04510 México D. F. e-mail: alvaradosanchezc@yahoo.com.mx, angelgs@servidor.unam.mx

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Abstract. Tramadol is a drug with analgesic properties. This compound and five of its analogous were synthesized: *N*-demethyl (M2), *O*-demethyl (M1), *O*-ethyl-*O*-demethyl, *O*-benzyl-*O*-demethyl and *N*-benzyl-*N*-demethyl. All compounds were prepared as their hydrochlorides and as racemic mixtures. The synthesis started with the aminoketones; 2-(*N*-benzyl, *N*-methyl)aminomethyl cyclohexanone and 2-dimethylaminomethyl cyclohexanone, prepared by means of a Mannich reaction of cyclohexanone, paraformaldehyde and the corresponding amino hydrochloride. The aminoketones were coupled with the organolithium compounds derived from the corresponding 3-bromoalkoxybenzenes.
Keywords: Tramadol, antiinflammatories, analgesics, nonsteroids, opioids.

Resumen. El tramadol es un fármaco con propiedades analgésicas. Este compuesto y cinco de sus análogos fueron sintetizados: *N*-desmetil (M2), *O*-desmetil (M1), *O*-etil-*O*-desmetil, *O*-bencil-*O*-desmetil y *N*-bencil-*N*-desmetil. Los compuestos fueron preparados como sus clorhidratos, en forma de mezcla racémica. La síntesis comenzó con la preparación de 2-(*N*-bencil, *N*-metil)aminometil ciclohexanona y 2-dimetilaminometil ciclohexanona mediante la reacción de Mannich de la ciclohexanona, paraformaldehido y el clorhidrato de la amina correspondiente. Las aminocetonas así obtenidas, fueron acopladas con los derivados organolitiados provenientes de la reacción de n-butillitio con los m-bromoalcoxibencenos correspondientes.
Palabras clave: Tramadol, antiinflamatorios, analgésicos, no esteroides, opioides.

Introduction

In personal daily life activities of people, injuries or stress conditons which can cause the appearance of pain are commonly produced. Studies about the relief of pain with drugs which cause such effect (analgesics) are very important. There are two types of analgesic drugs: opioids and nonsteriodal antiinflammatories (NSAIDs). Opioids were the first analgesics used by men. The first reference in relation to these compounds is poppy juice, found in the writings of Teophrastus during the third century B.C. Opium contains more than 20 distinct alkaloids, and in 1806, Sertüner reported the isolation of a pure substance from opium, which he named morphine.

In England, around the middle of the eighteenth century, Stone reported the fever cure with extracts obtained from willow bark, whose active ingredient was a bitter glycoside called salicine. In 1875, sodium salicylate was first used for the treatment of rheumatic fever and as antipiretic compound. Hoffman prepared acetylsalicylic acid and Dresser started using it as a medication in 1899 [1].

The known addiction caused by opioids stimulated the search of other analgesics free of addictive potential. Just prior and following World War II, meperidine and methadone were introduced with negative results, nevertheless nalorphine was an exception, because it antagonizes the effects of morphine. On the other hand, some NSAIDs are analgesics, they do not produce addiction and are cheaper. In the last 30 years a large quantity of NSAIDs were introduced starting with indomethacin, followed by naproxen, ketoprofen and ketorolac, among others; and currently, the selective COX-2 inhibitors celecoxib, rofecoxib and etoricoxib.

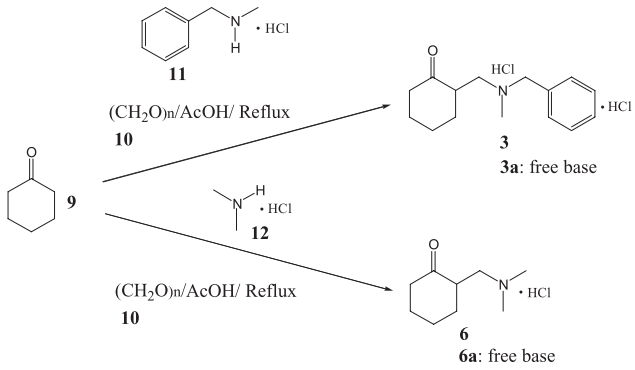
Tramadol **1a**, is a compound with analgesic properties which belongs to the opioids group. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable. The first one is the binding of **1a** and its metabolite *O*-demethyltramadol (M1) **2a**, to the opiod receptors; and the second, a weak inhibition of reuptake of norepinephrine and serotonin neurotransmitters [2,3].

Although **1a** produces the typical opioids symptoms (dizziness, somnolence, nausea, constipation, sweating and pruritus), it causes less respiratory depression and does not cause histamine release. However, like opioids, **1a** also causes tolerance development.

Tramadol hydrochloride **1** and some analogous have been synthesized previously by Chemie Gruenenthal [5, 6]. The approach consisted in the coupling between aminoketones with aryl derivatives by means of a Grignard's reaction. In this work, we carried out the same coupling reaction with organolithium derivatives with similar yields.

Results and discussion

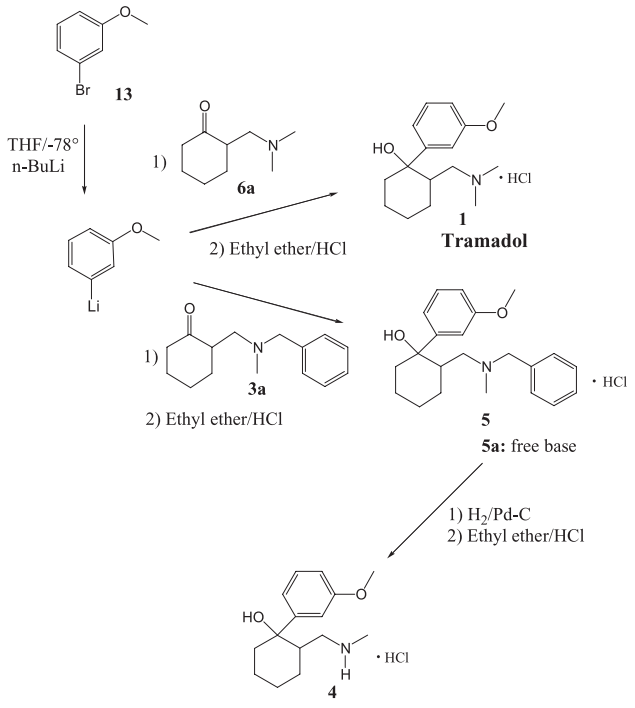
The synthesis of **1** and its analogous [3, 4-6], started with the preparation of the aminoketones: 2-(*N*-benzyl-*N*-methyl)aminomethylcyclohexanone hydrochloride **3** for the synthesis of *N*-demethyltramadol hydrochloride **4**, and *N*-benzyl-*N*-demethyltramadol hydrochloride **5**; 2-dimethylaminomethylcyclohexanone hydrochloride **6** for the synthesis of **1**, *O*-demethyltramadol hydrochloride **2**, *O*-ethyl-*O*-demethyltramadol hydrochloride **7** and *O*-benzyl-*O*-demethyltramadol hydrochloride **8**.



Scheme 1

The aminoketones synthesis was carried out by means of a Mannich reaction [7], using cyclohexanone **9**, paraformaldehyde **10** and benzylmethylamine hydrochloride **11** in case of compound **3**; the same ketone and dimethylamine hydrochloride **12** was used for the synthesis of **6.** The reaction mixture was heated in acetic acid at reflux temperature. Compounds **3** and **6** were obtained in 75% and 76% yields respectively. (Scheme 1)

The free bases of **3a** and **6a**, were separately coupled with the organolithium derivatives obtained from the reaction of 1.1 eq. of *n*-butyllithium with the corresponding 3-bromoal koxybenzenes in anhydrous THF.



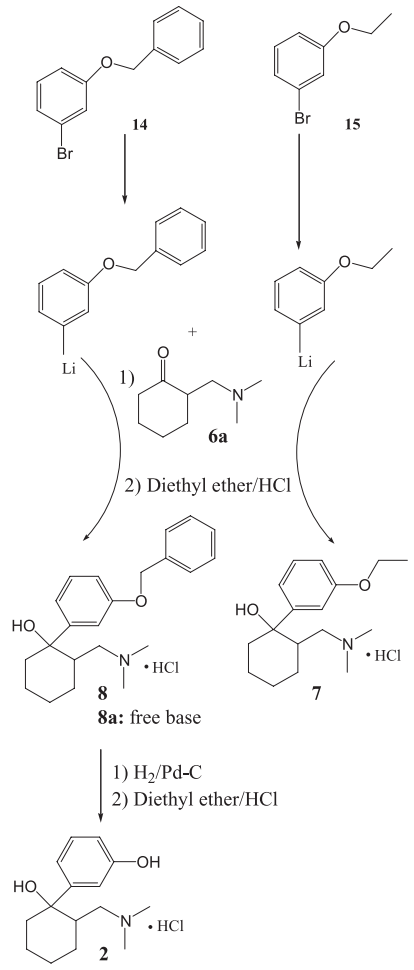
Scheme 2

3-Bromoanisol **13** was used for the synthesis of compounds **1**, **4** and **5**. Tramadol **1** and *N*-benzyl-*N*-demethyltramadol hydrochloride were obtained in 78.6% and 65% yields respectively. Free base **5a** was hydrogenolized to obtain *N*-demethyltramadol hydrochloride **4** in 85 % yield. (Scheme 2)

Benzyl, 3-bromophenyl ether **14** was used for the synthesis of *O*-demethyltramadol hydrochloride **2** and *O*-benzyl-*O*-demethyltramadol hydrochloride **8**; and 3-bromophenetol **15** for the synthesis of *O*-ethyl-*O*-demethyltramadol hydrochloride **7**. The derivatives **7** and **8** were obtained in 74% and 61% yield respectively. Finally, the free base of **8** was hydrogenolized and treated with hydrogen chloride to obtain **2** in 87% yield. (Scheme 3)

Experimental

All starting materials were research grade chemicals, commercially available and used without further purification. Silica gel 60 F_{254} was used for TLC and the spots were detected by UV light. IR spectra were determined on a Nicolet FX-SX and



Scheme 3

a Nicolet 55-X spectrophotometers on KBr. The NMR spectra were obtained with a Varian Gemini 200 and Unity 300 spectrometers using chloroform as solvent and TMS as an internal reference. Mass spectra were taken in a Jeol JMS-AX505 HA instrument. Melting points were obtained on a Büchi 510 apparatus and are uncorrected.

2–(*N*-benzyl-*N*-methyl)aminomethylcyclohexanone hydrochloride (3). A mixture of glacial acetic acid (20 mL), benzylmethylamine hydrochloride **11** (1.26 g, 8 mmol), cyclohexanone **9** (1.7 mL, 1.32 g, 16 mmol) and paraformaldehyde **10** (0.24 g, 8 mmol), was refluxed for 3 h. The acetic acid and the excess of cyclohexanone were removed in vacuo and the residue was purified by crystallization from acetone. Compound **3** was obtained as white crystals (1.6 g, 75%), mp 142-145°C. IR (KBr): 3380, 2852, 1710, 738 cm^{-1}; ^1H NMR ($DMSO_{d6}$, 300 MHz) δ 1.2-2.0 (8H, m), 2.49 (2H, m), 2.6 (3H, q, J = 4.7 Hz), 3.1 (1H, m), 4.3 (2H, m), 7.4-7.7 (5H, m), 10.1 (1H, bs); MS (EI): *m/z* 231 M^+ (4), 134 (100).

2–Dimethylaminomethylcyclohexanone hydrochloride (6). Aminoketone **6** was synthesized by the same procedure described for the preparation of **3**, using dimethylamine hydrochloride **12** (0.652 g, 8 mmol). Compound **6** was purified by crystallization from acetone and obtained as white crystals (1.16 g, 76%), mp 154-155°C. IR (KBr): 3380, 2935, 2827, 2782, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.6-1.8 (6H, m), 2.2 (2H, m), 2.3 (6H, s), 2.4-2.6 (3H, m), 9.8 (1H, bs); MS (EI): *m/z* 155 M^+ (4), 58 (100).

Tramadol hydrochloride (1). To a solution of 3-bromoanisol **13** (0.823 g, 4.4 mmol) in dry THF (10 mL), 1.75 M n-BuLi (2.5 mL, 4.4 mmol) was added dropwise at -78°C under argon atmosphere. The mixture was stirred at the same temperature during 45 minutes and a solution of 2-dimethylaminomethylcyclohexanone **6a** (0.62 g, 4mmol) in dry THF was added dropwise. The resulting mixture was stirred at -78°C for 2 h. and the solvent was removed in vacuo. Water (30 mL) was added and the product was extracted with ethyl ether (3X30 mL). The extracts were dried over sodium sulfate, filtered and evaporated in vacuum. The residue was treated with 5mL of ethyl ether saturated with hydrogen chloride; the ethyl ether was evaporated in vacuo and the resulting solid was purified by crystallization from acetone. Tramadol hydrochloride **1** was obtained as white crystals (0.94 g, 78.6%), mp 168-175°C. IR (KBr): 3410, 3185, 2935, 2826, 2782, 1601, 1249, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2-1.9 (10H, m), 2.15 (6H, s), 2.45 (1H, dd, J = 15.1, 4.4 Hz), 3.82 (3H, s), 6.76 (1H, dd, J = 8, 2.4 Hz), 7.04 (1H, d, 7.6 Hz), 7.14 (1H, s), 7.26 (1H, t, 3.9 Hz), 11.4 (1H, bs); MS (EI): *m/z* 263 M^+ (28), 58 (100).

***N*-Benzyl-*N*-demethyltramadol hydrochloride (5).** This derivative was synthesized using the same procedure described for the preparation of **1**, with **13** (0.823 g, 4.4 mmol), 1.75 M *n*-BuLi (2.5 mL, 4.4 mmol) and 2-(*N*-benzyl-*N*-methyl)aminomethyl cyclohexanone **3a** (0.92 g, 4 mmol). The product **5** was crystallized from acetone (0.97 g, 65%), mp 172-175°C. IR (KBr): 3420, 3190, 2935, 2851, 1599, 1251, 741, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2-1.9 (10H, m), 2.0 (3H, s), 2.6 (1H, dd, J = 14, 4.1 Hz), 3.3 (2H, dd, J = 68.4, 3.3 Hz), 3.8 (3H, s), 6.75 (1H, dd, J = 8.1, 2.6 Hz), 7.1 (1H, d, J = 7.7 Hz), 7.22 (1H, s), 7.26 (1H, t, J = 3.8 Hz), 7.28-7.4 (5H, m), 11.5 (1H, bs); MS (EI): *m/z* 339 M^+ (11), 134 (100).

***O*-Ethyl-*O*-demethyltramadol hydrochloride (7).** Compound **7** was synthesized using the same methodology described for the preparation of **1**. 3-bromophenetol **15** (0.88g, 4.4 mmol), 1.75 M n-BuLi (2.5 mL, 4.4 mmol) and **6a** (0.62 g, 4 mmol) were used. The product **7** was crystallized from acetone (0.46 g, 74%), mp 183-185°C. IR (KBr): 3390, 3190, 2934, 2827, 2782, 1602, 1249, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (3H, t, J = 7 Hz), 1.6-2.2 (8H, m), 2.46 (3H, d, J = 4.8), 2.49-2.6 (2H, m), 2.65 (3H, d, J = 4.8), 3.0 (1H, dd, J = 9.5, 1.8 Hz), 4.05 (2H, q, 7 Hz), 6.78 (1H, dd, J = 8, 2.5 Hz), 6.99 (1H, d, 7.8 Hz), 7.07 (1H, s), 7.28 (1H, t, 8 Hz), 11.6 (1H, bs); MS (EI): *m/z* 277 M^+ (26), 58 (100).

***O*-Benzyl-*O*-demethyltramadol hydrochloride (8).** Compound **8** was synthesized using the methodology described for the preparation of **1**. Benzyl, 3-bromophenyl ether **14** (1.16 g, 4.4 mmol), 1.75 M *n*-BuLi (2.5 mL, 4.4 mmol) and **6a** (0.62 g, 4 mmol) were used. The derivative **8** was crystallized from acetone-ethyl ether (0.92g, 61%), mp 141-143°C. IR (KBr): 3380, 3190, 2936, 2826, 2782, 1601, 1249, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2-2.0 (10H, m), 2.07 (6H, s), 2.39 (1H, dd, J = 13.6, 4.2 Hz), 3.0 (1H, bs) 5.08 (2H, s), 6.8 (1H, dd, J = 8, 2.6 Hz), 7.1 (1H, d, 7.8 Hz), 7.22 (1H, s), 7.26 (1H, t, 8 Hz), 7.3-7.5 (5H, m), 11.6 (1H, bs); MS (EI): *m/z* 339 M^+ (10), 58 (100).

***O*-Demethyltramadol hydrochloride (2).** To a solution of *O*-benzyl-*O*-demethyltramadol **8a** (1.02 g, 3 mmol) in methanol (20 mL), palladium on charcoal (0.1g) was added. The mixture was stirred under hydrogen atmosphere for 3 h and then filtered. The residue was treated with 5 mL of ethyl ether saturated with hydrogen chloride; the ethyl ether was evaporated in vacuo and the resulting solid was purified by crystallization from acetone-ethyl ether (0.89 g, 87%), mp 231-233°C. IR (KBr): 3224, 2937, 2830, 2786, 1601, 1256, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2-2.0 (10H, m), 2.12 (6H, s), 2.5 (1H, dd, J = 13.7, 4.3 Hz), 3.0 (1H, bs), 6.74 (1H, dd, J = 7.9, 2.5 Hz), 6.82 (1H, d, J = 7.4 Hz), 7.18 (1H, t, J = 7.9 Hz), 7.49 (1H, s), 11.4 (1H, bs); MS (EI): *m/z* 249 M^+ (12), 58 (100).

***N*-Demethyltramadol hydrochloride (4).** Derivative **4** was synthesized using the methodology described for the preparation of compound **2**. Thus, hidrogenolysis of *N*-benzyl-*N*-demethyltramadol **5a** (1.02 g, 3 mmol) provided compound **4**, which was crystallized from acetone-hexane (0.73 g, 85%), mp 165-168°C. IR (KBr): 3301, 3076, 2933, 2852, 1583,

1251, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2-2.0 (10H, m), 2.23 (3H, s), 2.44 (1H, dd, J = 12.4, 2.6 Hz), 3.80 (3H, s), 6.75 (1H, dd, J = 7.8, 2.4 Hz), 7.03 (1H, d, J = 7.6 Hz), 7.13 (1H, s), 7.26 (1H, t, J = 8 Hz), 11.5 (1H, bs); MS (EI): *m/z* 249 M^+ (35), 44 (100).

References

1. Goodman & Gilman; *The Pharmacological Basis of Therapeutics*, Int. Ed. 9th ed., McGraw Hill, New York, **1996**, 521, 617-618.
2. Lintz, W.; Erlacin, S.; Francus, E.; Uragg, H. *Chem. Abst.* **1982**, *96,* 62523p.; Lintz, W.; Erlacin, S.; Francus, E.; Uragg, H. *Arzneim-Forsch*. **1981**, *31*, 1932-43.
3. Flick, K.; Frankus, E.; Friderichs, E. *Chem. Abstr*. **1978**, *88*, 145970t. Flick, K.; Frankus, E.; Friderichs, E. *Arzneim-Forsch*. **1978**, *28*, 107-113.
4. Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*, Vol 2., John Wiley & Sons, New York, **1977**, 286-312.
5. Chemie Gruenenthal G.m.b.H. Brit. 997,399. *Chem Abst*. **1965**, *63*, 9871f.
6. Chemie Gruenenthal G.m.b.H. Neth. Appl. 6,610,022. *Chem. Abst*. **1967**, *67*, 21507u.
7. Blicke, F. F.; Mc Carty, F. J. *J. Org. Chem*. **1959**, *24*, 1069-1076.