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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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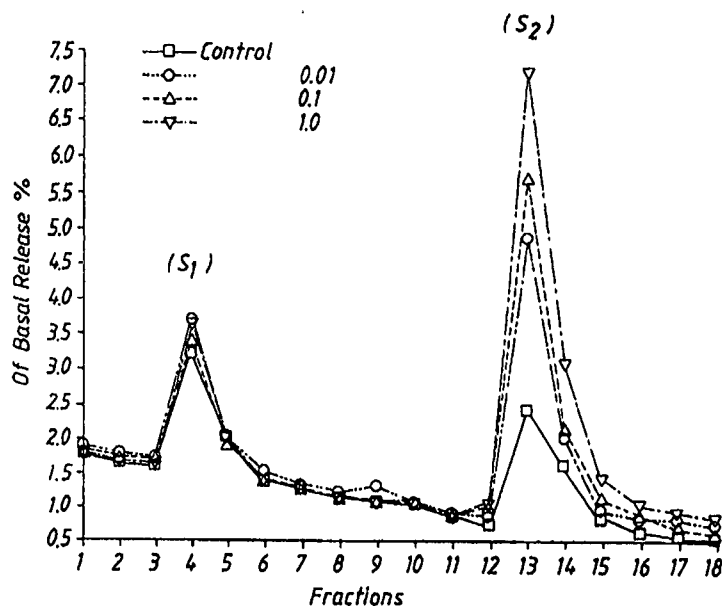
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(54) Title: SUBSTITUTED 1,2,3,4-TETRAHYDRONAPHTHALENE DERIVATIVES

(57) Abstract

The present invention relates to new piperidyl- or piperazinyl-substituted-1,2,3,4-tetrahydronaphthalene derivatives having formula (I) wherein X is N or CH; Y is NR₂CH₂, CH₂-NR₂, NR₂-CO, CO-NR₂ or NR₂SO₂ wherein R₂ is H or C₁-C₆ alkyl; R₁ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl; R₃ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl or (CH₂)_n-aryl, wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted, n is 0-4; R₉ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, OCF₃, OCHF₂, OCH₂F, halogen, CN, CF₃, OH, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, NR₆R₇, SO₃CH₃, SO₃CF₃, SO₂NR₆R₇, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C₁-C₆ alkyl; or COR₈; wherein R₆, R₇ and R₈ are as defined above, as (R)-enantiomers, (S)-enantiomers or racemates in the form of a free base or pharmaceutically acceptable salts thereof, a process for their preparation, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

3-H-5HT Release



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- (*R*)-*N*-[5-Methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- (*R*)-*N*-[5-Methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide;
- 5 (*R*)-*N*-[5-Methyl-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- (*R*)-*N*-[5-Bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide;
- N*-(4-Morpholinophenyl)-8-(4-methylpiperazinyl)-5-methoxy-1,2,3,4-
- 10 tetrahydronaphthalene-2-carboxamide;
- N*-(Morpholinocarbonylphenyl)-8-(4-methylpiperazin-1-yl)-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide;
- (*R*)-*N*-[5-Ethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- 15 (*R*)-*N*-[5-Ethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-(4-morpholinocarbonyl)benzamide;
- (*R*)-*N*-[5-Difluoromethoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide; and
- (*R*)-*N*-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-
- 20 morpholinobenzamide.

The compounds of the present invention are in the form of the racemate or the (*R*)- or (*S*)-enantiomer in the form of a free base or a pharmaceutically acceptable salt or solvate thereof. Compounds in the form of the (*R*)-enantiomer are preferred ones.

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Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, dibenzoyltartaric, diacetyltartaric, palmoic, ethanedisulfonic, sulfamic, succinic,

30 propionic, glycolic, malic, gluconic, pyruvic, phenylacetic, 4-aminobenzoic, anthranilic,

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salicylic, 4-aminosalicylic, 4-hydroxybenzoic, 3,4-dihydroxybenzoic, 3,5-dihydroxybenzoic, 3-hydroxy-2-naphthoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, naphthalenesulfonic, ascorbic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These salts are readily
5 prepared by methods known in the art. }

The preferred solvates of the compounds of this invention are the hydrates.

10 **Pharmaceutical Formulations**

In a second aspect the present invention provides a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I as an enantiomer or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof, optionally in association with diluents, excipients or inert carriers.

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According to the present invention the compound of the invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical formulations comprising the active ingredient either as a free base or a pharmaceutically acceptable non-toxic acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate,
20 sulfate, sulfamate, citrate, tartrate, oxalate and the like in a pharmaceutically acceptable dosage form. The dosage form may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5 and 20% by weight for preparations intended for injection and between 0.2 and 50% by weight for preparations suitable for oral administration.

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To produce pharmaceutical formulations containing the compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or poly-
30 vinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate,

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Example 23**(R)-2-N,N-Dibenzylamino-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

5 To a solution of (R)-8-bromo-2-N,N-dibenzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene (19 g, 44 mmol) in dry toluene (500 mL) under an argon atmosphere was added N-methylpiperazine (5.9 mL, 53 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.41 g, 0.44 mmol), (R)-BINAP (0.82 g, 1.3 mmol) and sodium *tert*-butoxide (0.40 mg, 4.2 mmol). The dark solution was stirred at 85
10 °C for 23 h and was then cooled, filtered and evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:2) as the eluent gave 19 g (97% yield) of a viscous colorless oil: $[\alpha]_D^{21} + 72^\circ$ ($c=1$, chloroform); EIMS (70eV) m/z (relative intensity) 455 (15, M⁺).

Example 24**(R)-2-Amino-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

The title compound was prepared from (R)-2-N,N-dibenzylamino-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene following the general method of Example 10. Yield: 5.3 g (82%) of a viscous colorless oil: $[\alpha]_D^{21} + 20^\circ$ ($c=1.1$,
20 chloroform); EIMS (70eV) m/z (relative intensity) 275 (53, M⁺).

Example 25**(R)-N-[5-Methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

25 To a solution of 4-morpholinobenzoic acid (0.92 g, 4.5 mmol; described in: Degutis, J.; Rasteikiene, L.; Degutiene, A. *Zh. Org. Khim.* 1978, 14(10), 2060-2064) in anhydrous N,N-dimethylformamide (75 mL) was added 1,1'-carbonyldiimidazole (0.76 g, 4.8 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 45 min), the reaction was cooled to room temperature and a solution of (R)-2-amino-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (1.2 g, 4.2 mmol)
30 dissolved in anhydrous N,N-dimethylformamide (20 mL) was added. The reaction was

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allowed to stir at ambient temperature for 48 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (180:5:0.5) as the eluent followed by recrystallization from ethyl acetate and a few drops of methanol gave 1.0 g (53% yield) of white crystals: mp 237-238 °C [α]_D²¹ - 40 ° (c=1, chloroform); EIMS (70eV) *m/z* (relative intensity) 464 (5, M⁺).

Example 26

(R)-N-[5-Hydroxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyanobenzamide

The title compound was prepared from (R)-2-amino-5-hydroxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene following the general method of Example 11. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 71 mg (45% yield) of lightbrown crystals: mp 144 °C (sinters); [α]_D²¹ +15 ° (c=0.25, methanol); EIMS (70eV) *m/z* (relative intensity) 390 (12, M⁺).

Example 27

(R)-N-[5-Methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide

The title compound was prepared from (R)-2-amino-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene following the general method of Example 16. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (96:4:0.3) as the eluent gave after recrystallization from ethyl acetate/diethyl ether 93 mg (52% yield) of white crystals: mp 209-210 °C; [α]_D²¹ -18 ° (c=1, chloroform); EIMS (70eV) *m/z* (relative intensity) 492 (36, M⁺).

Example 28

(R)-N-[5-Bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide

The title compound was prepared from (R)-2-amino-5-bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene following the general method of Example 16. Purification on

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were separated and the organic layer was washed with brine (30 mL). After drying (Na₂SO₄), and evaporation of the solvent *in vacuo*, 15 g of a crude product was obtained. Purification by column chromatography on silica using ethyl acetate/triethylamine (100:1) as the eluent afforded 11 g (82% yield) of the title compound as a brown oil: EIMS (70 eV) *m/z* (relative intensity) 439 (5, M⁺); [α]_D²² +86° (c 0.05, CHCl₃).

Example 75

(R)-2-Amino-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-naphthalene
(R)-2-N,N-Dibenzylamino-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetra-
hydronaphthalene (28 g, 64 mmol) was dissolved in acetic acid (280 mL) and charged into a Büchi glass autoclave (1 L). 10% Palladium on charcoal (2.8 g, containing 50% H₂O) was added. The reaction mixture was stirred at 70 °C and at 5 bar hydrogen pressure for 3.5 h. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was partitioned between ethyl acetate (400 mL) and water (100 mL) and cooled on an ice-bath. The pH was adjusted to 12 by addition of aqueous NaOH (45%) and the phases were separated. The aqueous phase was re-extracted with ethyl acetate (2 x 100 mL) and the combined organic layer was washed with brine (50 mL) and dried (Na₂SO₄). Evaporation of the solvent *in vacuo* gave 18 g (99% yield) of the title compound as a brown oil. EIMS (70 eV) *m/z* (relative intensity) 259 (34, M⁺); [α]_D²² -1.1° (c 0.09, CHCl₃).

Example 76

Salts of (R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide.

All melting points were determined using Differential Scanning Calorimetry (DSC). The temperature scanning rate was 10 °C per minute starting from room temperature. The samples were investigated in aluminum-pans with loose lids under nitrogen.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen (2S,3S)-Tartrate.

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(*R*)-*N*-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (150 mg, 0.33 mmol) was dissolved in tetrahydrofuran (3 mL) by heating and D-(-)-tartaric acid (110 mg, 0.69 mmol), dissolved in tetrahydrofuran (3 mL), was added dropwise. The white precipitate was filtered and washed with tetrahydrofuran to give 180 mg (86% yield). The crude salt (170 mg) was recrystallized from a 3% aqueous acetone solution (30 mL) and after standing for 3 h at room temperature the flask was put in the refrigerator for 65 h. The solid was filtered and washed with cold acetone to give 120 mg (61% yield) of white crystal: mp 142-148 °C. Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times C_4H_6O_6 \times 2H_2O$: C, 58.7; H, 7.0; N, 8.8. Found: C, 58.6; H, 7.1; N, 8.8.

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Example 77

(*R*)-*N*-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen (2*R*,3*R*)-Tartrate .

(*R*)-*N*-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (150 mg, 0.33 mmol) was dissolved in tetrahydrofuran (3 mL) by heating and L-(+)-tartaric acid (110 mg, 0.69 mmol), dissolved in tetrahydrofuran (3 mL), was added dropwise. The white precipitate was filtered and washed with tetrahydrofuran to give 180 mg (86% yield). The crude salt (180 mg) was recrystallized from a 3% aqueous acetone solution (48 mL) (some insoluble material was filtered) and after standing overnight at room temperature the solid was filtered to give 8 mg. The solvent was removed from the mother liquor by using a gentle stream of nitrogen so that 4 mL remained. The flask was allowed to stand at room temperature for 65 h and was then put in the refrigerator for 5 h. The solid was filtered and washed with cold acetone to give 61 mg (29% yield) of white crystal: mp 120-130 °C. Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times C_4H_6O_6 \times 2H_2O$: C, 58.7; H, 7.0; N, 8.8. Found: C, 58.9; H, 7.1; N, 8.6.

Example 78

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Benzenesulfonate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (2 mL) by heating and benzenesulfonic acid (40 mg, 0.24 mmol), dissolved in tetrahydrofuran (4 mL), was added dropwise. Diethyl ether was added and the resulting oil was titrated. The solid was filtered and washed with diethyl ether to give a white solid that was stored in an exicator over blue gel: mp >250 °C. Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times C_6H_6O_3S \times H_2O$: C, 63.4; H, 6.8; N, 9.0. Found: C, 63.1; H, 7.0; N, 8.7.

Example 79

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen 1,2-Ethanedisulfonate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (3 mL) by heating and 1,2-ethanedisulfonic acid dihydrate (55 mg, 0.24 mmol), dissolved in tetrahydrofuran (2 mL), was added dropwise. Diethyl ether (2 mL) was added, the solid was filtered and washed with tetrahydrofuran/diethyl ether to give a white solid that was stored in an exicator over blue gel: mp 220 °C (decom.). Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times C_2H_6O_6S_2 \times 4H_2O$: C, 48.9; H, 7.1; N, 7.9. Found: C, 49.1; H, 6.8; N, 7.6.

Example 80

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen Maleate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (2 mL) by heating and maleic acid (29 mg, 0.24 mmol), dissolved in tetrahydrofuran (1 mL), was added dropwise. Diethyl ether (5 mL) was added to the clear solution to give an oil. The solvent was decanted and the resulting oil was titrated from diethyl ether. The solid was

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filtered and washed with diethyl ether to give a white solid that was stored in an exicator over blue gel: mp 160 °C (decom.). Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times C_4H_4O_4 \times H_2O$: C, 63.8; H, 6.9; N, 9.6. Found: C, 63.7; H, 7.2; N, 9.3.

5 **Example 81**

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen Sulfate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (2 mL) by heating and sulfuric acid (25 mg, 0.24 mmol), dissolved in tetrahydrofuran (1 mL), was added dropwise. The white precipitate was filtered and washed with tetrahydrofuran to give 110 mg (89% yield). The crude salt (80 mg) was recrystallized from H_2O (12 mL) and allowed to stand in the refrigerator over night. The solid was filtered and washed with cold H_2O to give 28 mg (31% yield) a white solid: mp 230 °C (decom.). Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times H_2O_4S \times H_2O$: C, 57.4; H, 7.1; N, 9.9. Found: C, 57.7; H, 7.4; N, 9.9.

Example 82

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Gluconate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in ethanol (3 mL) and a 50% aqueous D-gluconic acid solution (80 μ L, 0.24 mmol) was added dropwise. The solvent was removed *in vacuo* to give a white viscous oil. The crude oil was recrystallized from a 5% H_2O in acetone solution (3 mL) and a 10% H_2O in acetone solution (3 mL), decanted, then allowed to stand at room temperature for 65 h. The solid was filtered and washed with a cold 3% H_2O in acetone solution to give 95 mg (65% yield) of a white solid: mp 130-140 °C. Anal. Calcd. for $C_{27}H_{36}N_4O_2 \times C_6H_{12}O_7 \times H_2O$: C, 59.8; H, 7.6; N, 8.5. Found: C, 60.0; H, 7.4; N, 8.3.

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Example 83

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen Succinate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (2 mL) by heating and succinic acid (56 mg, 0.46 mmol), dissolved in tetrahydrofuran (2 mL), was added dropwise. Diethyl ether (4 mL) was added until the solution was cloudy. The solution was heated to reflux and set aside to cool. The solid was filtered to give 42 mg (34% yield) of a white solid that was stored in an exicator over blue gel: mp 150 °C (decom.).

Example 84

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Methansulfonate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (15 mL) and methanesulfonic acid (42 mg, 0.44 mmol), dissolved in tetrahydrofuran (5 mL), was added dropwise. The solvent was removed *in vacuo* to give a white solid that was recrystallized from acetone (5 mL) and then from a 15% H₂O in acetone solution (7 mL). The crystals were filtered to give 37 mg (31% yield) of light yellow crystals that was stored in an exicator over blue gel: mp 250 °C (decom.). Anal. Calcd. for C₂₇H₃₆N₄O₂×CH₄O₃S×2H₂O: C, 57.9; H, 7.6; N, 9.7. Found: C, 58.1; H, 7.4; N, 9.6.

Example 85

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrogen (S)-Malate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (20 mL) and L-(-)-malic acid (59 mg, 0.44 mmol), dissolved in tetrahydrofuran (3 mL), was added dropwise. The precipitate was filtered and the solid material was recrystallized from a 15%

H₂O in acetone solution (7 mL). The solid was filtered to give 100 mg (77% yield) of white crystals: mp 200 °C (decom.). Anal. Calcd. for C₂₇H₃₆N₄O₂×C₄H₆O₅×2H₂O: C, 57.9; H, 7.6; N, 9.7. Found: C, 58.1; H, 7.4; N, 9.6.

5 **Example 86**

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Dihydrogen Citrate.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (15 mL) and
10 citric acid (51 mg, 0.27 mmol), dissolved in 10% H₂O in tetrahydrofuran (5 mL), was added dropwise. The solid material was filtered and recrystallized from a 20% H₂O in ethanol (5 mL). The solid was filtered to give 88 mg (62% yield) of white crystals: mp 160 °C (decom.). Anal. Calcd. for C₂₇H₃₆N₄O₂×C₆H₈O₇×2H₂O: C, 57.9; H, 7.6; N, 9.7. Found: C, 58.1; H, 7.4; N, 9.6.

15

Example 87

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide Hydrochloride.

(R)-N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (100 mg, 0.22 mmol) was dissolved in anhydrous tetrahydrofuran
20 (15 mL) and HCl in anhydrous diethyl ether (4 M) was added dropwise until the solution was acidic. The white precipitate was filtered and washed with diethyl ether to give the title compound as white crystals.

25 **PHARMACOLOGY**

Electrical field stimulation of [³H] -5-HT release from occipital cortex of guinea pigs
[³H] -5-HT is released by electrical field stimulation from slices of occipital cortex of guinea pigs which have been pre-incubated with [³H] -5-HT. This release is similar to that caused by nerve stimulation, i.e. exocytotical release from serotonergic nerve terminals,
30 depending on the presence of Ca²⁺ in the incubation medium. The 5-HT release is

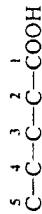
112

6. A compound according to any one of claims 1-4 wherein R_3 is $(CH_2)_n$ -aryl which is substituted with R_4 , an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O and S, or COR_8 .
- 5 7. A compound according to any one of claims 5 and 6 wherein $n=0$.
8. A compound according to claim 6 wherein R_8 is a heterocyclic ring containing two heteroatoms selected from N and O.
- 10 9. A compound according to any one of claims 1-8 wherein R_9 is C_1 - C_6 alkyl, $OCHF_2$, halogen or C_1 - C_6 alkoxy.
10. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is C_1 - C_6 alkoxy.
- 15 11. A compound according to claim 10 wherein X is N, Y is NR_2CO , R_4 is morpholino or COR_8 and R_9 is C_1 - C_6 alkoxy.
12. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is C_1 - C_6 alkyl.
- 20 13. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO , R_1 is H, R_3 is $(CH_2)_n$ -aryl and R_9 is C_1 - C_6 alkyl.
- 25 14. A compound according to claim 12 wherein X is N, Y is NR_2CO , R_4 is morpholino or COR_8 and R_9 is C_1 - C_6 alkyl.
15. A compound which is
(R)-N-[5-Methoxymethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- 30

M3

- (*R*)-*N*-[5-Bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide;
- (*R*)-*N*-[5-Bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- 5 (*R*)-*N*-[5-Bromo-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- (*R*)-*N*-[5-Hydroxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide;
- (*R*)-*N*-[5-Methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-
- 10 morpholinobenzamide;
- (*R*)-*N*-[5-Methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide;
- (*R*)-*N*-[5-Methyl-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-
- morpholinobenzamide;
- 15 (*R*)-*N*-[5-Bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide;
- N*-(4-Morpholinophenyl)-8-(4-methylpiperazinyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide;
- N*-(Morpholinocarbonylphenyl)-8-(4-methylpiperazin-1-yl)-5-methoxy-1,2,3,4-
- 20 tetrahydronaphthalene-2-carboxamide;
- (*R*)-*N*-[5-Ethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide;
- (*R*)-*N*-[5-Ethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-(4-morpholinocarbonyl)benzamide;
- 25 (*R*)-*N*-[5-Difluoromethoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide; or
- (*R*)-*N*-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,
- } in the form of a free base or pharmaceutical acceptable salt or solvate thereof.

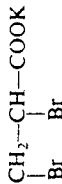
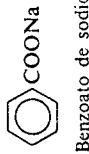
La posición de un sustituyente se indica de manera usual, mediante un número. Debemos observar que el carbono carbonílico siempre es considerado C-1, por lo que C-2 corresponde



Utilizado en nombres IUPAC

al α de los nombres comunes, C-3 a β, y así sucesivamente. (Advertencia: No se mezclan letras griegas con nombres IUPAC, o números arábigos con nombres comunes.)

El nombre de una sal de un ácido carboxílico se compone del nombre del ácido, cambiándole la terminación *ico* por *ato* de, seguido por el catión (*sodio, potasio, amonio*, etc.) Por ejemplo:



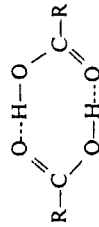
α,β-Dibromopropionato de potasio
(2,3-Dibromopropanoato de potasio)

23.3 Propiedades físicas

Sus estructuras hacen suponer que los ácidos carboxílicos son moléculas polares, y al igual que los alcoholes pueden formar puentes de hidrógeno entre sí y con otros tipos de moléculas. Por consiguiente, los ácidos carboxílicos se comportan de forma similar a los alcoholes en cuanto a sus solubilidades: los primeros son miscibles con agua, el ácido de cinco carbonos es parcialmente soluble y los superiores son virtualmente insolubles. No cabe duda de que la solubilidad en agua se debe a los puentes de hidrógeno entre el ácido carboxílico y el agua. El ácido aromático más simple, el benzoico, contiene demasiados átomos de carbono como para tener una solubilidad apreciable en agua.

Los ácidos carboxílicos son solubles en disolventes orgánicos menos polares, como éter, alcohol, benceno, etc.

En la tabla 23.1 se observa que, como clase, los ácidos carboxílicos hierven a temperaturas aún más elevadas que los alcoholes. El ácido propiónico (p.e. 141 °C), por ejemplo, hierve a unos 20 °C más que el alcohol de peso molecular comparable, el *n*-butílico (p.e. 118 °C). Estos puntos de ebullición tan elevados se deben a que un par de moléculas del ácido carboxílico se mantienen unidas no por un puente de hidrógeno, sino por dos:

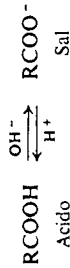


Problema 23.12. El ácido 4,4-dimetilpentanoico, el ácido 4,4-dimetilpentanoico y el ácido 4,4-dimetilpentanoico. ¿Cuál es el nombre IUPAC de cada uno de ellos? ¿Cuál es el nombre común de cada uno de ellos? ¿Cuál es el nombre común de cada uno de ellos?

Los olores de los ácidos alifáticos inferiores progresan desde los fuertes e irritantes del fórmico y acético, hasta los abiertamente desagradables del butírico, valerianoico y caproico. Los ácidos superiores tienen muy poco olor debido a sus bajas volatilidades.

23.4 Sales de los ácidos carboxílicos

Aunque mucho más débiles que los ácidos minerales fuertes (sulfúrico, clorhídrico, nítrico), los ácidos carboxílicos son sustancialmente más ácidos que los orgánicos muy débiles estudiados hasta el momento (alcoholes, acetileno); son mucho más ácidos que el agua, por lo que los hidróxidos acuosos los convierten en sus sales con facilidad, y los ácidos minerales acuosos reconvierten las sales en los ácidos carboxílicos correspondientes. Como es poco lo que podemos hacer con ácidos carboxílicos sin tropezar con esta conversión en sus sales, y viceversa, vale la pena examinar las propiedades de estas últimas.



Al igual que todas las sales, las de los ácidos carboxílicos con sólidos cristalinos no volátiles, constituidas por iones positivos y negativos, y sus propiedades corresponden a dichas estructuras. Las considerables fuerzas electrostáticas que mantienen a los iones en el retículo cristalino, sólo pueden superarse por un calentamiento a temperatura elevada o por medio de un disolvente muy polar. La temperatura requerida para fundirlas es tan alta que antes de lograrla se rompen los enlaces carbono-carbono y se descompone la molécula, generalmente entre los 300-400 °C. Raras veces es útil un punto de descomposición para la identificación de una sustancia, pues normalmente sólo refleja la velocidad de calentamiento y no la identidad del compuesto.

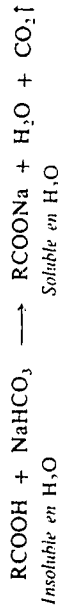
Las sales de metales alcalinos de los ácidos carboxílicos (sodio, potasio, amonio) son solubles en agua, pero no en disolventes no polares; la mayoría de las sales de metales pesados (hierro, plata, cobre, etc.) son insolubles en agua.

Podemos apreciar así que, salvo en el caso de ácidos de cuatro carbonos o menos, solubles tanto en agua como en disolventes orgánicos, los ácidos carboxílicos y sus sales de metales alcalinos exhiben un comportamiento de solubilidad exactamente opuesto. Debido a la fácil interconversión de ácido y sus sales, este comportamiento se puede utilizar de dos formas importantes: para la *identificación* y para la *separación*.

Un compuesto orgánico insoluble en agua que se disuelve en hidróxido de sodio acuoso, diluido y frío, debe ser un ácido carboxílico o uno de los pocos otros tipos de compuestos orgánicos más ácidos que el agua. Que es efectivamente un ácido carboxílico puede demostrarse de otras maneras.



En lugar de hidróxido de sodio podemos usar bicarbonato de sodio acuoso. Aunque la sustancia desconocida sea soluble en agua, queda comprobada su acidez por el burbujeo de CO₂.



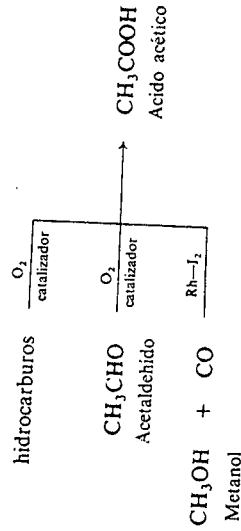
Podemos separar un ácido carboxílico de compuestos no ácidos aprovechando su solubilidad y la insolubilidad en base acuosa. Una vez lograda la separación, regeneraremos el ácido por acidulación de la solución acuosa. Si trabajamos con sólidos, simplemente agitamos la mezcla con base acuosa y luego filtramos la solución para separar las sustancias no ácidas insolubles. La adición de ácido al filtrado precipita el ácido carboxílico, el cual puede recogerse por filtración. Si estamos trabajando con líquidos, agitamos la mezcla con base acuosa en un embudo de decantación y separamos luego la capa acuosa de la orgánica insoluble. La acidificación de la fase acuosa nuevamente libera al ácido carboxílico, que puede separarse del agua. Para que la separación sea completa y de fácil manipulación, a menudo agregamos un disolvente insoluble en agua, como éter, a la mezcla acidificada. El ácido carboxílico es extraído del agua por el éter, en el que es más soluble. El éter volátil se separa con facilidad por destilación, ya que el ácido hierve a temperatura relativamente elevada.

Así, por ejemplo, un aldehído que se prepara por oxidación de un alcohol primario (Sec. 18.6), es posible que esté contaminado con el ácido carboxílico correspondiente, el cual puede eliminarse por simple lavado con una base acuosa diluida. El ácido carboxílico, preparado por oxidación de un alquilbenceno (Sec. 15.11), es posible que esté contaminado con material original no reaccionado: el ácido carboxílico puede extraerse con base acuosa, quedando separado del hidrocarburo insoluble, y luego se regenera por adición de ácido mineral.

Por ser las separaciones de este tipo más definidas y producir menor pérdida de material siempre que sea posible son preferidas a la recrystalización o destilación.

23.5 Fuente industrial

El ácido acético, el más importante de todos los ácidos carboxílicos, se prepara principalmente por la oxidación catalítica con aire de diversos hidrocarburos o de acetaldehído. Un método moderno implica la reacción entre metanol y monóxido de carbono en presencia de un catalizador de yodo-rodio: otro ejemplo más de catálisis mediante un complejo de metales de transición (véase Secs. 8.3, 17.6 y 20.5 a 20.8).

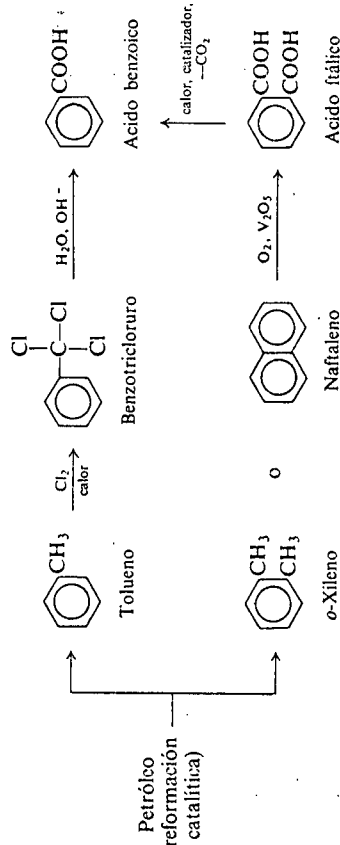


También se produce una cantidad importante de ácido acético en forma de una solución acuosa diluida, conocida como *vinagre*; este ácido también se prepara por oxidación con aire: el compuesto que se oxida es el alcohol etílico, y los catalizadores son enzimas de bacterias (*Acetobacter*).

Las fuentes de ácidos carboxílicos alifáticos más importantes son las grasas animales y vegetales (Secs. 37.2 a 37.4), de las que pueden obtenerse ácidos carboxílicos de cadena recta con número par de carbonos, con una pureza superior al 90%; el número de átomos de carbono va de seis hasta dieciocho. Estos ácidos pueden convertirse en los alcoholes

correspondientes (Sec. 23.18), que se pueden utilizar de las maneras ya vistas (Sec. 18.8) para transformarlos en muchos otros compuestos que contienen unidades de cadenas largas y rectas.

Los ácidos carboxílicos aromáticos más importantes, el benzoico y los ftálicos, se preparan a escala industrial por una reacción conocida: la oxidación de alquilbencenos (Sec. 15.11). El tolueno y los xilenos necesarios se obtienen del petróleo por reformación catalítica de hidrocarburos alifáticos (Sec. 15.5). Cantidades mucho menores de estos arenos se aíslan directamente del alquitrán de hulla. Otro precursor del ácido ftálico (el isómero *orto*) es el hidrocarburo aromático *naftaleno*, que también se encuentra en el alquitrán de hulla. Se utilizan agentes oxidantes baratos como cloro e incluso aire (en presencia de catalizadores).



Problema 23.2. En presencia de peróxidos los ácidos carboxílicos (o ésteres) se oxidan a ácidos más altos. ¿Cuáles son los ácidos más altos que se pueden preparar a partir de:

(a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido pentanoico) $\rightarrow$ $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido heptanoico)

(b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido hexanoico) $\rightarrow$ $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido octanoico)

(c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido heptanoico) $\rightarrow$ $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido nonanoico)

(d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido octanoico) $\rightarrow$ $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido decanoico)

Problema 23.3. (a) El monóxido de carbono convierte una solución en ácido sulfúrico de cada uno de los siguientes compuestos en ácido 2,2-dimetilbutanoico: (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido pentanoico), (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido hexanoico), (d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido heptanoico), (e) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido octanoico), (f) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido nonanoico), (g) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ (ácido decanoico).

23.6 Preparación

Los ácidos alifáticos de cadena recta hasta C_6 y aquéllos de número par de carbonos hasta C_{18} , existen comercialmente, lo mismo que los ácidos aromáticos simples. Utilizando los métodos que se ilustran a continuación pueden prepararse otros ácidos carboxílicos.

Como ya se dijo, los nitrilos aromáticos no se obtienen de halogenuros de arilo poco reactivos, sino de las sales de diazonio (Sec. 27.14).

Aunque a veces los nitrilos se citan como *cianuros* o *ciano-compuestos*, por lo general reciben el nombre de los ácidos que generan por hidrólisis. Se denominan eliminando la palabra *ácido* y cambiando la terminación *ico* del nombre común del ácido por *nitrilo*; por eufonía, se inserta normalmente una «o» entre la raíz y la terminación (por ejemplo, *acetónitrilo*). En el sistema IUPAC se denominan agregando la palabra *nitrilo* al nombre del hidrocarburo del cual se derivan (por ejemplo, *etanonitrilo*). Por ejemplo:



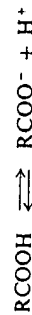
23.9 Reacciones

El comportamiento químico característico de los ácidos carboxílicos está determinado, evidentemente, por su grupo funcional, el **carboxilo**, —COOH . Este grupo se compone de un grupo carbonilo (C=O) y de un grupo hidroxilo (—OH). Veremos que el —OH es el que experimenta realmente casi todas las reacciones —pérdida de H^+ o reemplazo por otro grupo—, pero *lo hace de un modo que sólo es posible gracias a la presencia del C=O* .

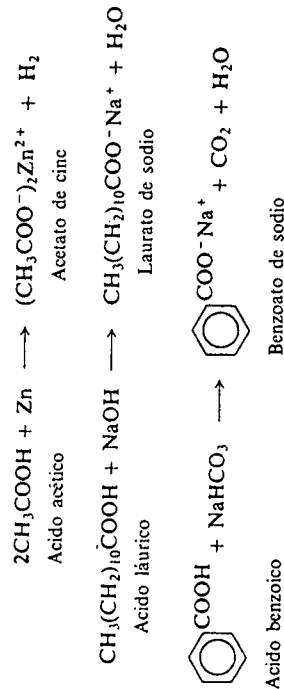
El resto de la molécula sufre reacciones que son características de su estructura, que puede ser alifática o aromática, saturada o no, y también contener muchos otros grupos funcionales.

REACCIONES DE ACIDOS CARBOXILICOS

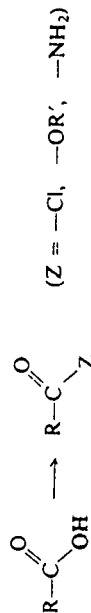
1. Acidez. Formación de sales. Estudiada en las secciones 23.4, 23.10 a 23.14.



Ejemplos:



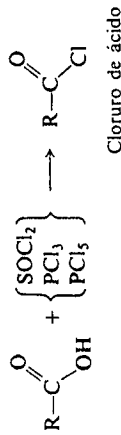
2. Conversión a derivados funcionales



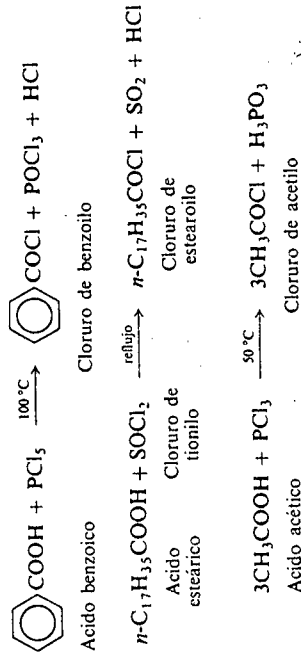
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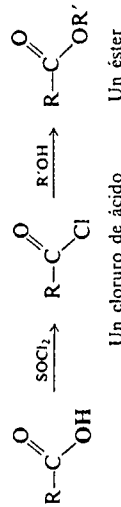
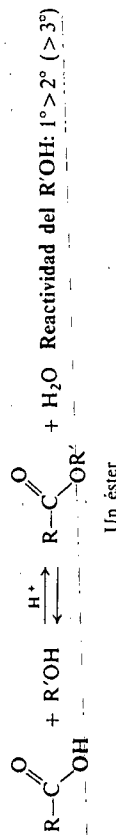
- (a) Conversión a cloruros de ácido. Estudiada en la sección 23.15.



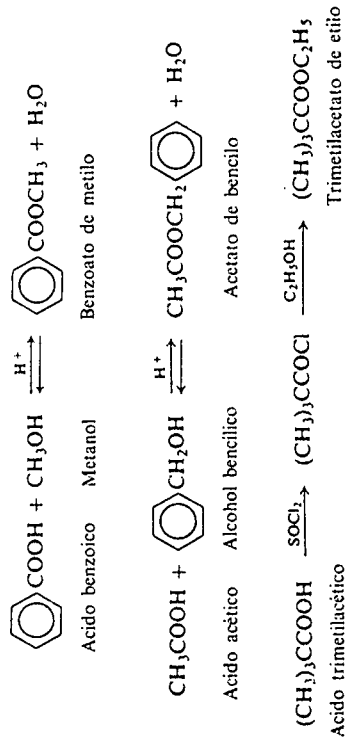
Ejemplos:



- (b) Conversión a ésteres. Estudiada en las secciones 23.16 y 24.15.



Ejemplos:



CONT.