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The preparation of pyrimidine analogs of the 2,6-di-*tert*-butylphenol antiinflammatory agents Prifelone (R-830), Tebufelone (NE-11740) and Ym-13,162 is described. Grignard addition to the *N*-methoxy-*N*-methylamide derived from 4,6-bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinecarboxylic acid yielded a series of 2-pyrimidinyl ketones. Further elaboration of an ethyl ketone and cyclization with sodium cyanate gave a pyrimidinylimidazole.

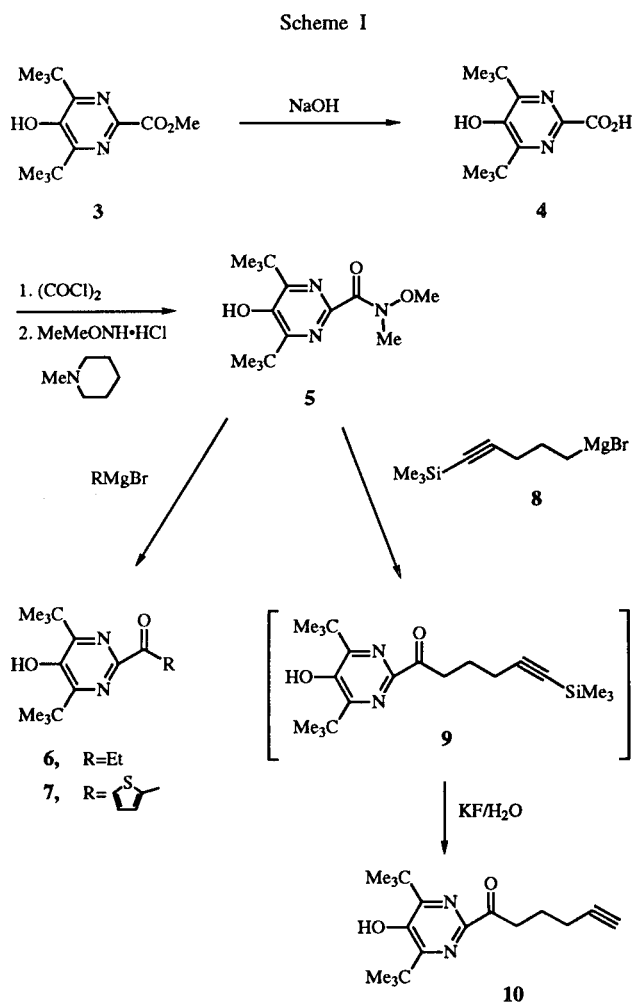
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We have previously described [3-6] the preparation of 2,6-di-*tert*-butylphenol derivatives **1** as potential antiinflammatory drugs. Many of these phenolic compounds are highly lipophilic, resulting in generally poor aqueous solubility and associated low oral bioavailability. Replacement of the benzene ring of **1** with a pyrimidine ring will permit salt formation and may improve aqueous solubility. In this paper, we report the preparation of pyrimidine analogs **2** of several well-studied di-*tert*-butylphenol antiinflammatory compounds.



Saponification of the pyrimidine ester **3** [7] (Scheme I) gave the carboxylic acid **4**, which was converted to the Weinreb [8] amide **5**. Reaction of **5** with ethylmagnesium bromide yielded the ethyl ketone **6**, while reaction with the Grignard reagent prepared [9] from 2-bromothiophene provided the thienyl ketone **7**, a pyrimidine analog of the di-*tert*-butylphenol Prifelone (R-830) [10]. Similarly, reaction of **5** with the Grignard reagent prepared from (5-bromo-1-pentynyl)trimethylsilane [11] gave the trimethylsilyl protected acetylenic ketone intermediate **9** as an oil. Deprotection of **9** provided the target ketone **10**, the pyrimidine analog of the di-*tert*-butylphenol Tebufelone (NE-11740) [12].

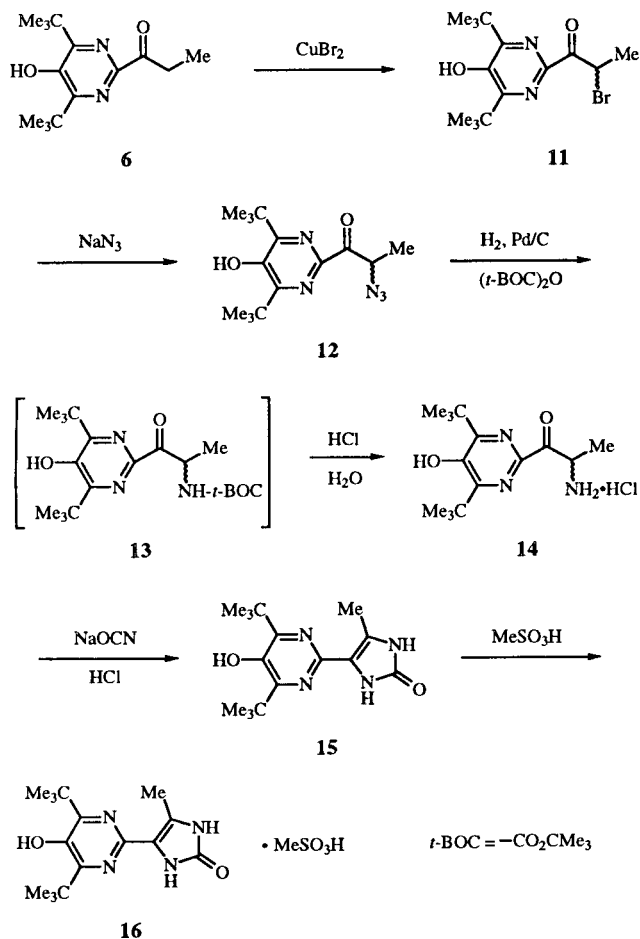
A pyrimidinylimidazole derivative was prepared (Scheme II) from the ethyl ketone **6**. Bromination of **6** with copper(II) bromide yielded the bromoketone **11**, which reacted with sodium azide to give a non-crystalline azido intermediate **12**. The crude azide was reduced in the presence of di-*tert*-butyl dicarbonate in order to form the *t*-BOC protected amine **13**. Acidic deprotection of **13** gave a non-stoichiometric amine hydrochloride **14**. The target imidazole **15**, representing the pyrimidine analog of



the di-*tert*-butylphenol Ym-13,162 [13], was obtained by cyclization of **14** with sodium cyanate.

Reaction of **15** with methanesulfonic acid gave the mesylate salt **16**. This salt was orally active (ID₅₀ of 10.8 mg/kg) in the carrageenan footpad edema [5] antiinflammatory test.

Scheme II



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Electrothermal capillary apparatus and are uncorrected. Elemental analyses were performed by the Analytical Chemistry staff of Parke-Davis (Ann Arbor, MI). The ir spectra were recorded as potassium bromide disks on a Mattson Cygnus 100 FTIR spectrometer. The ^1H nmr spectra were recorded on a Bruker AM 250 spectrometer (compounds 4-12) or on a Varian Unity 400 spectrometer (compounds 14-16), with chemical shifts reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a VG Masslab Trio-2A mass spectrometer. Reactions were usually run under a nitrogen atmosphere, and organic solutions were concentrated at aspirator pressure on a rotary evaporator. Flash chromatography was performed with E. Merck silica gel 60, 230-400 mesh ASTM, according to the method of Still [14].

4,6-Bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinecarboxylic Acid (4).

A solution of sodium hydroxide (11.3 g, 0.28 mole) in 250 ml of water was treated with ester 3 [7] (36.2 g, 0.14 mole). The

mixture was stirred at reflux for 2 hours, filtered warm, and the cooled filtrate extracted with ether. The aqueous layer was acidified with 4.0 *N* hydrochloric acid to pH 4.0. The precipitated solid was filtered and washed with water to yield 30.8 g (90%) of 4, mp 200° dec; ir: ν 3319, 1722, 1559, 1361 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.65 (s, 18 H, *t*-Bu), 8.80 (br s, 1 H, OH), 12.80 (br s, 1 H, CO_2H); ms: m/z 253 ($m+1$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.50; H, 7.93; N, 11.10.

4,6-Bis(1,1-dimethylethyl)-5-hydroxy-*N*-methoxy-*N*-methyl-2-pyrimidinecarboxamide (5).

A mixture of 4 (8.4 g, 33 mmoles) and *N,N*-dimethylformamide (0.50 ml, 0.47 g, 6.4 mmoles) in dichloromethane (120 ml) was cooled in ice and treated dropwise with a solution of oxalyl chloride (4.9 ml, 7.1 g, 56 mmoles) in dichloromethane (18 ml). The mixture was stirred with ice cooling for two hours, then filtered, and the filtrate evaporated. The residue was redissolved in dichloromethane (85 ml) and added dropwise to an ice cooled mixture of *N,O*-dimethylhydroxylamine hydrochloride (4.0 g, 41 mmoles) and 1-methylpiperidine (15 ml, 12.2 g, 123 mmoles) in dichloromethane (150 ml). The mixture was stirred at room temperature for 16 hours, then washed with 0.4 *N* hydrochloric acid, brine, 5% aqueous sodium bicarbonate, and brine again. The organic layer was dried (sodium sulfate) and evaporated. Recrystallization of the residue from ethyl acetate/hexane gave 6.4 g (65%) of 5, mp 140-142°; ir: ν 3124, 1643, 1542, 1231 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.40 (s, 18 H, *t*-Bu), 3.25 (s, 3 H, NCH_3), 3.67 (s, 3 H, OCH_3), 8.43 (br s, 1 H, OH); ms: m/z 296 ($m+1$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{25}\text{N}_3\text{O}_3$: C, 60.99; H, 8.53; N, 14.23. Found: C, 61.16; H, 8.89; N, 14.38.

1-[4,6-Bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-1-propanone (6).

A solution of 5 (8.4 g, 28 mmoles) in tetrahydrofuran (150 ml) was cooled in ice and treated dropwise with a 3.0 *M* solution of ethylmagnesium bromide in diethyl ether (40 ml, 120 mmoles). The mixture was stirred in ice for 2 hours, and then at room temperature for 16 hours. The mixture was again cooled in ice, and a saturated aqueous ammonium chloride solution (50 ml) was added dropwise to destroy excess Grignard reagent. The reaction mixture was added to an ammonium chloride solution (400 ml) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (sodium sulfate), and evaporated. Recrystallization of the residue from hexane yielded 5.0 g (67%) of 6, mp 123-125°; ir: ν 3489, 1703, 1356, 1229 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.22 (t, 3 H, $J = 7.3$ Hz, CH_3), 1.49 (s, 18 H, *t*-Bu), 3.18 (q, 2 H, $J = 7.3$ Hz, CH_2); ms: m/z 265 ($M+1$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.93; H, 8.95; N, 10.47.

[4,6-Bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl](2-thienyl)methanone (7).

A solution of 5 (0.50 g, 1.7 mmoles) in tetrahydrofuran (15 ml) was treated dropwise with a 1.1 *M* solution (3.5 ml, 3.9 mmoles) of the Grignard reagent prepared [9] from 2-bromothiophene in ether. The mixture was stirred for 16 hours, then diluted with additional ether and quenched with saturated aqueous ammonium chloride solution. The organic layer was washed with brine, dried (magnesium sulfate), and evaporated. The

crude product was purified by flash chromatography (dichloromethane), then recrystallized from aqueous methanol to give 0.40 g (74%) of **7**, mp 157-159°; ir: ν 3333, 1634, 1412, 1245 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.47 (s, 18 H, *t*-Bu), 7.29 (m, 1 H, ArH), 8.10-8.21 (m, 2 H, ArH), 8.98 (br s, 1 H, OH); ms: m/z 319 (M+1).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 64.12; H, 6.96; N, 8.80. Found: C, 63.93; H, 7.10; N, 8.89.

1-[4,6-Bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-5-hexyn-1-one (**10**).

A solution of **5** (1.0 g, 3.4 mmoles) in tetrahydrofuran (50 ml) was treated dropwise with a 0.11 *M* solution (80 ml, 8.8 mmoles) of the Grignard reagent prepared from (5-bromo-1-pentynyl)trimethylsilane [**11**] (3.9 g, 18 mmoles) and magnesium turnings (1.5 g, 62 mmoles) in tetrahydrofuran (140 ml). The mixture was stirred at room temperature for 16 hours, then worked up as described in the preparation of **6**. Purification of the crude product by flash chromatography (20% ethyl acetate in hexane) yielded 0.97 g (77%) of intermediate 1-[4,6-bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-6-trimethylsilyl-5-hexyn-2-one (**9**) as an oil; ^1H nmr (DMSO- d_6): δ 1.34 (s, 18 H, *t*-Bu), 1.70 (m, 2 H, CH_2), 2.23 (t, 2 H, $J = 6.8$ Hz, CH_2), 3.16 (t, 2 H, $J = 7.2$ CH_2), 8.78 (br s, 1 H, OH); ms: m/z 375 (M+1).

A sample of intermediate **9** (0.87 g, 2.3 mmoles) and potassium fluoride dihydrate (0.91 g, 9.7 mmoles) were heated at 50° for 48 hours in *N,N*-dimethylformamide (12 ml). The solvent was evaporated, and the residue was partitioned between water and ethyl acetate. The organic layer was washed with saturated ammonium chloride solution and brine, then dried (magnesium sulfate) and evaporated. Purification of the residue by flash chromatography (20% ethyl acetate in hexane) and recrystallization of the final product from aqueous methanol gave 0.48 g (69%) of **10**, mp 64-66°; ir: ν 3280, 2175, 1700, 1546 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.42 (s, 18 H, *t*-Bu), 1.79 (m, 2 H, CH_2), 2.24 (m, 2 H, CH_2), 2.80 (t, 1 H, $J = 2.5$ Hz, acetylenic CH), 3.22 (t, 2 H, $J = 7.0$ Hz, CH_2), 8.80 (br s, 1 H, OH); ms: m/z 303 (M+1).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.50; H, 8.72; N, 9.22.

1-[4,6-Bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-2-bromo-1-propanone (**11**).

A suspension of pulverized copper(II) bromide (9.5 g, 43 mmoles) in ethyl acetate (30 ml) was heated to reflux and treated dropwise with a solution of **6** (5.6 g, 21 mmoles) in chloroform (30 ml). The mixture was stirred at reflux for 2 hours, cooled, diluted with additional ethyl acetate, and filtered. The filtrate was washed with 5% aqueous sodium bicarbonate solution and brine, then dried (sodium sulfate) and evaporated. Purification of the residue by flash chromatography (0.20% methanol in dichloromethane) gave 6.4 g (88%) of **11**, mp 135-136°; ir: ν 3556, 1706, 1236, 1135 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.50 (s, 18 H, *t*-Bu), 1.90 (d, 3 H, $J = 6.7$ Hz, CH_3), 5.90 (q, 1 H, $J = 6.8$ Hz, CH); ms: m/z 345 (M+2).

Anal. Calcd. for $\text{C}_{15}\text{H}_{23}\text{BrN}_2\text{O}_2$: C, 52.49; H, 6.75; N, 8.16. Found: C, 52.43; H, 6.68; N, 8.05.

2-Amino-1-[4,6-bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-1-propane Hydrochloride (**14**).

A solution of **11** (8.1 g, 24 mmoles) in acetone (50 ml) was treated dropwise at room temperature with a solution of sodium

azide (1.7 g, 26 mmoles) in water (15 ml). The mixture was stirred for 18 hours, diluted with water (300 ml), and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (sodium sulfate), and evaporated to yield 6.7 g (93%) of intermediate 2-azido-1-[4,6-bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-1-propanone (**12**) as an amorphous solid, mp 89-91°; ir: ν 3313, 2120, 1712, 1345 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.50 (s, 18 H, *t*-Bu), 1.60 (d, 3 H, $J = 7.3$ Hz, CH_3), 5.24 (q, 1 H, $J = 7.0$ Hz, CH), 5.67 (br s, 1 H, OH); ms: m/z 306 (M+1).

A mixture of intermediate **12** (182 g, 0.60 mole), di-*tert*-butyl dicarbonate (260 g, 1.2 moles), triethylamine (124 ml, 90 g, 0.89 mole), and 10% palladium on carbon catalyst (1.0 g) in methanol (3 liters) was shaken for 2.5 hours with 50 psi of hydrogen. After filtration of the catalyst, the filtrate was evaporated and the residue treated with fresh methanol (1 liter). The mixture was again evaporated, and this process was repeated twice more in order to remove excess triethylamine. The final residue was cooled to 10° and stirred for 1 hour with acetonitrile (1.5 liters) and 6 *N* hydrochloric acid (1 liter). The bulk of the acetonitrile was evaporated, and the remaining mixture was stirred for 18 hours with ether (2 liters). The ether layer was separated and reserved, and the aqueous layer was concentrated at 60° until a heavy precipitate began to form. Acetonitrile (500 ml) was added, and a first crop (27 g) of hydrochloride **14** was filtered. Repeated concentration and acetonitrile addition to the filtrate gave an additional 90 g of **14**.

The reserved ether extract was stirred for 24 hours with 6 *N* hydrochloric acid (1 liter). The aqueous layer was separated and concentrated as described above to yield an additional 31 g of product, for a total yield of 148 g (79%) of **14**, mp 193-195°; ir: ν 3403, 1713, 1507, 1235 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.43 (s, 18 H, *t*-Bu), 1.55 (d, 3 H, $J = 7.2$ Hz, CH_3), 5.02 (m, 1 H, CH), 8.48 (br s, 3 H, NH), 9.41 (br s, 1 H, OH); ms: m/z 280 (M+1, -HCl).

Anal. Calcd. for $\text{C}_{15}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 1.25\text{HCl} \cdot 0.75\text{H}_2\text{O}$: C, 53.23; H, 8.26; N, 12.41; Cl, 13.09. Found: C, 53.31; H, 8.30; N, 12.67; Cl, 12.89; Water (Karl Fischer): Calcd. 3.99; Found 3.76.

4-[4,6-Bis[1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-5-methyl-1,3-dihydroimidazol-2-one (**15**).

A solution of **14** (90 g, 0.27 mole) in ethanol (600 ml) was treated dropwise with 300 ml of a solution of sodium cyanate (55 g, 0.85 mole) in water (550 ml). The pH of the reaction mixture was maintained at 1.0 by concurrent addition of concentrated hydrochloric acid. The remaining sodium cyanate solution was then added dropwise, with the pH permitted to increase to 3.0. After stirring for 15 minutes, the precipitated solid product was filtered and washed with water. The crude product was added to a mixture of water (200 ml) 1 *N* sodium hydroxide solution (280 ml) and ether (350 ml). The mixture was stirred for 30 minutes, then filtered, and the aqueous layer was separated. The aqueous layer was washed several times with fresh ether, treated with charcoal and filtered, then acidified to pH 3.0 with 1*N* hydrochloric acid. The precipitated product was filtered and washed with ethyl acetate to yield 58 g (72%) of **15**, mp 292-294°; ir: ν 3478, 1688, 1532, 1364 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.40 (s, 18 H, *t*-Bu), 2.38 (s, 3 H, CH_3), 7.87 (s, 1 H, OH), 9.53 (d, 1 H, $J = 2.4$ Hz, NH), 10.17 (d, 1 H, $J = 2.0$ Hz, NH); ms: m/z 304 (M+).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_2$: C, 63.13; H, 7.95; N, 18.41.

Found: C, 63.09; H, 7.89; N, 18.07.

4-[4,6-Bis(1,1-dimethylethyl)-5-hydroxy-2-pyrimidinyl]-5-methyl-1,3-dihydroimidazol-2-one Methanesulfonate (16).

A suspension of 15 (15 g, 49 mmol) in 2-propanol (275 ml) was warmed on the steam bath and treated with methanesulfonic acid (3.3 ml, 4.9 g, 51 mmol). The mixture was heated for a few minutes until nearly one phase, then filtered hot. Evaporation of the cooled filtrate gave a flaky residue. The residue was stirred three times in ether (350 ml) and filtered to yield 18.3 g (93%) of 16, mp 213-125°; ir: ν 3121, 1669, 1534, 1206 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.40 (s, 18 H, *t*-Bu), 2.39 (s, 3 H, CCH₃ or SCH₃), 2.47 (s, 3 H, CCH₃ or SCH₃), 9.76 (d, 1 H, J = 1.2 Hz, NH), 10.38 (s, 1 H, NH); ms: m/z 305 (M+1, -CH₄O₃S).

Anal. Calcd. for C₁₆H₂₄N₄O₂•CH₄O₃S: C, 50.98; H, 7.05; N, 13.99. Found: C, 50.94; H, 7.00; N, 13.94.

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