β-(5-Pyrimidinyl)ethanolamines

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Received June 4, 1976

2,4-Diphenyl-5-pyrimidinyl methyl ketone (**8**) and 2-phenyl-4-methyl-5-pyrimidinyl phenyl ketone (**12**) were prepared by condensation of benzamidine with 2-ethoxymethyl-1-phenyl-1,3-butanedione (**10**). Their structures were elucidated by the nmr spectra of their derivative alcohols **13** and **14**, respectively. The ketone **8** was converted by way of the bromoketone **15** to 2-[1-methylethylamino]-1-[2,4-diphenyl-5-pyrimidinyl]ethanol hydrochloride (**17**) and 2-amino-1-[2,4-diphenyl-5-pyrimidinyl]ethanol hydrochloride (**20**). Pharmacologic testing indicated that **17** and **20** did not possess either antihypertensive or beta adrenergic blocking activities.

J. Heterocyclic Chem., 13, 973 (1976).

The attachment of the β-hydroxyethylamino group ($-CH(OH)CH_2NH_2$) and the isopropyl derivative $-CH(OH)CH_2NHCH(CH_3)_2$ to aromatic functions has generally resulted in compounds possessing interesting pharmacologic properties. Although several reports of heterocycles containing these functions have appeared, synthesis of pyrimidines containing these two moieties have thus far received little attention. The preparation of two pyrimidines containing these groups and the results of pharmacologic evaluation of these compounds are the subject of this publication.

Christensen and co-workers (1) synthesized a series of aminopropanols **1** by a Mannich reaction on the appropriate pyrimidinyl ketone and subsequent reduction of the Mannich base. Subsequently, Christensen's group attempted conversion of the ketone **2** to the bromo derivative **3**, a potential precursor of the aminoethanol series **4**. However, bromination of **2** gave the bromomethyl compound **5** rather than **3** (2). More recently, the preparation of aminocarbinol **6** from phthalimide **7** was reported (3).

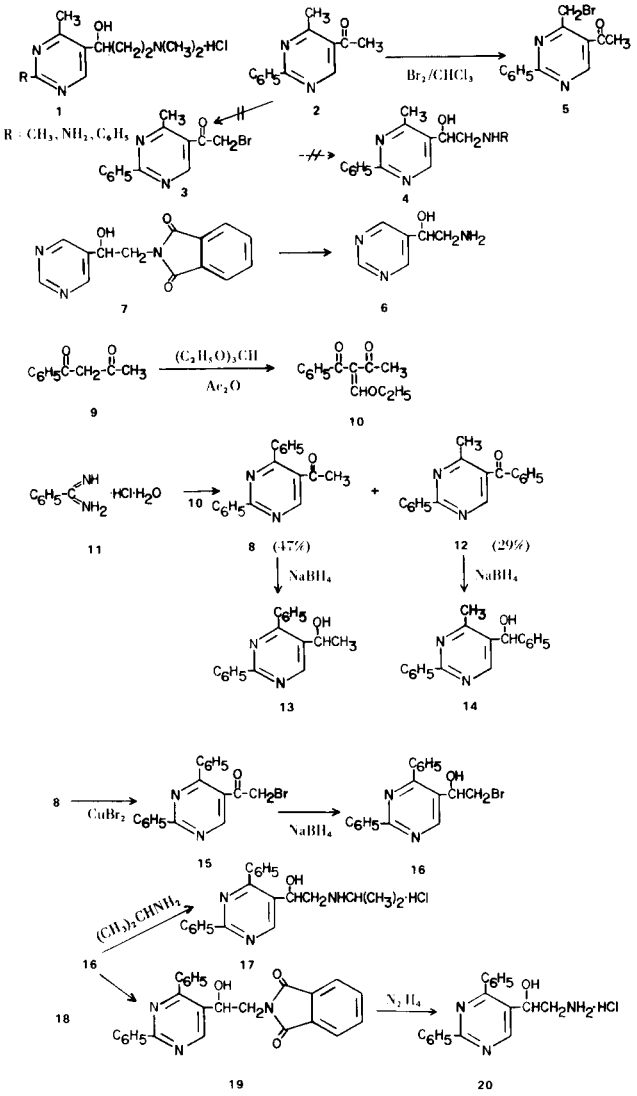
Since the ketone **8** contains no activated methyl group, bromination should occur at the acetyl function exclusively. Accordingly, a route to **8** was devised.

Treatment of benzoylacetone (**9**) with triethylorthoformate and acetic anhydride gave **10**. Condensation of **10** with benzamidine hydrochloride (**11**) gave two ketones, **8** and **12**, in yields of approximately 47% and 29%, respectively. Although elemental analysis and nmr spectral data failed to permit unequivocal structural elucidation of the two ketones, a tentative assignment was made on the basis of the carbonyl absorption frequencies in the infrared spectra of the two products. The compound obtained in higher yield was characterized by a strong band at 5.96 μ while the second product exhibited absorption at 6.01 μ. Bellamy reports that aryl-alkyl ketones and diaryl ketones exhibit carbonyl absorption at 5.88-5.91 μ and 5.99-6.03 μ, respectively (4). Therefore, the higher yield product was tentatively assigned the methyl ketone structure **8** while the second product was assigned the phenyl ketone structure **12**.

Evaluation of the nmr spectra of the borohydride reduction products of the two ketones verified this structural assignment. The methyl signal in **13**, the carbinol derived from the acetyl compound **8**, appears as a doublet which is attributed to the $CH_3-\underset{OH}{\underset{|}{C}}H$ function. The methyl signal in **14**, derived from **12**, appears as a singlet, indicating the methyl group in this carbinol is attached to the pyrimidine ring.

Treatment of **8** with cupric bromide in dioxane using the general method of Diofode and Marathey (5) gave the bromoketone **15** which upon borohydride reduction afforded the bromocarbinol **16**. Reaction of **16** with isopropylamine gave the isopropylamino ethanol **17** while treatment of **16** with potassium phthalimide (**18**) and subsequent reaction of the phthalimide **19** with hydrazine afforded the amine **20**.

Compounds **17** and **20** were tested for pharmacologic antihypertensive and beta adrenergic blocking activities. The test for antihypertensive activity was conducted in male 200-250 g. conscious Okamoto strain (6) spontaneously hypertensive rats raised at the Norwich Pharmacal Company's Animal Research Center. Twenty-four hours



prior to experiments, the rats were prepared by the Weeks-Jones (7) procedure to measure mean arterial blood pressure directly. Doses of 50 mg./kg. were intraperitoneally administered. All doses of drug were dispersed in a volume of 0.9% aqueous sodium chloride solution (saline) equivalent to 1 ml./kg. Within a 24 hour post-treatment period, **17** and **20** did not reduce mean arterial blood pressure below the control level. In anesthetized dog preparations, 1, 10 and 20 mg./kg. doses of **17** dissolved in distilled water and 1, 5, 10 and 50 mg./kg. doses of **20** dissolved in saline administered intravenously did not attenuate the depressor response to a 1 μg./kg. intravenous dose of L-isoproterenol hydrochloride as did 1 and 5 mg./kg. intravenous doses of pronethalide. It was concluded that **17** and **20** were void of antihypertensive and beta adrenergic blocking activities.

EXPERIMENTAL

Nuclear magnetic resonance spectra were determined on a Varian A-60A instrument and were compared with TMS as an internal standard. Infrared spectra were obtained on a Perkin-Elmer model 137 spectrophotometer. Melting points were taken in a Mel-Temp apparatus in open capillary tubes and were not corrected.

2-Ethoxymethylene-1-phenyl-1,3-butanedione (**10**) (8).

A mixture of 200 g. (1.23 moles) of benzoylacetone (**9**), 320 g. (2.16 moles) of triethyl orthoformate, and 360 g. (3.52 moles) of acetic anhydride was stirred and refluxed for 3.0 hours. The volatile components were distilled at atmospheric pressure at pot temperatures up to 140°. The residue was recrystallized from toluene to give, in two crops, 206 g. (77%) of the product, m.p. 68-71°. Recrystallization from toluene gave the analytical sample, m.p. 68-71°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.65; H, 6.47.

2,4-Diphenyl-5-pyrimidinyl Methyl Ketone (**8**) and 2-Phenyl-4-methyl-5-pyrimidinyl Phenyl Ketone (**12**).

To a solution of 108 g. (2.0 moles) of sodium methoxide in 1500 ml. of methanol cooled at 15° was added quickly 348 g. (2.0 moles) of benzamidine hydrochloride monohydrate (**11**). The mixture was maintained at 10-15° while a solution of 436 g. (2.0 moles) of **10** in 800 ml. of methanol was added over 30 minutes. The mixture was stirred at ambient temperatures for 18 hours, refluxed for 4 hours, and the methanol (2200 ml.) was removed by distillation. Chloroform (1000 ml.) and water (500 ml.) were added to the residue and the mixture was stirred for 20 minutes.

The organic layer was separated and the aqueous layer was extracted with two 150 ml. portions of chloroform. The combined extracts were washed with 500 ml. of water, dried (magnesium sulfate), and concentrated to dryness *in vacuo* to give 562 g. of an oily residue which crystallized at room temperature.

The residue was dissolved in 1600 ml. of boiling absolute ethanol. Upon standing at ambient temperatures for 15 hours, there separated 254 g. of **8**, m.p. 100-108°. After the filtrate stood at ambient temperatures for an additional 24 hours, another 6.3 g. of **8** was isolated, total yield, 260.3 g. (47%).

The analytical sample of **8**, m.p. 107-110°, was obtained by recrystallization from absolute ethanol; nmr (deuteriochloroform): δ 2.15 (s, 3, CH_3); 7.50-7.90 (m, 8, aromatic C-H); 8.55-8.70 (m, 2, aromatic C-H); 8.96 (s, 1, C_6-H); infrared (Nujol) μ: 5.96 (C=O); 6.21, 6.30 (C=C).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.46; H, 5.11; N, 10.15.

The filtrate from the isolation of **8** was concentrated to 500 ml. and stored at ambient temperatures for 72 hours. The product (212 g.) was filtered and recrystallized from 500 ml. of absolute ethanol to give 157 g. (29%) of **12**, m.p. 58-68°. Further recrystallization from ethanol gave the analytical sample, m.p. 68-72°; nmr (deuteriochloroform): δ 2.62 (s, 3, CH_3); 7.41-7.91 (m, 8, aromatic C-H); 8.46-8.63 (m, 2, aromatic C-H), 8.71 (s, 1, C_6-H); infrared (Nujol) μ: 6.01 (C=O); 6.27, 6.37 (C=C).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.64; H, 5.18; N, 10.29.

α-Methyl-2,4-diphenyl-5-pyrimidinemethanol (**13**).

To a mixture of 41.1 g. (0.15 mole) of **8** in 500 ml. of methanol stirred at 5-10° was added over 20 minutes, 11.4 g.

(0.03 mole) of sodium borohydride. The solution was stirred at 5-10° for 30 minutes, then stirred at ambient temperatures for 2 hours. The solvents were removed *in vacuo* and the residue was partitioned between 500 ml. of chloroform and 500 ml. of water. The aqueous layer was re-extracted with two 500 ml. portions of chloroform; the combined organic extracts were washed with 250 ml. of water, dried (magnesium sulfate) and concentrated to dryness *in vacuo*. Crystallization from 100 ml. of toluene gave, in two crops, 34 g. (82%) of the carbinol, m.p. 108-113°. Further recrystallization from heptane gave the analytical sample, m.p. 110-113°; nmr (deuteriochloroform): δ 1.45 (d, J = 6.5 cps, 3, -CH-C*H*$_3$); 5.10 (q, 1, C*H*-CH$_3$); 7.40-7.66 (m, 8, aromatic C-H); 8.43-8.58 (m, 2, aromatic C-H); 9.06 (s, 1, C$_6$-H); infrared (Nujol) μ: 3.0 (O-H); 6.30, 6.40, 6.50 (C=C); 9.27, 9.41 (C-OH).

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.39; H, 5.90; N, 10.06.

4-Methyl-α,2-diphenyl-5-pyrimidinemethanol (**14**).

Sodium borohydride reduction of 41.1 g. (0.15 mole) of **12**, as described above for ketone **8**, gave 17.4 g. (42%) of **14**, m.p. 130-136°. Further recrystallization from toluene gave the analytical sample, m.p. 135-137°; nmr (deuteriochloroform): δ: 2.37 (s, 3, CH$_3$); 5.86 (s, 1-C*H*(OH)C$_6$H$_5$); 7.30 (s, 5, aromatic C-H); 7.41-7.53 (m, 3, aromatic C-H); 8.03-8.20 (m, 2, aromatic C-H); 8.76 (s, 1, C$_6$-H); infrared (Nujol) μ: 3.17 (O-H); 6.28, 6.33, 6.45 (C=C); 9.52 (C-OH).

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.22; H, 5.79; N, 10.15.

2,4-Diphenyl-5-pyrimidinyl Bromomethyl Ketone (**15**).

A mixture of 86 g. (0.31 mole) of **8**, 136 g. (0.61 mole) of cupric bromide, and 100 ml. of dioxane was stirred at ambient temperatures for 15 hours and was then stirred and refluxed for 3.0 hours. The mixture was cooled, stirred, and filtered. After the solid was washed twice with 300 ml. of chloroform, the filtrate and combined washings were concentrated to dryness *in vacuo*. Recrystallization from 200 ml. of ethanol gave 57 g. (52%) of the product, m.p. 131-133°; infrared (Nujol) μ: 5.89 (C=O); 6.23, 6.30, 6.41 (C=C).

Anal. Calcd. for $C_{18}H_{13}BrN_2O$: C, 61.20; H, 3.71; N, 7.93. Found: C, 61.68; H, 3.68; N, 7.95.

2-Bromo-1-[2,4-diphenyl-5-pyrimidinyl]ethanol (**16**).

Sodium borohydride reduction of 71 g. (0.20 mole) of **15**, as described above for **8**, gave 67.5 g. (95%) of the crude product **16**, a viscous oil which was employed directly in subsequent reactions; infrared (film) μ: 2.95-3.05 (O-H); 6.30, 6.39, 6.50 (C=C); 9.35, 9.79 (C-OH); no C=O at 5.80-6.10 μ.

2-[1-Methylethylamino]-1-[2,4-diphenyl-5-pyrimidinyl]ethanol Hydrochloride (**17**).

A mixture of 67.5 g. (0.19 mole) of **16**, 26.2 g. (0.19 mole) of potassium carbonate, 24.0 g. (0.14 mole) of potassium iodide, and 150 ml. of isopropylamine was stirred and gently refluxed (40-42°) for 24 hours. The mixture was concentrated to dryness *in vacuo* and the residue was partitioned between 1500 ml. of water and 1200 ml. of chloroform. The organic extract was washed with 1000 ml. of water, dried (magnesium sulfate) and concentrated to dryness to give 72 g. of the free base which crystallized at room temperature.

Treatment of a solution of the crude product in 2-propanol with methanolic hydrogen chloride gave, after recrystallization from ethanol, 40 g. (57%) of **17**, m.p. 207-208°. Further recrystallization from acetonitrile gave the analytical sample, m.p. 203-206°; nmr (DMSO-d$_6$) δ: 1.25 (d, J = 7.5 cps, 6, C*H*$_3$-CH); 3.20-3.36 (m, 3, C*H*$_2$(NH)CH and C*H*(CH$_3$)$_2$); 5.11-5.28 (m, 1, C*H*(OH)CH$_2$); 6.50-6.70 (broad m, exchangable, 1, CH-O*H*); 7.48-7.81 (m, 8, aromatic C-H); 8.41-8.60 (m, 2, aromatic C-H); 9.00-9.40 (broad m, exchangable, 1, $^+$NH); 9.23 (s, 1, C$_6$-H); infrared (Nujol) μ: 3.12 (O-H); 6.31, 6.39, 6.50 (C=C); 9.47, 9.85 (C-OH).

Anal. Calcd. for $C_{21}H_{23}N_3O\cdot HCl$: C, 68.19; H, 6.54; N, 11.36. Found: C, 67.90; H, 6.59; N, 11.30.

2-[1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl]-1-[2,4-diphenyl-5-pyrimidinyl]ethanol (**19**).

A mixture of 33.5 g. (0.095 mole) of **16** and 19.2 g. (0.104 mole) of potassium phthalimide in 430 ml. of dimethylsulfoxide was stirred at 90-95° for 20 hours and poured into 3 l. of cold water. The mixture was stirred at 35° for 2.0 hours and the solid was filtered, washed with 800 ml. of water, and dried to give 33 g. of the crude product. Recrystallization from absolute ethanol gave 27 g. (68%) of **19**, m.p. 178-180°. Further recrystallization from ethanol gave the analytical sample, m.p. 179-180°; nmr (DMSO-d$_6$) δ: 3.79-3.95 (m, 2, C*H*$_2$-CH(OH)); 5.08-5.30 (m, 1, C*H*(OH)CH$_2$), 5.95, 6.01, (d, 1, exchangable, CH-O*H*); 7.33-7.66 (m, 8, aromatic C-H); 7.81 (s, 4, aromatic C-H); 8.31-8.48 (s, 2, aromatic C-H); 9.21 (s, 1, C$_6$-H); infrared (Nujol) μ: 3.05 (O-H); 5.65, 5.80 (C=O); 6.31, 6.40, 6.50 (C=C).

Anal. Calcd. for $C_{26}H_{19}N_3O_3$: C, 74.09; H, 4.54; N, 9.97. Found: C, 73.97; H, 4.60; N, 9.83.

2-Amino-1-[2,4-diphenyl-5-pyrimidinyl]ethanol (**20**).

A mixture of 40 g. (0.095 mole) of **19** and 120 ml. of 85% hydrazine hydrate in 1200 ml. of alcohol was stirred and refluxed for 18 hours and cooled. To the slurry was added 10% hydrochloric acid (1300 ml.) and the mixture was refluxed for 2.0 hours, cooled, and made alkaline with 1400 ml. of 10% sodium hydroxide. The aqueous mixture was extracted 5 times with 1000 ml. of chloroform and the combined extracts were washed with water, dried (magnesium sulfate), and concentrated to dryness *in vacuo*.

Treatment of the free base with methanolic hydrogen chloride and subsequent removal of the solvents gave the crude product **20**. The solid was boiled with 200 ml. of ethyl acetate and filtered to give 23.5 g. (76%) of **20**. Recrystallization from ethyl acetate-2-propanol (2:1) gave the analytical sample, m.p. 242-243° dec.; nmr (DMSO-d$_6$) δ: 3.00-3.33 (m, 2, C*H*$_2$-(CHOH)NH$_2$); 5.03-5.25 (m, 1, C*H*(OH)CH$_2$NH$_2$); 5.75-6.08 (broad m, exchangable, 1, CH-O*H*), 7.41-7.96 (m, 12, 2 exchangable, aromatic C-H, $\overset{+}{N}$-H); 8.40-8.56 (m, 2, aromatic C-H); 9.20 (s, 1, C$_6$-H); infrared (Nujol) μ: 3.05, 3.20 (O-H, $\overset{+}{N}$H$_2$); 6.20, 6.27; 6.36, 6.51 (C=C).

Anal. Calcd. for $C_{18}H_{17}N_3O\cdot HCl$: C, 65.95; H, 5.53; N, 12.82. Found: C, 65.66; H, 5.62; N, 12.97.

Acknowledgements.

The authors thank Ms. Patricia Curtis for running the nmr spectra and Mr. Grant Gustin, Mr. Marvin Tefft, and Ms. Donna George for the elemental analyses.

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