chloride as a white solid, ν_{max} 3320 (OH), 1720 (C=O) cm^{-1} (Nujol).

The crude hydroxy acid hydrochloride was refluxed with *p*-toluenesulfonic acid (0.15 g) and EtOH (300 ml) for 16 hr. The solution was concentrated at reduced pressure and the residue was treated with 10% aqueous Na_2CO_3 (200 ml). The H_2O solution was extracted with $CHCl_3$ (three 250-ml portions), the combined extracts were washed with H_2O (100 ml), dried (Na_2SO_4), and concentrated at reduced pressure to a clear liquid. The ethyl 4-hydroxypiperidine-4-carboxylates (Table III) were purified by distillation and had ν_{max} 3520 (OH) and 1715 (C=O) cm^{-1} (7% in $CHCl_3$), and analyzed correctly (C, H, N).

2-Amino-2-oxazolin-4-one-5-spiro(4′-piperidines) (3a–f).—A solution of Na (2.30 g, 0.1 g-atom) in EtOH (145 ml) was added to a solution of guanidine hydrochloride (9.56 g, 0.1 mole) in EtOH (45 ml). The precipitated NaCl was removed by filtration and a solution of the ethyl 4-hydroxypiperidinecarboxylate (0.1 mole) in EtOH (50 ml) was added. The solution was refluxed for 1 hr and cooled. The white precipitate obtained was filtered, the filtrate was concentrated at reduced pressure, and the residue was treated with EtOH (20 ml). A further quantity of white solid was obtained. This material was combined with the precipitate and recrystallized from EtOH to give the required product (Table IV). All of the compounds (**3a–f**) had ν_{max} 3150 (NH), 1725 (sharp, C=N), and 1650 (C=O) cm^{-1} (Nujol) and analyzed correctly (C, H, N).

2-Amino-3,8-diazaspiro[4.5]dec-2-en-4-one (3g).—2-Amino-8-benzyl-3,8-diazaspiro[4.5]dec-2-en-4-one (**3d**, 5.20 g, 0.02 mole) was dissolved in ethylene glycol monomethyl ether (100 ml) and hydrogenated over 5% Pd–C (1.0 g) at 2 atm of pressure and 25°. Uptake of H_2 was complete after 0.25 hr but the reaction was continued for a further 0.5 hr. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure to *ca.* 25 ml. The product was obtained as a white crystalline precipitate, collected, washed (Et_2O, 25 ml), and dried; 3.30 g (97.2% yield); mp 313–317° (from EtOH); ν_{max} 3260, 3125, (NH), 1715 (sharp, C=N), and 1625 (C=O) cm^{-1}; analyzed correctly (C, H, N).

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N-Aminonormorphine[1a]

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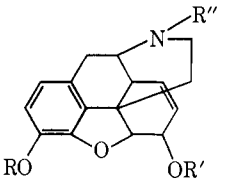
In the course of a study of centrally acting emetics, a sample of N-aminonormorphine (**1**) was required; a search of the literature did not reveal that this compound has been reported. Attempts to utilize a Raschig hydrazine synthesis[2] between chloramine and normorphine or norcodeine were unsuccessful. Schöpf and coworkers[3] had reduced N-nitrosopiperidine derivatives to N-amino systems with LAH, and Neurath and Duenger[4] had used this reagent to convert N-nitrosonor tobacco alkaloids to the hydrazine derivatives. However, treatment of N-nitrosonormorphine (**2**) and N-nitroso-O,O′-diacetylnormorphine (**3**) with LAH did not result in identifiable materials. Similar reduction of N-nitrosonorcodeine (**5**) gave a low yield of impure N-aminonorcodeine (**6**) which could be characterized



1, R = R′ = H; R″ = NH_2
2, R = R′ = H; R″ = NO
3, R = R′ = Ac; R″ = NO
4, R = R′ = Ac; R″ = NH_2
5, R = Me; R′ = H; R″ = NO
6, R = Me; R′ = H; R″ = NH_2
7, R = Me; R′ = H; R″ = N=$(CH_3)_2$

only as its acetone adduct **7**. Pure N-aminonorcodeine was prepared by a literature method:[5] Zn–AcOH reduction of N-nitrosonorcodeine (**5**). This method also permitted conversion of N-nitroso-O,O′-diacetylnormorphine (**3**) to its N-amino derivative (**4**). Zn–AcOH treatment of N-nitrosonormorphine (**2**) gave a complex mixture of unidentifiable products; however, acid-catalyzed hydrolysis of the ester links of N-amino-O,O′-diacetylnormorphine (**4**) permitted isolation of **1** in good yield. It appears that these N-aminomorphine derivatives undergo deep-seated decomposition in the presence of base.

Pharmacology.—N-Amino-O,O′-diacetylnormorphine (**4**), N-aminonormorphine hydrochloride (**1**), and N-aminonorcodeine hydrochloride (**6**) were dissolved in water and administered subcutaneously to Swiss–Webster male mice, weighing 17–20 or 30–35 g, and analgetic activity was tested by the hot plate method of Eddy and Leimbach.[6] Ten mice were used for each group and tested just prior to giving the drug and after 30 and/or 60 min. The reaction times of animals given the test drugs were compared with reaction times of mice given morphine sulfate, 7.5 mg/10 ml per kg.

Mice injected with **4** (28.4 mg/10 ml per kg, 60 mg/15 ml per kg, and 90 mg/20 ml per kg) showed prolongation of reaction times as compared with the control reaction times. The analgetic potency of **4** was estimated to be 0.1–0.067 times that of morphine. The mice injected with either **1** (15 mg/10 ml per kg, 30 mg/10 ml per kg, and 45 mg/10 ml per kg) or **6** (4.43 mg/1.65 ml per kg and 26.5 mg/10 ml per kg) showed no significant differences in reaction times between the control and the "after drug" periods.

Experimental Section[7]

N-Aminonorcodeine (6) was prepared in 40% yield by the method of von Braun,[5] mp 172.5–174°, lit.[5] mp 174°.

Acetone N-Aminonorcodeinyl Hydrazone (7).—Compound **6** (1.7 g, 0.0056 mole) was refluxed with 10 ml of Me_2CO for 0.25

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(7) Melting points were determined on a Thomas–Hoover apparatus in open capillaries and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

hr, then the hot solution was filtered. The filtrate was reduced to half its volume under reduced pressure, and on cooling a solid separated which was recrystallized (Me_2CO) to yield 0.55 g (29%) of light yellow cubes, mp 152–153°. *Anal.* ($C_{19}H_{24}N_2O_4$) C, H, N.

N-Amino-O,O′-diacetylnormorphine (4). To 1.9 g (0.005 mole) of N-nitroso-O,O′-diacetylnormorphine (**3**[8]) in 9 ml of glacial AcOH at 35° was added 9.5 g (0.145 g-atom) of Zn dust at such a rate that the temperature remained at 45–50°. H_2O (9.5 ml) was then added and the reaction mixture was maintained at 50° for 15 min. The mixture was filtered and the solid on the filter was washed with H_2O which was added to the filtrate. The solution was saturated with $NaHCO_3$ and extracted with $CHCl_3$, and the solvent was removed from the extract under reduced pressure at 40°. Recrystallization of the solid residue (EtOH) produced 0.85 g (46%) of white crystals: mp 171–172°; ir (KBr) 1738, 1764 cm^{-1} (C=O). *Anal.* ($C_{20}H_{22}N_2O_5$) C, H, N.

N-Aminonormorphine Hydrochloride (1). A solution of 0.2 g (0.0005 mole) of **4** in 10 ml of 10% HCl was maintained at 70–75° for 24 hr. The solvent was removed under reduced pressure, and the solid residue was recrystallized (absolute EtOH) to yield 0.12 g (70%) of light yellow crystals, mp 257–258° dec. *Anal.* ($C_{16}H_{19}ClN_2O_3$) C, H, Cl, N.

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Receptor Binding of the Analgetic Aryl Moiety. I. α-Prodine Analogs

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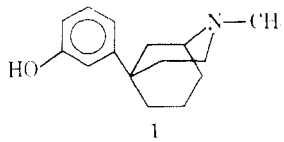
The study of strong analgetics has been the subject of several reviews.[1–5] Compounds of diverse chemical structure have been highly active in the laboratory and in the clinic. However, the mode of interaction of these analgetic drugs with their receptors is not very well understood.

In 1956, Beckett[6] postulated that the analgetic activity of a drug can be correlated with its absolute stereochemistry, and introduced a theoretical analgetic receptor site which has an anionic site, a cavity, and a flat portion allowing for van der Waal's forces binding the aromatic ring of the analgetic drug. Beckett's hypothesis fails to explain the analgetic activity of some compounds. For example, **1**[7] is as potent as



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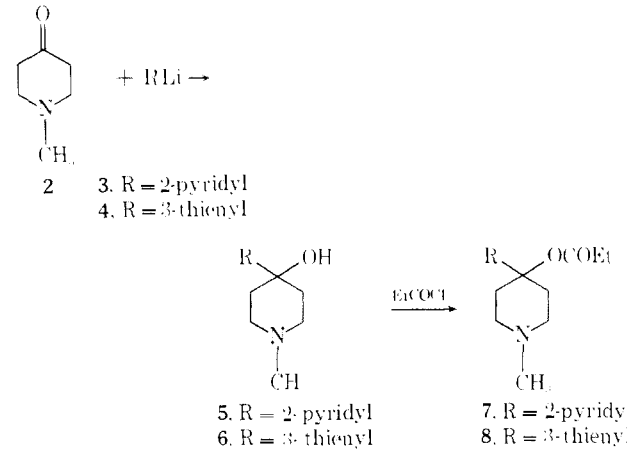
morphine, yet the aromatic group is fixed in the equatorial position while Beckett's hypothesis demands the aromatic group to be in the axial position.

Because of this and other exceptions,[8] Portoghese[8] recently postulated a new concept to explain the analgetic activity of conformationally unrelated analgetic drugs. The binding of the aromatic ring in analgetic molecules had been attributed to van der Waal's forces.[9] Since such forces are highly distance specific, Portoghese[8] assumed that hydrophobic attractive rather than van der Waal's forces are operative. However, it appears that the type of interaction between the aromatic group of the analgetic molecules and the postulated receptor has yet to be studied experimentally.

We would like to report the synthesis of two new compounds designed to study the type of interaction between the aromatic group of the analgetic molecules and the receptor site.

Synthetic Methods.—Analogs of the prodine analgetics were synthesized according to Scheme I. The

SCHEME I



Li salts of pyridine and thiophene were prepared by treatment of the corresponding bromo compounds with *n*-BuLi. Addition of these Li salts to **2** afforded the corresponding alcohols which were esterified by treatment with propionyl chloride.

Experimental Section[10]

1-Methyl-4-(2-pyridyl)-4-hydroxypiperidine (5).—To 0.1 mole of pyridyllithium in 150 ml of dry Et_2O was added dropwise at −70° with stirring under N_2 a solution of 0.1 mole of **2** in 100 ml of dry Et_2O over 10 min. The temperature was then allowed to rise to 0° and was maintained for 45 min. The reaction mixture was decomposed by pouring it onto ice–HCl (1:1). The Et_2O layer was separated and washed with dilute HCl and the acid solution was returned to the reaction mixture. This was made basic with cold 10% NaOH and extracted with Et_2O which was then dried (Na_2SO_4). Removal of Et_2O gave 10.5 g of **5** which distilled at 96° (0.1 mm). This fraction solidified on standing, mp 70–72°. For microanalysis **5** was converted to the corresponding methiodide salt by treating a small amount of **5** with excess MeI in MeOH at room temperature. The quaternary salt was recrystallized from MeOH–Et_2O, mp 250–251°. *Anal.* ($C_{12}H_{19}N_2OI \cdot H_2O$) C, H, N.

1-Methyl-4-(2-pyridyl)-4-propionoxypiperidine (7).—To 3.6 g of **5** in 50 ml of dry PhMe was added dropwise with stirring at room temperature a solution of 5.3 g of propionyl chloride in 20 ml of dry PhMe. The mixture was refluxed for 8 hr and allowed to stand overnight at room temperature. Removal of solvent *in vacuo* gave a white solid which was made alkaline with 5% $NaHCO_3$, extracted with Et_2O, and dried (Na_2SO_4). Removal of Et_2O *in vacuo* gave 4.6 g of **7**. For microanalysis, **7** was con-

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