title compound, bp 50–55 °C (0.05 mmHg). IR 1710 (C=O), 1610 (C=C); NMR 10.40 (1 H, s, CHO).

This compound was converted to 71 via method B, utilizing 1-phenyl-1,7-octadiyne (vide infra).

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Ligand–Receptor Interactions via Hydrogen-Bond Formation. Synthesis and Pharmacological Evaluation of Pyrrolo and Pyrido Analogues of the Cardiotonic Agent 7-Hydroxycyclindole

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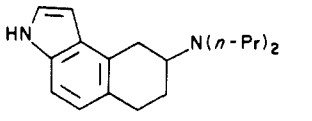
The syntheses of *N,N*-dimethyl-6,7,8,9-tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-amine (**8**), *N,N*-dimethyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-amine (**9a**), and the *N,N*,11-trimethyl analogue (**9b**) are described. The in vitro inotropic activity of these compounds, as well as the known cardiotonics amrinone and 7-hydroxycyclindole (**7**), was investigated. Compound **8**, a pyrrolo analogue of **7**, was devoid of inotropic activity, while the pyrido analogues **9** were equiactive to **7** and amrinone. These results suggest that the hydroxyl group of **7** functions as an H-bond acceptor, rather than a donor, and that on interaction of **7**, and the pyrido analogues **9**, with a common receptor, an orbital occupied by one of the oxygen lone pair electrons of **7** must assume the same orientation as the orbital occupied by the pyridine nitrogen lone pair.

Bioisosterism between a phenolic hydroxyl group and a pyrrolo ring has been demonstrated in two instances. Thus, the pyrrolo analogue **1** of the dopamine agonist **2** was shown also to be a potent dopaminergic agent,[1] and the pyrrolo analogue **3** of the antihypertensive α/β-adrenergic blocker labetalol (**4**) was shown also to have similar pharmacological properties.[2]



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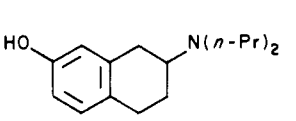

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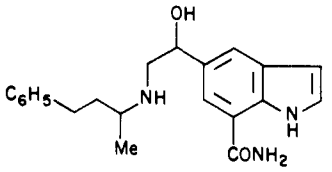

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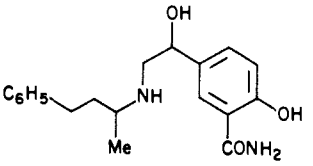

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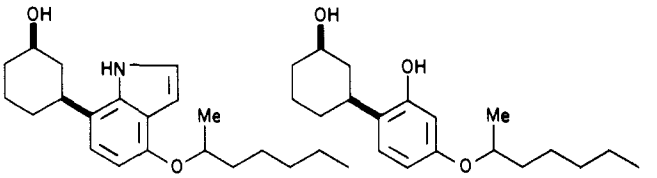
The observed bioisosterism was ascribed to "bioisofunctionality" between the phenolic hydroxyl and pyrrolo groups, in the sense that both of these groups can function as H-bond donors to a common acceptor nucleus on a receptor macromolecule with which the ligands interact.[1,2]

A third probe of bioisofunctionality between phenolic hydroxyl and pyrrolo groups was, however, negative; the pyrrolo analogue **5** of the analgesic **6** was found to be devoid of analgesic activity.[3] The absence of bioisofunctionality in this third instance may be due to one or more of several factors: (1) the phenolic hydroxyl of **6** may



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not function as an H-bond donor; (2) the receptor may not be able to accommodate the incremental volume requirements of the pyrrolo ring; (3) the unique directional vector of the H bond involving the pyrrolo ring may not coincide with the one (of the mulitple directional vectors that a freely rotating hydroxyl group can assume) that is required for interaction with a uniquely located acceptor nucleus on the receptor; and/or (4) a conformation of the flexible **6** required for interaction with its receptor may be unfavorably perturbed by the replacement of a phenolic hydroxyl by a pyrrolo group.

The following is an investigation, in a broader sense, of ligand–receptor interactions via hydrogen-bond formation. We chose the cardiotonic agent 7-hydroxycyclindole,[4,5] **7**, as our target. In this compound, the 7-hydroxyl group is necessary for activity, as the deshydroxy compound is inactive.[4]

We wished to investigate whether the hydroxyl group functions as an H-bond donor or acceptor. To this end, we have synthesized and evaluated the pyrrolo analogue **8**, the pyrido analogue **9a**, and analogue **9b** in which the indolic nitrogen is methylated. Pyrido analogues were selected for investigation, since the pyridine nitrogen atom can function as an acceptor nucleus in H-bond formation.

Chemistry. The reactions leading to the synthesis of the pyrrolo[3,2-*a*]carbazol-7-amine **8** are outlined in Scheme I. The α-arylation of cyclohexanone by very reactive aryl halides using enamines as intermediates was shown by Kuehne[6] to occur in high yields. The pyrrolidino

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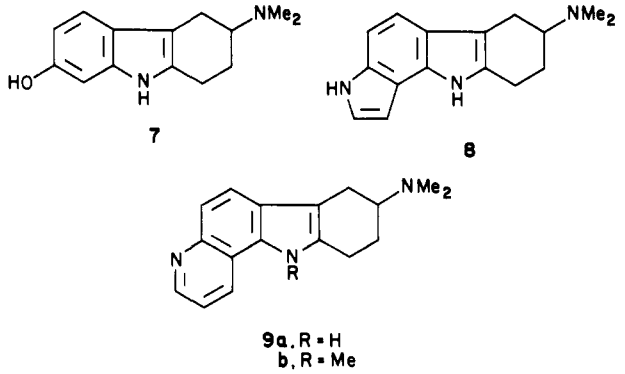


enamine **11** was prepared from the known *N*-(4-oxocyclohexyl)acetamide,[10] which is available from 4-acetamidophenol through catalytic reduction using Raney nickel at elevated temperature and pressure,[8-10] followed by a sodium dichromate oxidation in dilute sulfuric acid.[7] The α-arylation of the pyrrolidino enamine **11** with 2,4-dinitrochlorobenzene afforded the key intermediate **12** in 70% yield. Reductive cyclization of this nitroarylketone by catalytic hydrogenation afforded in one step the 3,7-diaminotetrahydrocarbazole derivative **13**.

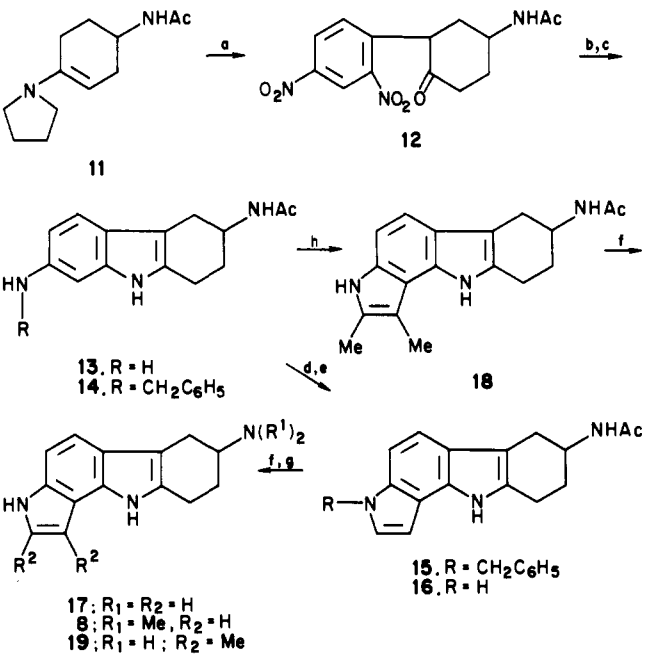
The desired pyrrolo[3,2-*a*]carbazole ring system was prepared by building the pyrrolo ring from the 7-amino function using the Bischler indole synthesis. Best yields were obtained when the secondary amine **14**, resulting from the reductive amination of benzaldehyde with the aminocarbazole **13**, was condensed with glycolaldehyde in ethylene glycol at reflux. Removal of the benzyl group by Birch reduction with sodium in liquid ammonia afforded the 1,2,3-unsubstituted pyrrolo[3,2-*a*]carbazole system **16**. Cleavage of the *N*-acetyl group with exces potassium hydroxide and hydrazine in ethylene glycol[11] at reflux afforded the primary amine **17**. Methylation with formaldehyde and sodium cyanoborohydride afforded the target compound **8**.

Ring closure to form the pyrrolocarbazole system can occur ortho or para to the indolic nitrogen in **14**. A single isomer was isolated from the reaction mixture. Due to the presence of the benzyl group in **15**, structure determination was not possible via NMR spectral analysis. The two benzenic protons in **16** and **17** have identical chemical shifts and appear together as a singlet. The NMR spectrum of the final compound **8** indicates that the cyclization took place at the ortho position. The two benzenic protons undergo ortho coupling and form a multiplet with the C_2-H of the indole.

Confirmation of this interpretation was made by preparation of the pyrrolocarbazole **18** via Bischler condensation of **13** with 3-hydroxybutanone. The two aromatic protons of **18** exhibit typical ortho coupling (J = 8 Hz). Upon cleavage of the acetyl group, these protons in compound **19** again have identical chemical shifts and appear as a singlet, as in **16** and **17**.

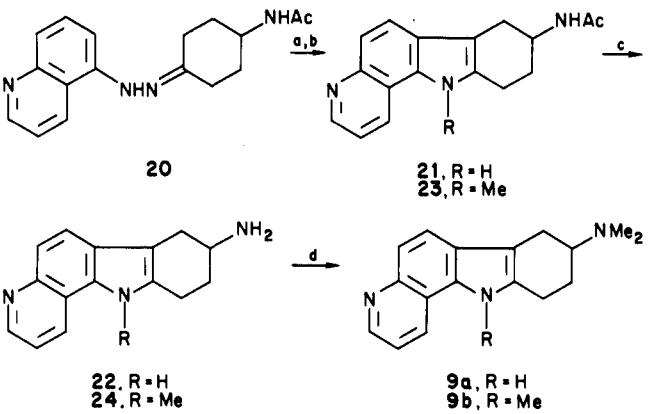
The related pyrido[3,2-*a*]carbazole system **9** was synthesized, as shown in Scheme II, by Fisher indole cyclization of the cyclohexanone hydrazone **20** resulting from the condensation of the known 5-hydrazinoquinoline[12] with

Scheme I[a]



[a] Key: (a) 2,4-$(NO_2)_2C_6H_3Cl$; (b) H_2, Pd/C, HOAc; (c) C_6H_5CHO, $NaBH_3CN$; (d) $HOCH_2CHO$; (e) Na/NH_3, (f) KOH/H_2NNH_2; (g) HCHO, $NaBH_3CN$; (h) $CH_3CH(OH)COCH_3$.

Scheme II[a]



[a] Key: (a) H_2SO_4/HOAc; (b) NaH/DMF, MeI; (c) 6 N HCl; (d) HCOOH, HCHO.

Table I. Positive Inotropic Activity in Vitro on Cat Papillary Muscle

compd	% increase over base-line contractility at 1×10^{-4} M
7	50
8	15
9a	80
9b	69
amrinone	50

the above-mentioned *N*-(4-oxocyclohexyl)acetamide.[10] The 5-hydrazinoquinoline was prepared from 5-nitroquinoline via sodium borohydride–stannous chloride reduction[13] to 5-aminoquinoline,[14] and diazotization using sodium nitrite followed by reduction of the diazotized aminoquinoline. Cyclization was performed in acetic acid in the presence of sulfuric acid to give the pyrdiocarbazole intermediate **21**. Hydrolysis of the acetamide moiety with 6 N hydro-

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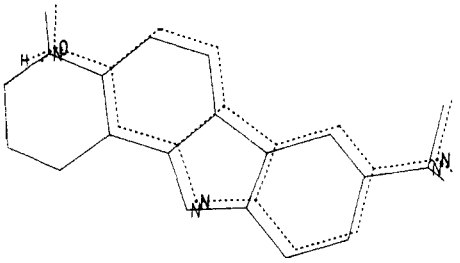


Figure 1. Superpositioning of 7 (dashed lines) and **9a** (solid lines) with an indication of the orbitals occupied by the lone pair electrons on the pyridine nitrogen and the oxygen atom. All hydrogen atoms are deleted except for that of the hydroxyl group.

chloric acid at reflux temperature afforded the amino derivative **22**. Methylation under Eschweiler–Clarke conditions gave the dimethylamino derivative **9a**.

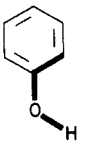
Alkylation of the indolic nitrogen was achieved by reacting the acetamido intermediate **21** with methyl iodide in the presence of sodium hydride in dimethylformamide. Hydrolysis of the *N*-acetyl product **23** and Eschweiler–Clarke methylation of the resulting amine **24** yielded the tertiary amine **9b**.

Results and Discussion

Compounds **7–9** and the clinically active cardiotonic agent amrinone[15] were evaluated for positive inotropic activity in isolated cat ventricular papillary muscle, and the results are shown in Table I. Both amrinone and 7-hydroxycyclindole, **7**, increased contractility by ~50% at 1×10^{-4} M, while the pyrido analogues **9a** and **9b** demonstrated a similar or greater level of inotropic activity. In contrast, the pyrrolo analogue **8** produced only a weak inotropic response and was considered inactive in this test. The lack of activity in the pyrrolo analogue **8** suggests that the phenolic hydroxyl group of 7-hydroxycyclindole (**7**) does not function as an H-bond donor, as do the phenolic hydroxyl groups in **2** and **4**. A hydroxyl group can function both as an H-bond donor or acceptor, and the activity observed with the pyrido analogue **9a**, which can function only an an H-bond acceptor, suggests that in this instance, the oxygen atom of the hydroxyl group of **7** may be functioning as an acceptor nucleus. The implication is that the orbital occupied by the pyrido nitrogen lone pair electrons in **9a** and one of the orbitals occupied by an oxygen lone pair in **7** must nearly coincide when the molecules are superimposed if they are involved in H-bond formation with the same donor group on the "receptor" with which they interact to produce their like biological effects. Figure 1 shows a superpositioning of **7** and **9a**, which is consistent with the above requirement.

In **9a**, the pyrido group is the equivalent of the rigid conformer of the hydroxyl group in **7**, in that the orbital occupied by the nitrogen lone pair electrons has a unique directional vector. In Figure 1, a unique conformation of the hydroxyl group of **7** is defined; it requires that the O–H bond in **7** must be almost perpendicular to the plane of the benzene ring.

We have examined the preferred conformation of the phenolic hydroxyl group by semiempirical molecular orbital calculations; by use of CNDO/2 (complete neglect of differential overlap) and PCILO (perturbative configuration interaction with localized orbitals) methods with phenol, the C–C–O–H torsion angle shaded in structure **10** was scanned by rotating through 360° using 10° increments.[16] The CNDO/2 method showed minima at 0°



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and 180° that were 2.8 kcal/mol below the maxima at 90° and 270°; the PCILO method showed the same minima, with maxima at 110° and 250° that were 1.3 kcal/mol above the minima. Thus, the O–H bond of a phenolic hydroxyl group shows a preference for being in the plane of the benzene ring; the destabilization of 1.3–2.8 kcal/mol in the conformation shown in Figure 1 could readily be compensated for through the formation of an H bond (at least 3 kcal/mol) with a donor nucleus on the receptor.

The *N*-methylpyrido analogue **9b** was found to have inotropic activity about equal to that of **9a**, suggesting that the indolic NH of **9a** does not participate in binding to its "receptor" via H-bond formation.

The nature of the "receptor" with which 7-hydroxycyclindole (**7**), **9a**, and **9b** interact to elicit inotropic activity is uncertain. It has been reported[4] that the in vitro inotropic activity of **7** was abolished by reserpine pretreatment and that in the anesthetized dog, the positive inotropic activity of **7** was blocked by propranolol, suggesting that the inotropic activity was consequent to the release of norepinephrine from adrenergic nerve endings. Thus, a candidate "receptor" could be the uptake mechanism by which these compounds gain access to neuronal stores of norepinephrine.

The results of the present investigation and those obtained previously[1-3] show that the study of pyrrolo and pyrido analogues of drugs containing a phenolic hydroxyl group essential for the manifestation of their pharmacological activities can provide valuable information about the mode of interaction of the drug with its "receptor", as well as information about topological features of the receptor itself.

Experimental Section

Biological Methodology. The potential for positive inotropic activity was examined in isolated right ventricular papillary muscles obtained from cat hearts. The preparations were suspended in tissue baths containing Tyrode's solution (Ca^{2+}, 2.4 mM) at 36 °C bubbled with 95:5 O_2–CO_2. The muscles were stimulated to contract at a rate of 0.5 Hz using rectangular pulses 2–4 ms in width at 10% above threshold voltage via platinum point electrodes incorporated into the tissue holder. The other end of the muscle was attached to a force displacement transducer (Gould UC-2) for measurement and recording of contractility on a Beckman R511A polygraph. The muscles were gradually stretched until optimum twitch tension was obtained, and then they were allowed to equilibrate for at least 1 h. Test compounds were added to a final concentration of 1×10^{-4} M, and percent increase over base-line contractility was measured. The activity of each compound was assessed in at least one preparation obtained from each of two to five different animals.

Chemistry. Melting points, determined in open capillary tubes on a Thomas-Hoover apparatus, are uncorrected. IR spectra were taken on a Perkin-Elmer 225 spectrophotometer. ^1H NMR spectra were determined in the indicated solvent on a Varian CFT-20 instrument with tetramethylsilane as internal standard. Chemical shifts are given in δ units, and coupling constants are in Hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, muliplet. Mass spectra were obtained on an LKB-9000 S spectrometer and ultraviolet

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(16) Calculations were performed on a VAX 11/780 using the CHEMLAB program package supplied by Molecular Design Limited. The SCAN command was used to calculate the energy by CNDO/2 and PCILO methods.

spectra on a Zeiss DMR-21 spectrophotometer. CHN were measured on a perkin-Elmer 240 Analyzer. Silica gel 60 F-254 (Merck) was used for thin-layer chromatography (TLC).

4-Acetamido-1-pyrrolidinocyclohexene (11). To a stirred suspension of 4-acetamidocyclohexanone[10] (5.7 g, 0.0368 mol) in toluene (30 mL) was added pyrrolidine (3.7 mL, 0.0442 mol). This mixture was refluxed for 3 h under nitrogen using a Dean-Stark water separator. On cooling, a solid crystallized out. The beige crystals were filtered, washed with a little toluene, and dried under high vacuum at 78 °C for 2 h to give 11 (6.54 g, 85%): mp 150–158 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3 H), 1.4–2.6 (m, 10 H), 2.95 (br, 4 H), 4.0 (br, 1 H), 5.55 (br, 1 H); MS, *m/e* 208 M^+.

The 4-acetamidocyclohexanone[10] was prepared as follows: A solution of *p*-acetamidophenol (200 g, 1.32 mol) in ethanol (2.0 L) was hydrogenated over Raney nickel (150 mL) at 180 °C at an initial pressure of 1750 psi for 3 h. Filtration of the reaction mixture and distillation of the solvent gave 205.2 g of a colorless oil, which crystallized slowly on standing. No attempt was made to separate the known cis and trans isomers of this compound.[8-10] The product was homogeneous on TLC (10% methanol–chloroform) and was used as such.

A solution of sodium dichromate dihydrate (24 g, 0.08 mol) and concentrated sulfuric acid (27 mL) in water (100 mL) was added dropwise over a period of 15–20 min to a mechanically stirred solution of the cyclohexanol derivative described above (31.4 g, 0.2 mol) in water (40 mL). The temperature rose gradually to 85–90 °C; at this point, a water bath was introduced to maintain the temperature at 65–75 °C for the rest of the addition. After the addition, the mixture was stirred for an additional 20 min. The solution was saturated with sodium chloride, and the product was extracted with chloroform (4×). The organic solution was dried ($MgSO_4$) and evaporated in vacuo to give 4-acetamidocyclohexanone (22.5 g, 72%), mp 134–135 °C (lit.[10] mp 135–136 °C).

4-Acetamido-2-(2,4-dinitrophenyl)cyclohexanone (12). To a cooled solution of 1-chloro-2,4-dinitrobenzene (111.5 g, 0.546 mol) and triethylamine (79.27 mL, 0.570 mol) in dry methylene chloride (355 mL) under nitrogen was added a solution of the enamine 11 (113.7 g, 0.546 mol) in methylene chloride (542 mL). After standing for 24 h at room temperature, the dark purple solution was evaporated in vacuo, and the residue was stirred in the presence of 3.5% HCl (1.4 L) for 24 h. The precipitated yellow solid was isolated by filtration, washed with water to neutrality, and dried to give the crude compound (163.3 g). This was triturated in ether and filtered to remove a soluble impurity. The yellow solid was dried to give 12 (144 g, 82%), which was homogeneous on TLC (10% methanol–chloroform) and was used as such in the next step. For analysis, a sample was recrystallized from methanol: mp 196–197 °C; ^{1}H NMR (Me_2SO) δ 1.8 (s, 3 H), 1.8–3.0 (m, 6 H), 4.23 (br s, 1 H), 4.5 (m, 1 H), 8.2 (m, 3 H), 7.95 (d, 1 H, J = 7.5 Hz). Anal. ($C_{14}H_{15}N_3O_6$) C, H, N.

***N*-(7-Amino-1,2,3,4-tetrahydro-9*H*-carbazol-3-yl)acetamide (13) 2,3-Dihydroxybutanedioate.** A solution of the dinitro derivative 12 (40 g, 0.125 mol) in glacial acetic acid (900 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (4.0 g) using a Burell shaker. After 2 h, 16.07 L of hydrogen was absorbed, and hydrogenation was continued for an additional hour (total hydrogen absorption, 16.58 L). Filtration of the catalyst and evaporation of solvent gave a gum, which was dried under high vacuum for 2 days. This gum (51 g) was filtered on silica gel (900 g) using 20% methanol in chloroform as eluant to give a tan gum (35.0 g), which was triturated in ether (300 mL) to give 13 (28.05 g, 92.5%) as a light green solid after filtration. A sample (1.3 g) was dissolved in methanol and treated with tartaric acid (617 mg) in methanol. Ether was added to this solution to precipitate 1.5 g of the salt, which was recrystallized from methanol and then from water: ^{1}H NMR (Me_2SO) δ 1.80 (s, 3 H), 1.85 (m, 2 H), 2.65 (m, 4 H), 3.95 (br s, 1 H), 4.23 (s, 1 H), 5.29 (br, 4 H), 6.28 (d, 1 H, J = 8 Hz), 6.45 (m, 1 H), 6.95 (d, 1 H, J = 8 Hz), 7.82 (d, 1 H, J = 8 Hz) 10.0 (br s, 1 H). Anal. ($C_{14}H_{17}N_3O \cdot 0.5C_4H_6O_6$) H, N; C: calcd, 60.36; found, 59.49.

***N*-[7-[(Phenylmethyl)amino]-1,2,3,4-tetrahydro-9*H*-carbazol-3-yl]acetamide (14).** To a stirred solution of 13 (15.7 g, 0.0646 mol) in ethanol (180 mL) and water (150 mL) was added acetic acid (54 mL), sodium acetate trihydrate (17.42 g, 0.127 mol), and benzaldehyde (7.4 mL, 0.07 mol). This was stirred for 10 min at room temperature. Then sodium cyanoborohydride (6.45 g, 0.098 mol) was added gradually over a period of 15–20 min. After the addition, the resulting mixture was stirred for 15 min at room temperature and then poured into 1 N NaOH solution (1.5 L). Ice was added, and the precipitated product was isolated by filtration and dried to give 14 (12.7 g, 59%). A sample was recrystallized from benzene: mp 178–180 °C; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.0 (m, 2 H), 2.3–3.15 (m, 4 H), 3.95 (br, 1 H), 4.31 (s, 2 H), 5.57 (d, 1 H, J = 8 Hz), 6.5–7.5 (m, 9 H). Anal. ($C_{21}H_{23}N_3O$) C, H, N.

***N*-[3-(Phenylmethyl)-6,7,8,9-tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-yl]acetamide (15).** Glycolaldehyde (2.0 g, 0.0334 mol) was added to a solution of the 7-benzylamino derivative 14 (10.0 g, 0.03 mol) in ethylene glycol (350 mL). The system was flushed with nitrogen, the house vacuum applied, and the solution refluxed for 30 min. The solution was cooled, and additional glycolaldehyde (500 mg) was added. The solution was refluxed for an additional 15 min under house vacuum. After cooling, the solution was poured into water (1 L), and the product was extracted with ethyl acetate (3×). The organic solution was washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent gave the crude title compound as a foam (10.64 g), which was used as such in the next step. For characterization, a sample (2.41 g) was chromatographed on silica gel (170 g) using 3% methanol in chloroform as eluant to give 15 (0.762 g, 31%) as a tan solid, which was crystallized from benzene: mp 220–222 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.05 (m, 2 H), 2.8 (m, 4 H), 4.45 (br, 1 H), 5.35 (s, 2 H), 6.57 (d, 1 H, J = 4 Hz), 6.9–7.4 (m, 8 H), 8.07 (br s, 1 H). Anal. ($C_{23}H_{23}N_3O$) C, H, N.

***N*-(6,7,8,9-Tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-yl)acetamide (16).** A solution of the crude *N*-benzyl derivative 15 (15.6 g, 0.0437 mol) in freshly distilled THF (95 mL) was added to a stirred solution of sodium (5.78 g, 0.25 mol) in liquid ammonia (400 mL). The resulting solution was stirred at −33 °C for 5 min, and then solid ammonium chloride was added portionwise until discoloration of the solution occurred. The ammonia was then allowed to evaporate overnight. The residue was partitioned between water and ethyl acetate. The aqueous layer was washed with ethyl acetate (2×), and the combined organic solution was washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent gave a foam (6.15 g), which was chromatographed on silica gel (500 g) using first 5% and then 8% methanol in chloroform as eluant to give 16 (3.76 g, 32%) as a tan solid. For analysis, a sample was recrystallized from methanol: mp 290–295 °C dec; ^{1}H NMR (Me_2SO) δ 1.82 (s, 3 H), 1.85 (m, 2 H), 2.8 (m, 4 H), 4.0 (br, 1 H), 6.5 (br s, 1 H), 7.0 (s, 2 H), 7.1 (br s, 1 H), 7.85 (d, 1 H, J = 8 Hz), 10.75 (br, 2 H). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

6,7,8,9-Tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-amine (17). A solution of the acetamido derivative 16 (4.0 g, 0.015 mol), potassium hydroxide (28 g, 0.5 mol), and 99% hydrazine hydrate (14.45 mL) in ethylene glycol (150 mL) was refluxed for 5 h under nitrogen. After cooling, the solution was poured into water and ice (1.2 L) to precipitate the product; it was isolated by filtration and dried to give 2.26 g of the title compound. The filtrate was extracted with chloroform (3×). The organic layer was washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent gave 0.44 g more of the title compound 17 (total 2.70 g, 80%), which was homogeneous on TLC (10% triethylamine–methanol) and was used as such in the next step. For analysis, a sample was recrystallized from methanol: mp 275–279 °C; ^{1}H NMR (Me_2SO) δ 1.90 (m, 2 H), 2.2–3.3 (m, 5 H), 6.49 (br s, 1 H), 6.95 (s, 2 H), 7.10 (br s, 1 H), 10.13 (s, 1 H), 10.31 (s, 1 H). Anal. ($C_{14}H_{15}N_3$) C, H, N.

***N*,*N*-Dimethyl-6,7,8,9-tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-amine (8) 2,3-Dihydroxybutanedioate.** To a stirred solution of 17 (2.96 g, 0.0132 mol) in acetonitrile (180 mL) was added a 37% aqueous solution of formaldehyde (4.75 mL) and sodium cyanoborohydride (1.36 g, 0.0204 mol). This was stirred at room temperature for 2 h, and the initial suspension gradually became a solution. The solution was poured into 2 N KOH solution (1 L), and the product was extracted with chloroform (3×) and dried ($MgSO_4$). Evaporation of solvent gave 8 (2.74 g), which was homogeneous on TLC (10% triethylamine–methanol). This was triturated in ether and filtered. The solid was dissolved in hot acetone, and then a solution of tartaric acid

in methanol was added to precipitate the tartrate salt (1.68 g, 32%): mp >350 °C; ^{1}H NMR (Me_2SO) δ 2.65 (s, 6 H), 3.94 (s, 1 H), 5.46 (s, 1 H), 6.52 (d, 1 H, J = 3), 6.55 (br s, 4 H), 7.11 (m, 3 H), 10.8 (br, 1 H). Anal. ($C_{20}H_{25}N_3O_6$) C, H; N: calcd, 10.42; found, 10.96.

***N*-(1,2-Dimethyl-6,7,8,9-tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-yl)acetamide (18).** Aqueous (85%) 3-hydroxybutanone (11.75 mL, 0.132 mol) was added to a solution of the free base of the amino derivative **13** (25 g, 0.103 mol) in ethylene glycol (375 mL). The system was flushed with nitrogen, the house vacuum applied, and the solution refluxed for 15 min. After cooling, the solution was poured into water (1 L), and the product was extracted with ethyl acetate (3×). The organic solution was washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent gave 26.2 g of the crude title compound. Chromatography on silica gel (750 g) using 1:9 (MeOH–$CHCl_3$) as eluant gave **18** (13 g, 43%) as a yellow solid: mp 287–292 °C; ^{1}H NMR (Me_2SO) δ 1.80 (s, 3 H), 2.45 (s, 6 H), 2.75 (m, 4 H), 3.95 (br, 1 H), 6.9 (d, 1 H, J = 8 Hz), 7.42 (d, 1 H, J = 8 Hz), 7.85 (d, 1 H, J = 8 Hz), 10.45 (s, 1 H), 11.15 (s, 1 H); MS shows molecular ion at m/e 295.

1,2-Dimethyl-6,7,8,9-tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-amine (19). A solution of the acetamido derivative **18** (8.06 g, 0.027 mol), potassium hydroxide (50.8 g, 0.907 mol), and 99% hydrazine hydrate (26 mL) in ethylene glycol (275 mL) was refluxed for 4 h under nitrogen. After cooling, the solution was poured into water and ice (2 L), and the precipitated product was filtered and dried to give **19** (4.4 g). The filtrate was extracted with chloroform (3×). The organic layer was washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent gave 690 mg more of **19** (total 5.09 g, 75%), which was homogeneous on TLC (10% Et_3N–methanol). The compound was crystallized from methanol: mp 252–256 °C; ^{1}H NMR (Me_2SO) δ 1.85 (m, 2 H), 2.25 (s, 3 H), 2.37 (s, 3 H), 2.75 (m, 4 H), 2.90 (m, 1 H), 6.83 (s, 2 H), 10.15 (s, 1 H), 10.31 (s, 1 H). Anal. ($C_{16}H_{19}N_3$) C, H, N.

***N*-(7,8,9,10-Tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-yl)acetamide (21).** A solution of 5-hydrazinoquinoline[12] (11.75 g, 0.0738 mol) and 4-acetamidocyclohexanone[10] (prepared as described above, 12.19 g, 0.081 mol) in ethanol (120 mL) was refluxed for 20 min. After cooling, the solid was filtered, washed with water, and dried to give the 5-quinolylhydrazone **20** (19.5 g, 89%, mp 212–214 °C) as a yellow solid, which was homogeneous on TLC (15% methanol–chloroform). A suspension of **20** (17.58 g, 0.059 mol) in acetic acid (93 mL) containing concentrated sulfuric acid (5.85 mL) was heated at 100 °C for 40 min. The mixture was cooled, and the solution was decanted from the formed gummy solid. This solid was dissolved in water, and the solution was basified with 50% NaOH solution to precipitate a solid that was isolated by filtration and dried to give **21** (13.09 g, 61%), which was homogeneous on TLC (15% methanol–chloroform) and was used as such in the next step. A sample was recrystallized from ethanol and hexane: mp 285–290 °C; ^{1}H NMR (Me_2SO) δ 1.9 (s, 3 H), 2.0 (m, 2 H), 3.0 (m, 4 H), 4.16 (br, 1 H), 7.8 (m, 4 H), 8.75 (m, 1 H), 8.8 (s, 1 H), 11.9 (s, 1 H). Anal. ($C_{17}H_{17}N_3O$) C, H, N.

The 5-hydrazinoquinoline[12] was prepared as follows: A solution of 5-nitroquinoline (35 g, 0.20 mol) and stannous chloride dihydrate (225 g, 0.998 mol) in ethanol (1.2 L) was heated at 60 °C for 1 h. Then sodium borohydride (3.75 g, 0.099 mol) was added, and the resulting mixture was stirred for 30 min at 60 °C. After cooling, the ethanol was evaporated in vacuo and the residue dissolved in water. The mixture was basified with 40% NaOH solution (cooling), and this mixture was extracted with ethyl acetate (3×). The organic solution was washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent gave 5-aminoquinoline[14] (25 g, 86%) as a yellow solid (mp 106–108 °C) that was pure enough to be used as such.

A solution of sodium nitrite (12.75 g, 0.184 mol) in water (56 mL) was added gradually to a stirred solution of the 5-aminoquinoline (25 g) in concentrated hydrochloric acid (210 mL) at 0 °C. After the addition, the resulting solution was stirred for 1 h at 0 °C. Maintaining the temperature below 10 °C, a solution of stannous chloride dihydrate (20.7 g, 0.0917 mol) in concentrated hydrochloric acid (24 mL) was added. The resulting mixture was allowed to stand at 7 °C for 18 h. The yellow stannic chloride complex was filtered, and the solid was poured into hot water (1 L). Hydrogen sulfide was bubbled into that solution for 1 h. The resulting mixture was filtered, and the filtrate was basified with 50% NaOH solution to precipitate a solid, which was filtered and dried to give 5-hydrazinoquinoline (11.75 g, 43%). A sample was recrystallized from benzene; mp 160–165 °C (lit.[12] mp 163 °C).

7,8,9,10-Tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-amine (22) Dihydrochloride. A mixture of the acetamido derivative **21** (6.4 g, 0.023 mol) in concentrated hydrochloric acid (100 mL) and water (100 mL) was refluxed for 22 h. After cooling, the solution was poured into 1 N NaOH solution (500 mL), and the precipitated solid was filtered, washed with water, and dried to give **22** (3.84 g). This was dissolved in ethanol and treated with an excess of ethereal hydrogen chloride solution to precipitate the hydrochloride salt, which was crystallized from methanol and water to give **22**·2HCl (2.9 g, 40%): mp >350 °C; ^{1}H NMR (D_2O) δ 1.5–3.2 (m, 6 H), 3.5 (br, 1 H), 6.34 (d, 1 H, J = 9 Hz), 6.90 (d, 1 H, J = 9 Hz), 7.20 (m, 1 H), 7.64 (d, 1 H, J = 8 Hz), 8.20 (d, 1 H, J = 8 Hz).

***N*,*N*-Dimethyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-amine (9a) Dihydrochloride.** To the amino derivative **22** (3.0 g, 0.0126 mol) in a flask cooled in an ice bath was added 98–100% formic acid (4.5 mL) and 37% aqueous formaldehyde solution (7.2 mL). The resulting solution was then stirred at 80 °C (oil bath) for 20 h. After cooling, the solution was poured into 1 N NaOH solution (300 mL). The precipitated solid was filtered, washed with water, and dried to give 2.49 g of the free base of the title compound as a beige solid. This was dissolved in methanol and treated with an excess of ethereal hydrogen chloride to precipitate **9a**·2HCl (2.73 g), which was crystallized from acetone and water to give the title compound (1.4 g, 33%): mp >350 °C; ^{1}H NMR (D_2O) δ 3.09 (s, 6 H), 3.60 (br, 1 H), 6.85 (d, 1 H, J = 8 Hz), 7.35 (m, 1 H), 2.95 (m, 1 H), 8.35 (m, 1 H); MS, m/e 265 (M^+). Anal. ($C_{17}H_{21}Cl_2N_3$) H, N; C: calcd, 60.36; found, 59.22.

***N*-(11-Methyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-yl)acetamide (23).** Sodium hydride (1.8 g of a 50% dispersion in oil, 0.038 mol) was added to a stirred solution of the pyridotetrahydrocarbazole derivative **21** (9.0 g, 0.032 mol) in DMF (180 mL). The resulting solution was stirred for 15 min at room temperature, and methyl iodide (2.7 mL, 0.043 mol) was added. The resulting solution was stirred for 15 min at room temperature, then poured into water and ice. The precipitated solid was filtered and dried to give **23** (9.32 g, 97%), which was homogeneous on TLC (10% methanol–chloroform) and was used as such in the next step. For analysis, a sample was recrystallized twice from acetone: mp 227–228 °C; ^{1}H NMR (Me_2SO) δ 1.83 (s, 3 H), 2.0 (m, 2 H), 2.9 (m, 4 H), 4.03 (s, 3 H), 4.1 (br, 1 H), 8.0 (m, 5 H), 7.95 (s, 1 H). Anal. ($C_{18}H_{19}N_3O$) C, H, N.

11-Methyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-amine (24) Dihydrochloride. A mixture of the acetamido derivative **23** (9.0 g, 0.032 mol) in 6 N hydrochloric acid (500 mL) was refluxed for 7 h. On cooling, a solid slowly crystallized out. This was filtered and dried to give **24**·2HCl (8.76 g, 90%): mp >360 °C; ^{1}H NMR (D_2O) δ 2.3 (m, 2 H), 3.0 (m, 4 H), 3.82 (s, 3 H), 7.20 (d, 1 H, J = 8 Hz), 7.8 (m, 2 H), 8.66 (d, 1 H, J = 5 Hz), 9.10 (d, 1 H, J = 8 Hz); MS, m/e 251 (M^+).

***N*,*N*,11-Trimethyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-amine (9b) Dihydrochloride.** To the amino derivative **24** (3.2 g, 0.012 mol) in a flask cooled in an ice bath was added 98–100% formic acid (4.48 mL) and 37% aqueous formaldehyde solution (7.63 mL). The resulting solution was then stirred at 80 °C (oil bath) for 2 h. After cooling, the solution was poured into 2 N NaOH (100 mL). The product was extracted with methylene chloride (3×), washed with water (1×), and dried ($MgSO_4$). Evaporation of solvent gave the free base of the title compound (2.8 g), which was dissolved in chloroform and treated with an excess of ethereal hydrogen chloride to precipitate the salt (3.1 g). This was crystallized from methanol to give **9b**·2HCl (2.2 g, 52%): mp >360 °C; ^{1}H NMR (D_2O) δ 3.0 (s, 6 H), 3.79 (s, 3 H), 7.40 (d, 1 H, J = 8 Hz), 7.90 (m, 2 H), 8.65 (d, 1 H, J = 5 Hz), 9.06 (d, 1 H, J = 8 Hz); MS, m/e 279 (M^+). Anal. ($C_{18}H_{25}Cl_2N_3O$) N. Calcd C, 58.37; H, 6.80. Found: C, 57.86; H, 6.35.

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Registry No. **7**, 32212-00-3; **8**, 102745-84-6; **8**·tartrate, 102745-85-7; **9a**, 102745-91-5; **9a**·2HCl, 102745-92-6; **9b**, 102745-95-9; **9b**·2HCl, 102745-96-0; **11**, 102745-76-6; **12**, 102745-77-7; **12**

(pyrrolidinium chloride), 102779-91-9; **13**, 102745-78-8; **13**·$^1/_2$tartrate, 102745-79-9; **14**, 102745-80-2; **15**, 102745-81-3; **16**, 102745-82-4; **17**, 102745-83-5; **18**, 102745-86-8; **19**, 102779-92-0; **20**, 102745-87-9; **21**, 102745-88-0; **22**, 102745-89-1; **22**·2HCl, 102745-90-4; **23**, 102745-93-7; **24**·2HCl, 102745-94-8; 4-acetamidocyclohexanone, 27514-08-5; *p*-acetamidophenol, 103-90-2; *p*-acetamidocyclohexanol, 23363-88-4; 1-chloro-2,4-dinitrobenzene, 97-00-7; 3-hydroxybutanone, 513-86-0; 5-hydrazinoquinoline, 15793-79-0; 5-nitroquinoline, 607-34-1; 5-aminoquinoline, 611-34-7; amrinone, 60719-84-8.

Synthesis and Analgesic Evaluation of 4-(2-Heptyloxy)-7-[(*Z*)-(3-hydroxycyclohexyl)]indole: A Caveat on Indole–Phenol Bioisosterism

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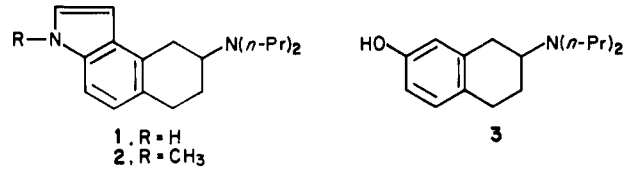
The synthesis of 4-(2-heptyloxy)-7-[(*Z*)-(3-hydroxycyclohexyl)]indole (**7**) is described. Compound **7** was tested for analgesic properties in the phenylbenzoquinone writhing test and was found to be essentially devoid of activity. In contrast, *cis*-3-[4-(2-heptyloxy)-2-hydroxyphenyl]cyclohexanol (**8**), the analogue in which the pyrrolo ring is replaced by a hydroxyl group, had an ED_{50} of 8.3 mg/kg, sc, in the same model. The absence of bioisosterism between the pyrrolo ring and the phenolic hydroxyl group, in this instance, is discussed in terms of the circumstances that control the manifestation of bioisofunctionality between a pyrrolo ring and a phenolic hydroxyl group, which functions as a hydrogen-bond donor.

We have demonstrated, in two instances,[1,2] that a phenolic hydroxyl group in a drug molecule can be replaced by a pyrrolo grouping with retention of similar biological activity. Thus, the benz[*e*]indole **1**,[1] the pyrrolo analogue of the dopaminergic agonist **3**,[3-5] was found also to be a potent dopaminergic agonist,[1] while **4**, the pyrrolo analogue of labetalol, **6**,[6] was shown also to block α- and β-adrenergic receptors.[2]



1, R = H
2, R = CH_3

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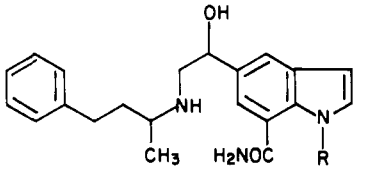

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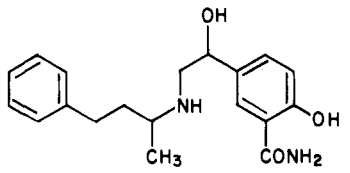
5, R = CH_3



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The biological activities of these pyrrolo analogues were ascribed to the capacity of the pyrrolo NH groups to function as hydrogen-bond donors to acceptor nuclei on the receptor macromolecules with which they interact, and this conclusion was supported by the lack of activity of the *N*-methylpyrroles **2** and **5** as dopaminergic agonist[1] and as adrenergic blocker,[2] respectively.

Having explored the scope of this indole–phenol equivalency in other drug molecules, we now report the synthesis and a comparison of the analgesic activities of the indole **7** with the phenol **8**.[7]

Compound **8**, an analgesic, is a member of a series of simplified cannabinoids lacking the dihydropyran ring, among which **9** (CP-47497) has been extensively studied.[8,9] Compound **8** also bears the 2-heptyloxy side chain, which has been shown to be compatible with high analgesic activity in the cannabinoid-related compound **10**,[10] and a phenolic hydroxyl group, which has been shown to be essential for activity in cannabinoid-derived analgesics. For example, phenol **11** has been shown to be up to 436 times more potent than **12** as an analgesic.[10]

These structural features of compound **8**, viz, the heptyloxy side chain and the phenolic hydroxyl group, as well as the alcohol and the aryl ring, are through to be necessary for the binding of cannabinoid-derived analgesics with their receptor.[11] Compound **8** thus provides an appropriate model for testing the scope and generality of indole–phenol bioequivalency.

Chemistry. It was anticipated that the 1,3-relationship between the hydroxyl group and the indolyl moiety in **7** could be secured by a Michael addition to cyclohexenone

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