Synthesis and Antiinflammatory Activity of Some 2-Aryl-6-benzoxazoleacetic Acid Derivatives

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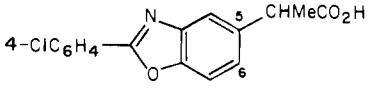
Various approaches to the synthesis of 2-aryl-6-substituted benzoxazoles are described. The products, which included the 6-methyl derivative **4a**, ethylamines **10** and **19**, ethanols **12** and **14**, the acetic and α-methylacetic acids **9** and **16a–f**, and the acetic ester **11**, were screened for antiinflammatory activity on the carrageenan-induced rat paw edema test. Some of the compounds possessed activity superior to that of phenylbutazone and of the same order as that of benoxaprofen.

Benoxaprofen, 2-(4-chlorophenyl)-α-methyl-5-benzoxazoleacetic acid (**1**),[1] is a potent new antiinflammatory agent which is currently undergoing clinical trials. This paper describes the preparation of the isomeric α-methyl-6-benzoxazoleacetic acid and some related compounds, together with their activity on the carrageenan rat paw edema assay. The syntheses and antiinflammatory activities of a number of other close analogues of benoxaprofen have been published previously.[1,2]



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Chemistry. The synthetic routes to the 2-aryl-6-substituted benzoxazole derivatives are illustrated in Schemes I–IV. Complete details are given in the Experimental Section and only points of particular interest will be discussed in this section.

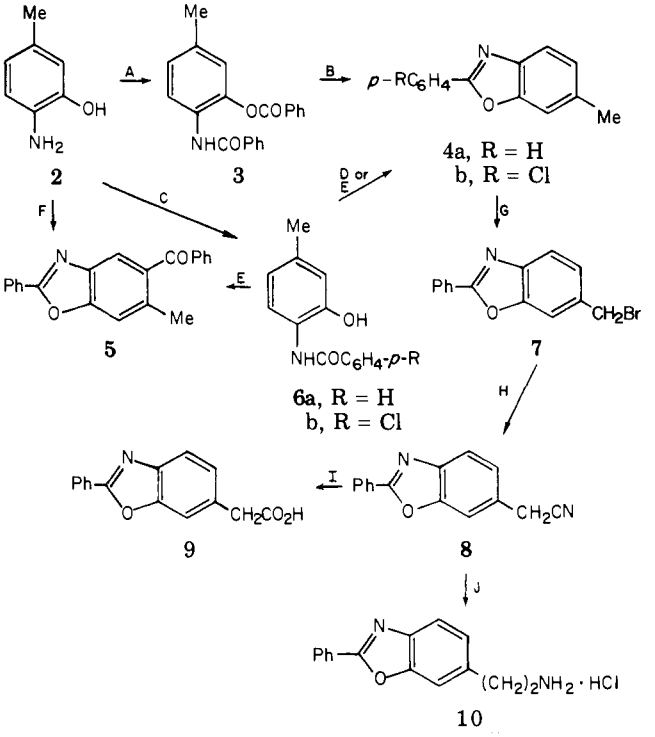
Schemes I and II show the methods which were used to prepare some of the 6-substituted benzoxazole derivatives from 6-amino-3-methylphenol (**2**). Reaction of this phenol with ethyl benzoate in hot polyphosphoric acid, a reaction which has been used previously to prepare 2-arylbenzoxazoles,[3] unexpectedly yielded the novel 6-methyl-2-phenyl-5-benzoxazolylphenylmethanone (**5**) in addition to the normal product **4a**. The same mixture of products was obtained when the *o*-amidophenol **6a** was heated in polyphosphoric acid.

Hydrolysis of the benzoxazole ester **13** with concentrated hydrochloric acid at different temperatures yielded different major products. At 100 °C, the main product was the α-methylbenzoxazoleacetic acid **16a** while at 160 °C the product was the *o*-aminophenol **17**.

More direct approaches to the synthesis of useful building blocks of the type **17** are summarized in Schemes III and IV, together with examples of the conversion of **17** into the 2-aryl-α-methylbenzoxazoleacetic acids **16b–f**. Displacement of the halogen of the *o*-halogenonitrobenzenes **22**, **23**, **29**, and **30** by various oxygen bases was unsuccessful. Decomposition problems possibly associated with the formation of a benzylic anion with **22** were not overcome with **23**, **29**, and **30** where formation of a benzylic anion would not be possible. Other investigations have previously reported obtaining mixtures and tars in similar displacement reactions with oxygen bases.[4] A successful direct preparation of **17** was achieved by the nucleophilic displacement of chlorine by the anion of diethyl methylmalonate from 5-chloro-2-nitroanisole (**31**) to give the *o*-methoxynitrobenzene **32a**. The latter was converted into **17** by the method outlined in Scheme IV.

Antiinflammatory Activity. The antiinflammatory activity of the compounds was assessed in a similar manner to that described previously[1] for the related 2-aryl-5-benzoxazoleacetic acids.

Scheme I. Synthetic Routes to 2-Phenyl-6-benzoxazoleacetic Acid (**9**) and the Corresponding Ethylamine **10**[a]



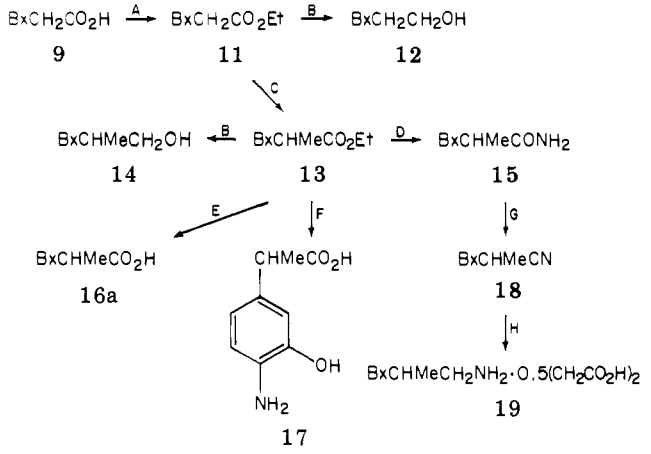
[a] Reagents/conditions for method A were PhCOCl + pyridine; B, 200–210 °C; C, *p*-RCOCl + pyridine; D, pyridine hydrochloride, 200 °C; E, polyphosphoric acid, 200–210 °C; F, $PhCO_2Et$ + polyphosphoric acid, 180–210 °C; G, *N*-bromosuccinimide; H, NaCN + DMAc; I, 50% H_2SO_4; J, H_2 + Raney Ni + EtOH + NH_3.

The compounds were tested initially on a carrageenan-induced rat paw edema test[1] similar to that described by Winter et al.[5] Subsequently, representative examples of the active acids were tested on a modified version[1] of the carrageenan test to establish the dose necessary to reduce the foot swelling by 30% (ED_{30}) 2.5 and 5.0 h after the injection of the irritant. When compared with similar data for phenylbutazone and benoxaprofen, the ED_{30} values gave a measure of the relative potency and duration of action of the compounds.

The activities of the compounds on the initial carrageenan test are summarized in Table I, together with those of hydrocortisone and phenylbutazone, which were tested concurrently. Data for benoxaprofen are also included for comparative purposes.

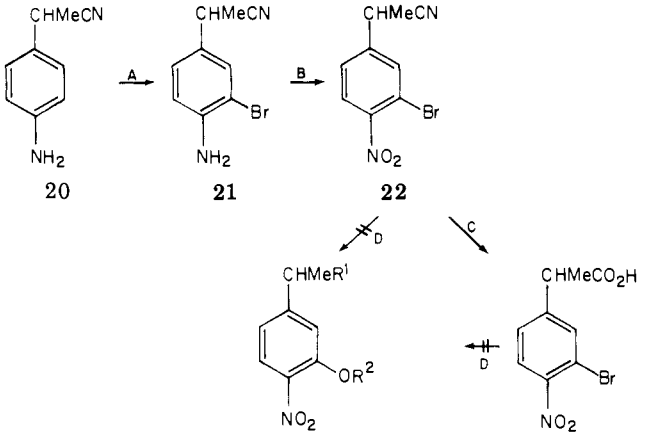
Compounds **9–12**, **14**, and **16a–f** were active and the 6-methyl derivative **4a** and the amine **19** were inactive. The activity of amine **10** in normal rats would appear to be due to adrenal stimulation since the compound was

Scheme II. Synthetic Routes to 2-Phenyl-α-methyl-6-benzoxazoleacetic Acid (16a), the Corresponding Ethylamine 19, and the Useful Intermediate 17[a]



[a] Bx = 2-phenyl-6-substituted benzoxazole. Reagents/conditions for method A were EtOH + p-$MeC_6H_4SO_3H$; B, $LiAlH_4$; C, $NaNH_2$ + liquid NH_3, MeI; D, NH_3 + glycerol, 150 °C; E, concentrated HCl, 100 °C; F, concentrated HCl, 160 °C; G, $POCl_3$; H, H_2 + Raney Ni + EtOH + NH_3, then $(CH_2CO_2H)_2$.

Scheme III. Attempted Synthetic Routes to the Potentially Useful Intermediate 24[a]



[a] Reagents/conditions for method A were 2,4,4,6-tetrabromo-2,5-cyclohexadienone; B, CF_3CO_3H; C, 50% H_2SO_4; D, NaOH, NaOAc, NaOMe, or t-BuOK in various solvents.

inactive in adrenalectomized animals. In contrast, the acids **9**, **16b**, and **16d** were approximately equiactive in normal and adrenalectomized animals.

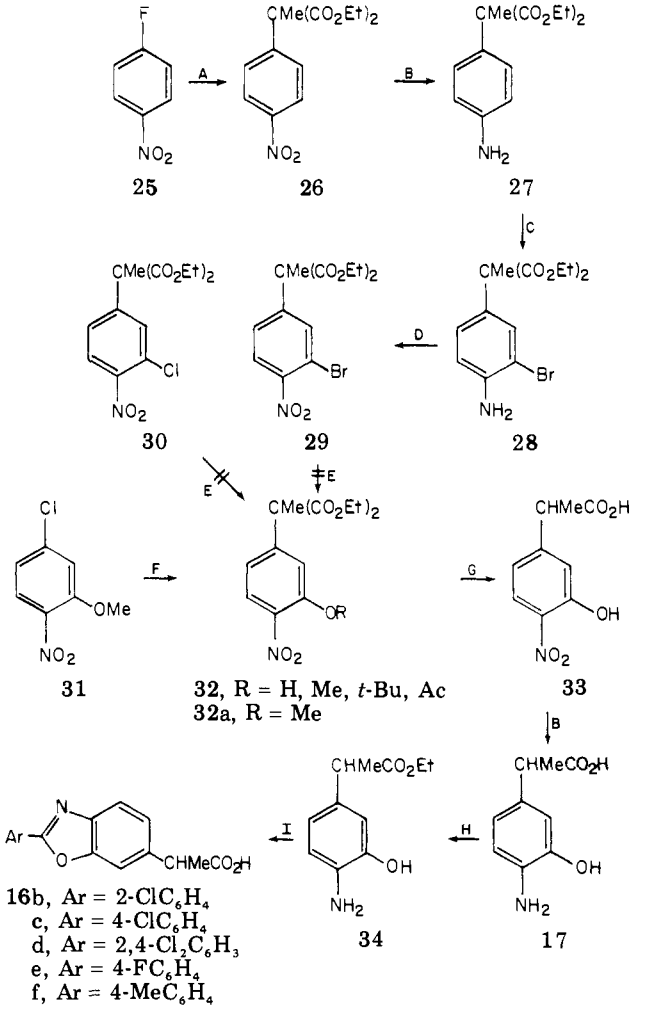
Compounds **16b** and **16c** were selected as representative examples of the active acids of the series and their ED_{30} values were determined. The results are reported in Table II, together with the corresponding figures for benoxaprofen and phenylbutazone. It can be seen that the new compounds compared favorably with the comparator drugs and data not presented in this paper showed that this was also true of their activity against rat adjuvant arthritis.[10]

Table II also shows that compounds **16b**, **16c**, and benoxaprofen were the most effective of the group after 5 h. This is of some significance since compounds with a long duration of action possess obvious advantages in the treatment of chronic diseases such as rheumatoid arthritis.

Experimental Section

Microanalyses were carried out by Mr. G. Maciak, Eli Lilly & Company, Indianapolis, Ind. Where analyses have been carried out as indicated by the symbols of the elements, the results obtained were within 0.4% of the theoretical values. The melting points are uncorrected. The IR and NMR spectra of all new compounds were consistent with their structures.

Scheme IV. Alternative Synthetic Route to the Useful Intermediate 17 and the 2-Aryl-α-methyl-6-benzoxazoleacetic Acids 16[a]



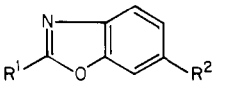
[a] Reagents for method A were $CNaMe(CO_2Et)_2$; B, H_2 + Pd/C; C, 2,4,4,6-tetrabromo-2,5-cyclohexadienone; D, CF_3CO_2H; E, NaOH, NaOAc, NaOMe, or t-BuOK in various solvents; F, $CNaMe(CO_2Et)_2$; G, HBr + HOAc + H_2O; H, EtOH + HCl, then NaOH; I, (a) ArCHO, then $Pb(OAc)_4$, NaOH + EtOH + H_2O, HCl, or (b) ArCOCl + pyridine, then 220 °C, NaOH + EtOH + H_2O, HCl.

2′-*N*-Benzamido-5′-methylphenyl Benzoate (3). Benzoyl chloride (20 mL, 0.17 mol) was slowly added to a stirred solution of 6-amino-3-methylphenol (10 g, 0.08 mol) in pyridine (100 mL). The solution was then heated on a steam bath for 2 h. The solvent was removed in vacuo and the residue was crystallized from EtOH–H_2O to give 3 (15.7 g, 58%): mp 148–150 °C. Anal. ($C_{21}H_{17}NO_3$) C, H, N.

2′-Hydroxy-4′-methylbenzanilide (6a). Benzoyl chloride (210 mL, 1.81 mol) was steadily added to a solution of 6-amino-3-methylphenol (200 g, 1.60 mol) in pyridine (1400 mL). The temperature was kept at 5 °C throughout the addition and was then allowed to rise to ambient temperature. The solution was heated on a steam bath for 2 h and evaporated to dryness. A small amount was washed with H_2O and crystallized from i-PrOH–H_2O to give white crystals of **6a**: mp 170 °C. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

4-Chloro-2′-hydroxy-4′-methylbenzanilide (6b). Preparation analogous to **6a** using 4-chlorobenzoyl chloride afforded, after crystallization from EtOH, **6b**: mp 214 °C. Anal. ($C_{14}H_{12}ClNO_2$) C, H, N.

Table I. Biological Activity of the 2-Aryl-6-Substituted Benzoxazoles on the Carrageenan-Induced Rat Paw Edema Test[a]



No.	R^1	R^2	Approx LD_{50} in mice, mg/kg po	Antiinflammatory act. vs. carrageenan[a] Test compd Dose, mg/kg × 2	Test compd % inhibn of edema	Comparator drug Compd	Comparator drug Dose, mg/kg × 2	Comparator drug % inhibn of edema
4a	Ph	Me	<1600	50	10[b]	HC[c]	50	62
9	Ph	CH_2CO_2H	1200	100	60	HC	50	60
				(100	50)[d]			
10	Ph	$(CH_2)_2NH_2 \cdot HCl$	300	25	59	PB[e]	100	62
				(25	0)[d]			
11	Ph	CH_2CO_2Et	1200	100	61	PB	100	60
12	Ph	$(CH_2)_2OH$	>1600	100	47	HC	50	51
14	Ph	$CHMeCH_2OH$	800	100	61	PB	50	53
16a	Ph	$CHMeCO_2H$	600	50	60	HC	50	51
16b	2-ClC_6H_4	$CHMeCO_2H$	1200	50	41	PB	50	40
				(50	58)[d]			
16c	4-ClC_6H_4	$CHMeCO_2H$	1200	50	28	PB	50	39
16d	2,4-$Cl_2C_6H_3$	$CHMeCO_2H$	300	25	49	HC	50	42
				(25	56)[d]			
16e	4-FC_6H_4	$CHMeCO_2H$	1200	50	48	HC	50	58
16f	4-MeC_6H_4	$CHMeCO_2H$	1200	50	43	HC	50	42
19	Ph	$CHMeCH_2NH_2 \cdot 0.5(CH_2CO_2H)_2$	300	25	0	HC	50	51
Benoxaprofen			800	50	78	PB	50	61

[a] The method described in ref 1 was used. The compounds, in carboxymethylcellulose, were dosed orally 3 and 0.5 h prior to an injection of 0.1 mL of a 1% suspension of carrageenan in 0.9% saline into the plantar surface of the right hind foot of each of four rats. The edema was measured 2.5 h after the carrageenan injection. [b] Result not significant on Student's t test at $p > 0.02$. [c] Hydrocortisone. [d] Result in rats 5 days after adrenalectomy. [e] Phenylbutazone.

Table II. Carrageenan Test ED_{30} Values[a] for Acids 16b, 16c, Benoxaprofen, and Phenylbutazone

Compd	ED_{30} values, mg/kg 2.5 h	5 h
16b	1.98 ± 3.02	23.04 ± 7.97
16c	2.40 ± 4.35	11.0 ± 7.79
Benoxaprofen	13.4 ± 2.9	10.6 ± 7.0
Phenylbutazone	23.8 ± 12.1	52.6 ± 7.6

[a] The method described in ref 1 was used. Three different doses of the compounds, in carboxymethylcellulose, were dosed orally 1 h before an injection of 0.1 mL of a 1% suspension of carrageenan in 0.9% saline into the plantar surface of the right hind foot of each of four rats. The edema was measured at 2.5 and 5 h after the carrageenan injection. ED_{30} = dose ± standard error required to give 30% reduction of foot swelling.

6-Methyl-2-phenylbenzoxazole (4a). (i) The impure 2′-hydroxy-4′-methylbenzanilide (**6a**)–pyridine hydrochloride mixture was heated at 220 °C for 1 h. The residue was cooled and extracted with Et_2O. The solution was washed successively with 2 N HCl (twice) and 2 N NaOH, dried (Na_2CO_3), treated with C, and evaporated to dryness to give **4a** (315 g, 93% over two stages): mp 93 °C. Anal. ($C_{14}H_{11}NO$) C, H, N.

(ii) Compound **3** (8.0 g, 0.024 mol) was heated at 200–210 °C for 20 min. The cooled residue was dissolved in $CHCl_3$ (70 mL), extracted with 2 N NaOH (25 mL), and washed with H_2O (3 × 50 mL). The dried (Na_2SO_4) organic solution was evaporated to yield an off-white solid (4.9 g, 97%), mp 92–93 °C, identical with the previous sample.

2-*p*-Chlorophenyl-6-methylbenzoxazole (4b). Cyclization of 4-chloro-2′-hydroxy-4′-methylbenzanilide (**6b**) as described for the formation of **4a** gave a solid, **4b** (81% over two stages): mp 151 °C. Anal. ($C_{14}H_{10}ClNO$) C, H, N.

6-Methyl-2-phenyl-5-benzoxazolylphenylmethanone (5). (i) A mixture of 6-amino-3-methylphenol (10 g, 0.08 mol), ethyl benzoate (15 mL, 0.10 mol), and polyphosphoric acid (80 mL) was heated at 180–210 °C for 20 min. The solution was poured onto ice and the resulting emulsion was extracted with Et_2O. The Et_2O solution was washed with H_2O (twice), dried (Na_2CO_3), and evaporated to dryness. GC analysis of the residual oil showed that it was a mixture of **4a** and **5**. In repeat experiments, the ratio of the two products varied and the variation is thought to be due to the different qualities of polyphosphoric acid which were used. Pure **4a** was isolated from the mixture as well as pure **5**: mp 121–123 °C. Anal. ($C_{21}H_{15}NO_2$) C, H, N.

(ii) Compound **6a** (5.0 g, 0.022 mol) was heated with polyphosphoric acid (100 g) at 200–210 °C for 20 min. The product was again a mixture of **4a** and **5**.

6-Bromomethyl-2-phenylbenzoxazole (7). A solution of **4a** (50 g, 0.239 mol) in CCl_4 (250 mL) containing *N*-bromosuccinimide (50 g, 0.281 mol) was heated under reflux in the presence of UV light for 3 h. The solution was filtered and allowed to cool. The resulting crystals were recrystallized from CCl_4 to yield **7** (30 g, 46%): mp 163 °C. Anal. ($C_{14}H_{10}BrNO$) C, H, Br, N.

2-Phenyl-6-benzoxazoleacetonitrile (8). A mixture of **7** (15 g, 0.052 mol), NaCN (60 g, 1.22 mol), and dimethylacetamide (300 mL) was stirred at room temperature for 7 h and evaporated under reduced pressure. The residue was extracted with $CHCl_3$. This filtered solution was washed with H_2O and evaporated to dryness. The solid product was crystallized from EtOAc–Et_2O to give **8** (5.2 g, 43%): mp 145 °C. Anal. ($C_{15}H_{10}N_2O$) C, H, N.

2-Phenyl-6-benzoxazoleacetic Acid (9). The nitrile **8** (10 g, 0.042 mol) was dissolved in 50% H_2SO_4. The solution was heated under reflux for 1.5 h and was poured into ice–H_2O. A solid was produced which was removed by filtration and crystallized from Et_2O–EtOAc to yield **9** (1.2 g, 13%): mp 170 °C. Anal. ($C_{15}H_{11}NO_3$) C, H, N.

2-Phenyl-6-benzoxazoleethylamine Hydrochloride (10). A solution of **8** (8.9 g, 0.038 mol) in EtOH (300 mL) saturated with NH_3 was hydrogenated over Raney nickel W2 catalyst (250 mg, 0.003 mol) at room temperature at 60 psi for 24 h. The solution was filtered and evaporated to dryness. The residue was dissolved in 2 M HCl and the solution was washed with $CHCl_3$. The aqueous solution was evaporated to a small volume when crystallization occurred. This yielded **10** (2.2 g, 21%): mp 268 °C. Anal. ($C_{15}H_{14}ClN_2O$) C, H, N.

Ethyl 2-Phenyl-6-benzoxazoleacetate (11). A solution of **9** (150 g, 0.593 mol) and *p*-toluenesulfonic acid (500 mg, 0.003 mol) in C_6H_6 (1400 mL)–EtOH (600 mL) was heated under reflux for 24 h and the C_6H_6–EtOH–H_2O azeotrope was removed. The

residue, after removal of solvent, was dissolved in $CHCl_3$ and this solution was washed with 2 N NaOH, dried (Na_2CO_3), and evaporated. This yielded **11** (166 g, 99%): mp 76 °C. Anal. ($C_{17}H_{15}NO_3$) C, H, N.

2-Phenyl-6-benzoxazoleethanol (12). Ester **11** (20 g, 0.071 mol) was slowly added to a solution of $LiAlH_4$ (3.0 g, 0.079 mol) in dry Et_2O (200 mL). The resulting mixture was heated at 100 °C for 3 h and poured carefully into ice (1 kg)–concentrated HCl (100 mL). The Et_2O layer was separated and the H_2O layer was extracted with Et_2O (twice). The extracts were combined and dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was crystallized from EtOH–H_2O to give **12** (12 g, 71%): mp 89 °C. Anal. ($C_{15}H_{13}NO_2$) C, H, N.

Ethyl α-Methyl-2-phenyl-6-benzoxazoleacetate (13). A suspension of **11** (8 g, 0.028 mol) in dry Et_2O (50 mL) was added to a solution of sodamide (from Na, 750 mg, 0.033 mol) in liquid NH_3 (120 mL). The red solution was stirred for 10 min. A solution of MeI (2.0 mL, 0.049 mol) in Et_2O (10 mL) was added as rapidly as possible. After the vigorous exothermic reaction, the solution was stirred for 1 min; then NH_4Cl (2 g, 0.038 mol) was added and the solvent was evaporated. The residue was extracted with Et_2O. The filtered solution was treated with C and evaporated to dryness to give **13** (8.1 g, 97%): mp 46 °C. Anal. ($C_{18}H_{17}NO_3$) C, H, N.

β-Methyl-2-phenyl-6-benzoxazoleethanol (14). $LiAlH_4$ (0.8 g, 0.021 mol) was added to a stirred solution of **13** (8.7 g, 0.029 mol) in dry Et_2O (50 mL). The mixture was stirred for 1 h at room temperature and poured carefully into ice (500 g)–concentrated HCl (50 mL). The Et_2O layer was separated and the H_2O layer was extracted twice with Et_2O. The extracts were combined and washed with 2 N NaOH and then H_2O. The solution was dried (Na_2CO_3) and the solvent was removed in vacuo. The residue was crystallized from EtOH–H_2O to give **14** (2.1 g, 28%): mp 98 °C. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

β-Methyl-2-phenyl-6-benzoxazoleethanol (14). $LiAlH_4$ (0.8 g, 0.021 mol) was added to a stirred solution of **13** (8.7 g, 0.029 mol) in dry Et_2O (50 mL). The mixture was stirred for 1 h at room temperature and poured carefully into ice (500 g)–concentrated HCl (50 mL). The Et_2O layer was separated and the H_2O layer was extracted twice with Et_2O. The extracts were combined and washed with 2 N NaOH and then H_2O. The solution was dried (Na_2CO_3) and the solvent was removed in vacuo. The residue was crystallized from EtOH–H_2O to give **14** (2.1 g, 28%): mp 98 °C. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

α-Methyl-2-phenyl-6-benzoxazoleacetamide (15). A suspension of **13** (27 g, 0.092 mol) in saturated NH_3–glycerol (100 mL) was heated in a bomb at 150 °C for 24 h. The mixture was then diluted with ice–H_2O (150 mL). The solid was removed by filtration and crystallized from EtOH–DMF to give **15** (20 g, 82%): mp 193 °C. Anal. ($C_{16}H_{14}N_2O_2$) C, H, N.

Diethyl 3-Methoxy-α-methyl-4-nitrophenylmalonate (32a). A solution of diethyl methylmalonate (110 g, 0.63 mol) in dry DMF (100 mL) was steadily added to a stirred suspension of NaH (14.5 g, 0.61 mol) in dry DMF (100 mL) as the temperature was kept <20 °C by external cooling. After the addition, the mixture was stirred for 2 h. A solution of 5-chloro-2-nitroanisole[6] (100 g, 0.53 mol) in dry DMF (100 mL) was added and the solution was stirred at 100 °C for 24 h. The solution was evaporated to dryness and the residue was dissolved in Et_2O. This solution was washed with H_2O (three times) and evaporated to dryness. Vacuum distillation of the residue afforded pure **32a** (50.9 g, 29%): bp 170–174 °C (0.1 mm). Anal. ($C_{15}H_{19}NO_7$) C, H, N.

3-Hydroxy-α-methyl-4-nitrobenzeneacetic Acid (33). A solution of **32a** (70.5 g, 0.22 mol) in 49% HBr–H_2O (500 mL) and 33% HBr–AcOH (300 mL) was heated under reflux for 9 h. The solution was filtered and evaporated to dryness. The residue was dissolved in an aqueous solution of $NaHCO_3$. This solution was washed with $CHCl_3$, treated with C, and acidified (pH 1) with concentrated HCl. The mixture was extracted with $CHCl_3$ and the organic solution was treated with C, filtered, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from toluene–petroleum ether (bp 80–100 °C) to give **33** (34.4 g, 75%): mp 95–97 °C. Anal. ($C_9H_9NO_5$) C, H, N.

4-Amino-3-hydroxy-α-methylbenzeneacetic Acid (17). (i) A solution of **33** (1 g, 0.005 mol) in EtOH (10 mL)–H_2O (5 mL) containing 10% Pd/C (100 mg) was hydrogenated at 60 psi for 3 h at ambient temperature. The mixture was filtered and the filtrate was evaporated to dryness. The residue was crystallized from H_2O–AcOH to give **17** (700 mg, 82%): 169–170 °C. Anal. ($C_9H_{11}NO_3$) C, H, N.

(ii) A solution of **13** (10 g, 0.034 mol) in concentrated HCl (150 mL) was heated in a bomb at 160 °C for 24 h and evaporated to dryness. The residue was dissolved in H_2O and this solution was washed with $CHCl_3$ and evaporated to dryness to give the hydrochloride of **17** (5 g, 68%): mp 197–199 °C. This, on neutralization with aqueous NH_4OH, gave pure **17**, identical with the previous sample.

Ethyl 4-Amino-3-hydroxy-α-methylbenzeneacetate (34). A solution of the hydrochloride of **17** (4.9 g, 0.023 mol) in saturated EtOH–HCl (100 mL) was heated under reflux for 6 h and evaporated to dryness. The residue was dissolved in H_2O and the solution was neutralized (pH 7) with 2 N NaOH. The product was continuously extracted with $CHCl_3$ and organic solution was washed once with H_2O. Evaporation of the solvent afforded **34** (2.5 g, 52%): mp 114–115 °C. Anal. ($C_{11}H_{15}NO_3$) C, H, N.

α-Methyl-2-phenyl-6-benzoxazoleacetic Acid (16a). A solution of impure **13** (15 g, 0.051 mol) in concentrated HCl (150 mL) was heated on a steam bath for 6 h and poured into ice–H_2O. The solid which was produced was filtered off and dried. The solid was dissolved in $CHCl_3$ and chromatographed on a SiO_2 column. Evaporation of the eluent afforded **16a** (7.8 g, 57%): mp 132 °C. Anal. ($C_{16}H_{13}NO_3$) C, H, N.

2-(2-Chlorophenyl)-α-methyl-6-benzoxazoleacetic Acid (16b). A solution of 2-chlorobenzaldehyde (4.3 g, 0.031 mol) and **34** (6 g, 0.029 mol) in toluene (100 mL) was heated under reflux and the H_2O which formed was removed using a Dean-Stark apparatus. The solvent was removed in vacuo and the residue was dissolved in AcOH (100 mL). This solution was treated with $Pb(OAc)_4$ (15 g, 0.034 mol) below 25 °C. The solution was kept overnight and poured into ice–H_2O. The resulting mixture was extracted with Et_2O (200 mL). The organic solution was washed with H_2O and 2 N NaOH, dried (Na_2CO_3), and evaporated to give slightly impure ethyl 2-(2-chlorophenyl)-α-methyl-6-benzoxazoleacetate (6.6 g, 70%). This was dissolved in EtOH (20 mL) and treated with a solution of NaOH (1.5 g, 0.038 mol) in H_2O (10 mL). After being stirred for 0.5 h, further H_2O (20 mL) was added. After 1.5 h, the solution was evaporated to dryness in vacuo. The residue was dissolved in H_2O and the solution was washed with CH_2Cl_2. The solution was acidified (pH 3) with concentrated HCl and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and treated with C, and the solvent was removed in vacuo. The residual oil was crystallized from Et_2O to give **16b** (2 g, 33%): mp 108–110 °C. Anal. ($C_{16}H_{12}ClNO_3$) C, H, Cl, N.

2-(4-Chlorophenyl)-α-methyl-6-benzoxazoleacetic Acid (16c). Compound **34** was treated with 4-chlorobenzoyl chloride in the same manner as in the preparation of **6a** and the product was cyclized by method (i) for **4a**. The slightly impure ethyl ester of **16c** was hydrolyzed by the procedure used for **16a**. The product was crystallized from H_2O–acetone to give pure **16c** (1.4 g, 10% over three stages): mp 195–196 °C. Anal. ($C_{16}H_{12}ClNO_3$) C, H, Cl, N.

2-(2,4-Dichlorophenyl)-α-methyl-6-benzoxazoleacetic Acid (16d). Compound **34** was condensed with 2,4-dichlorobenzaldehyde and the product was cyclized and hydrolyzed under the conditions described for **16b** to give, after crystallization from toluene–petroleum ether (bp 80–100 °C), pure **16d** (24% over three stages): mp 143–145 °C. Anal. ($C_{16}H_{11}Cl_2NO_3$) C, H, Cl, N.

2-(4-Fluorophenyl)-α-methyl-6-benzoxazoleacetic Acid (16e). This compound was prepared from **34** and 4-fluorobenzoyl chloride by a method similar to that described for **16c**, except that the hydrolysis was as described for **16b**. Recrystallization from EtOH–H_2O gave pure **16e** (54% over three stages): mp 147 °C. Anal. ($C_{16}H_{12}FNO_3$) C, H, F, N.

α-Methyl-2-(4-methylphenyl)-6-benzoxazoleacetic Acid (16f). This compound was prepared from **34** and 4-methylbenzoyl chloride by the method described for **16c**, but the hydrolysis was as described for **16b**. Recrystallization from EtOH–H_2O afforded pure **16f** (46% over three stages): mp 167–168 °C. Anal. ($C_{17}H_{15}NO_3$) C, H, N.

α-Methyl-2-phenyl-6-benzoxazoleacetonitrile (18). A solution of **15** (9 g, 0.034 mol) in $POCl_3$ (100 mL) was heated under reflux for 2 h and then the solvent was removed in vacuo. Ice (20 g) was added to the residual oil and the mixture was extracted

with $CHCl_3$. The organic solution was dried (Na_2CO_3) and evaporated to dryness to give **18** (8.2 g, 98%): mp 121 °C. Anal. ($C_{16}H_{12}N_2O$) C, H, N.

β-Methyl-2-phenyl-6-benzoxazoleethylamine Hemisuccinate (19). Compound **18** was reduced as described for **10a** and the hemisuccinate derivative was prepared. This was crystallized from EtOH–DMF to give pure **19** (4.9 g, 39%): mp 205 °C. Anal. ($C_{18}H_{19}N_2O_3$) C, H, N.

4-Amino-3-bromo-α-methylbenzeneacetonitrile (21). 2,4,4,6-Tetrabromo-2,5-cyclohexadienone[7] (103 g, 0.31 mol) was slowly added to a stirred solution of 4-aminophenyl-α-methylacetonitrile[8] (**20**) (36.5 g, 0.25 mol) in CH_2Cl_2 (650 mL) at −30 °C. When the addition was complete the mixture was stirred for a further 1 h at −20 °C. When the solution reached ambient temperature, it was washed with cold 2 N NaOH, dried (Na_2CO_3), and evaporated to give **21** (51.5 g, 92%) as an oil: NMR (aryl) δ 6.65 (d, 5-H), 7.00 (dd, 6-H), 7.29 (d, 2-H). Anal. ($C_9H_9BrN_2$) C, H, Br, N.

3-Bromo-α-methyl-4-nitrobenzeneacetonitrile (22). Trifluoroacetic anhydride (78 mL) was added to a stirred suspension of 90% H_2O_2 (12.3 mL, 0.3 mol) in CH_2Cl_2 (300 mL) at 0 °C, and the stirred mixture was cooled in Drykold–acetone. After 5 min, a solution of **21** (22.5 g, 0.1 mol) in CH_2Cl_2 (30 mL) was slowly added so that gentle reflux conditions were maintained. The solution was then heated under reflux for 1 h, cooled, and washed with ice–H_2O and an aqueous solution of Na_2CO_3. The dried (Na_2CO_3) solution was evaporated to give **22** (24 g, 94%) as a yellow oil: NMR (aryl) δ 7.55 (dd, 6-H), 7.79 (d, 2-H), 7.90 (d, 5-H). Anal. ($C_9H_7BrN_2O_2$) C, H, Br, N.

Diethyl 4-Amino-α-methylphenylmalonate (27). The reaction of 4-fluoronitrobenzene (**25**) with the anion of diethyl methylmalonate was carried out as described for the preparation of **32a**. Impure **26** was isolated as an oil (about 80% pure by NMR analysis). A solution of this material in EtOH (100 mL) containing 10% Pd/C (1 g) was hydrogenated at 60 psi for 4 h at room temperature. The solution was filtered and the solvent was removed in vacuo. The residual oil was distilled in vacuo to yield the amine **27** (88.3 g, 32% over two stages), bp 156–161 °C (0.3 mm), as a yellow oil. The amine was characterized as its acetyl derivative in the following way. Acetyl chloride (3.87 g) was added to a stirred mixture of some of the amine (13.05 g) and $KHCO_3$ (4.95 g) in toluene (50 mL). The mixture was stirred under reflux for 1.5 h and filtered. Evaporation of the filtrate gave an oil which solidified on standing. This was pure diethyl 4-acetylamino-α-methylphenylmalonate (14.8 g, 98%): mp 74–75 °C. Anal. ($C_{16}H_{21}NO_5$) C, H, N.

Diethyl 3-Bromo-α-methyl-4-nitrophenylmalonate (29). 2,4,4,6-Tetrabromo-2,5-cyclohexadienone[7] (31 g, 0.094 mol) was slowly added to a stirred solution of **27** (20 g, 0.08 mol) in CH_2Cl_2 (300 mL) at room temperature. After being stirred for 2 h, the solution was washed with 2 N NaOH and H_2O, dried (Na_2CO_3), and evaporated to give slightly impure **28** (22.6 g, 86%). A solution of this product (3 g) in CH_2Cl_2 (3 mL) was added in one portion to a stirred solution of 30% H_2O_2 (8 mL), 0.2 mol) in trifluoracetic anhydride (55 mL). The solution was stirred for 3 h, washed with H_2O and 2 N NaOH, dried (Na_2CO_3), and evaporated to dryness to give **29** as an oil (2.2 g, 68%): NMR (aryl) δ 7.48 (dd, 6-H), 7.77 (d, 2-H), 7.83 (d, 5-H). Anal. ($C_{14}H_{16}BrNO_6$) C, H, Br, N.

Attempted Preparation of Compounds 24 and 32. Attempted displacements of halogen from compounds **22**, **23** (slightly impure by NMR analysis, prepared from **22** by hydrolysis as for **9**), **29**, and **30**[9] were unsuccessful under the following conditions: (i) reaction of the compounds with hot or cold solutions of NaOH in H_2O and also in the presence of DMF; (ii) with NaOAc in AcOH and H_2O; (iii) with NaOMe and NaOEt in MeOH, EtOH, Me_2SO, and HMPT at various temperatures and concentrations; (iv) with KO-*t*-Bu in *t*-BuOH.

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3,4-Methylenedioxyphenyl-, Isopropylidenedioxyphenyl-, and Benzyl-Substituted Chiral 2-Aminosuccinimides and 3-Aminopyrrolidines. Stereoselective Investigations of Potential Anti-Parkinsonian, Antipsychotic, and Anticonvulsant Activities[1]

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The chiral title compounds **2**–**11** were assessed for their potential anti-Parkinsonian, antipsychotic, and anticonvulsant properties. The most striking differences in the biological activity of enantiomeric pairs were noted for D-(*R*)-2-amino-*N*-(3,4-methylenedioxyphenyl)succinimide hydrochloride (**2**) vs. L-(*S*)-**3** and D-(*R*)-2-amino-*N*-(3,4-isopropylidenedioxyphenyl)succinimide (**4**) vs. L-(*S*)-**5**. D-(*R*)-**2** partially attenuated amphetamine-induced stereotyped behavior, whereas D-(*R*)-**4** antagonized oxotremorine-induced tremors. Their respective enantiomorphs were inactive in these tests. No differences in anticonvulsant potency of enantiomeric pairs were observed. The stereoselective actions of D-(*R*)-**2** and **4** were rationalized on the basis of the presence or absence of *gem*-dimethyl functions in isopropylidenedioxy vs. methylenedioxy groups; the data seem to indicate that these methyl groups influence selective receptor site interaction in the D-(*R*) series.

Piribedil (**1**), like apomorphine, is thought to act by direct stimulation of central dopaminergic receptors but possesses a more prolonged duration of action.[2,3] Whereas this compound exhibits anti-Parkinsonian activity, it is less