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Synthesis and Antiinflammatory Activity of Some 2-Heteroaryl-α-methyl-5-benzoxazoleacetic Acids

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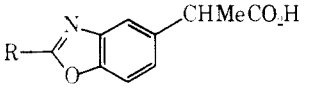
The syntheses of eight of the title compounds are described. The compounds possessed activity comparable with that of the previously tested 2-substituted phenyl analogs in the carrageenan-induced rat paw edema test.

2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetic acid, benoxaprofen (Ia),[1] is a potent new antiinflammatory agent which is currently undergoing clinical trials. The antiinflammatory activities of some related 2-substituted phenylbenzoxazoles,[1] benzimidazoles,[2] benzothiazoles,[3] and benzothiazolines[3] have been reported recently.

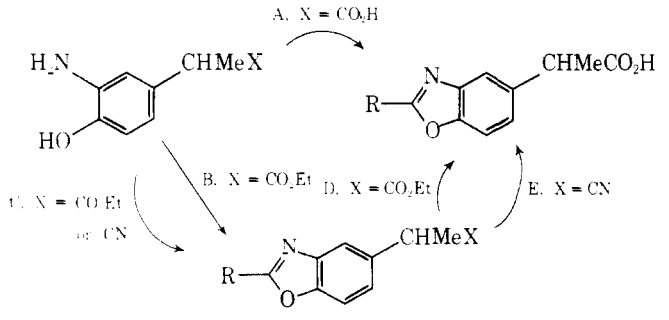


Ia, R = *p*-chlorophenyl
b, R = heteroaryl

The present communication describes the synthesis and antiinflammatory activity of a series of 2-heteroaryl-α-methyl-5-benzoxazoleacetic acids (Ib) which were investigated as part of a general program designed to define the structural requirements which were consistent with retention of activity in benoxaprofen analogs.

The new compounds are listed in Table I and they were prepared from 3-amino-4-hydroxy-α-methylbenzeneacetic acid, or the corresponding ester or nitrile,[1] by the methods outlined in Scheme I. Further details of the methods are given in the Experimental Section.

Scheme I. Synthesis of 2-Heteroaryl-α-methyl-5-benzoxazoleacetic Acids[a]



[a] Main reagents for method A, RC(NH)OMe; B, RCOCl, then heat; C, RCHO, then $Pb(OAc)_4$; D, aqueous KOH or NaOH; E, concentrated HCl

The compounds were screened for antiinflammatory activity in the carrageenan-induced rat paw edema test.[1] Oral doses of the compounds were given to Wistar rats 3 and 0.5 hr before an injection of carrageenan and the amount of inflammation produced was compared with that formed in a control group of rats dosed with saline. The results are summarized in Table I, together with those for phenylbutazone which was tested concurrently as a control compound. The data for benoxaprofen are included for comparative purposes.

The heterocyclic derivatives **1, 2,** and **4–8** possessed significant activity at 50 mg/kg × 2 but none were superior to benoxaprofen on this test. The results also indicate that the 2-heteroarylbenzoxazoles possess activity of the same order as the previously tested 2-substituted phenyl analogs.[1]

Experimental Section

Elemental analyses were carried out by Mr. G. Maciak, Eli Lilly & Co., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The ir spectra were recorded on a Perkin-Elmer 457 spectrophotometer and the NMR spectra on a Varian A-60A spectrometer. The ir and NMR spectra for all of the analyzed compounds were consistent with the given structures. All of the prepared compounds are new.

α-Methyl-2-(2-pyridyl)-5-benzoxazoleacetic Acid (1). 2-Cyanopyridine (5.2 g, 0.05 mol) was added to a solution of sodium methoxide (0.005 mol) in MeOH (45 ml) and the solution was kept overnight at room temperature. AcOH (300 mg, 0.005 mol) was added, followed by 3-amino-4-hydroxy-α-methylbenzeneacetic acid[1] (9.05 g, 0.05 mol). The reaction mixture was stirred under reflux for 5 hr and evaporated under reduced pressure. The residue was dissolved in 2 *N* NaOH (150 ml) and extracted with Et_2O. The pH of the aqueous solution was adjusted to 6 with concentrated HCl. This yielded a solid which was filtered off and recrystallized from EtOH–H_2O. The dried cream crystals (7.5 g, 56%) had mp 177–179°. Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

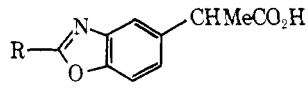
α-Methyl-2-(3-pyridyl)-5-benzoxazoleacetic Acid (2). This was prepared in the same way as the foregoing product to give cream crystals (43%), mp 197–200°, from DMF–EtOH. Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

α-Methyl-2-(4-pyridyl)-5-benzoxazoleacetic Acid (3). This was prepared in the same way as compound 1. The cream crystals (60%), mp 247–250°, were obtained by recrystallization from DMF. Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

α-Methyl-2-(2-thienyl)-5-benzoxazoleacetic Acid (4). 2-Thenoyl chloride (9.9 g, 0.068 mol) was added carefully to a solution of ethyl 3-amino-4-hydroxy-α-methylbenzeneacetate[1] (12.9 g, 0.062 mol) in anhydrous pyridine (50 ml). This solution was heated at 100° for 3.5 hr and evaporated under reduced pressure. The residue was heated at 230° for 15 min while the vapor was allowed to escape. The cooled residue was then dissolved in EtOH (50 ml) to which a solution of KOH (10 g) in H_2O (10 ml) had been added previously. The reaction was stirred at room temperature for 19 hr and the expected product was isolated in the conventional manner. The cream crystals (7.5 g, 45%) had mp 161–163°. Anal. ($C_{14}H_{11}NO_3S$) C, H, N.

2-(5-Choro-2-thienyl)-α-methyl-5-benzoxazoleacetic Acid (5). A solution of ethyl 3-amino-4-hydroxy-α-methylbenzeneace-

Table I. Activity of Compounds 1-8, Phenylbutazone, and Benoxaprofen in the Carrageenan-Induced Rat Paw Edema Test



Compd no.	R	Act. of test compd: Dose,[b] mg/kg × 2	Act. of test compd: % redn[c]	Act. of phenylbutazone[a]: Dose,[b] mg/kg × 2	Act. of phenylbutazone[a]: % redn[c]
1	2-Pyridyl	100	47	50	43
		50	36	50	32
2	3-Pyridyl	50	37	50	46
3	4-Pyridyl	50	15*	50	48
4	2-Thienyl	100	40	50	38
		50	24	50	32
5	5-Chloro-2-thienyl	50	34	50	43
6	2-Furyl	50	23	50	23
7	5-Chloro-2-furyl	100	46	50	39
		50	27	50	32
8	1-Methyl-2-pyrrolyl	50	17	50	39
Benoxaprofen	4-ClC_6H_4	50	78	50	61

[a]When tested at the same time as the test compound. [b]Doses were given orally at 3 and 0.5 hr prior to carrageenan. [c]The edema was measured 2.5 hr after the carrageenan injection. All of the results except the one marked * were significant ($p > 0.02$) on Student's t test.

tate (5.5 g, 0.026 mol) and 5-chloro-2-thiophenecarboxaldehyde (5.0 g, 0.031 mol) in toluene (75 ml) was heated under reflux and the H_2O which formed was removed in a Dean-Stark apparatus. The solvent was evaporated and the residue was dissolved in AcOH (100 ml). Lead tetraacetate (17 g, 0.043 mol) was added and the reaction mixture was stirred overnight at room temperature. H_2O (10 ml) was added and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 and the organic solution was dried (Na_2SO_4) and treated with C. The solvent was evaporated and the residue was dissolved in warm EtOH (50 ml). A solution of NaOH (1.0 g, 0.026 mol) in H_2O (5 ml) was added and the resulting solution was stirred for 1 hr at room temperature. H_2O (150 ml) was added and, after a further 2 hr, the solution was concentrated to a small volume. The aqueous solution was extracted with $CHCl_3$ and acidified (pH 1) with concentrated HCl. The required product was extracted with $CHCl_3$ and the organic solution was dried (Na_2SO_4) and evaporated. The residue was recrystallized from toluene and EtOH–H_2O to give pure **5** (1.7 g, 19%): mp 185°. Anal. ($C_{14}H_{10}ClNO_3S$) C, H, Cl, N.

2-(2-Furyl)-α-methyl-5-benzoxazoleacetic Acid (6). This was made in a similar manner to compound **4**. The acid was obtained as light cream crystals (19%), mp 160–162°, after recrystallization from Me_2CO and EtOH–H_2O. Anal. ($C_{14}H_{11}NO_4$) C, H, N.

2-(5-Chloro-2-furyl)-α-methyl-5-benzoxazoleacetic Acid (7). A mixture of ethyl 3-amino-4-hydroxy-α-methylbenzeneacetate (6.0 g, 0.029 mol), 5-chloro-2-thiophenecarboxaldehyde (5.5 g, 0.038 mol), sodium sulfate (20 g, 0.14 mol), and toluene was stirred for 2 hr at room temperature. The filtered solution was evaporated and the residue was oxidized and hydrolyzed as described for the preparation of **5**. This gave, after recrystallization from H_2O, pure **7** (15%): mp 161°. Anal. ($C_{14}H_{10}ClNO_4$) C, H, Cl, N.

α-Methyl-2-(1-methyl-2-pyrrolyl)-5-benzoxazoleacetic Acid (8). 3-Amino-4-hydroxy-α-methylbenzeneacetonitrile[1] (4.0 g, 0.025 mol) was condensed with 1-methyl-2-pyrrolecarboxaldehyde (2.5 g, 0.02 mol) and the product was oxidized using the conditions described for the preparation of **5**. The resulting α-methyl-2-(1-methyl-2-pyrrolyl)-5-benzoxazoleacetonitrile (4.4 g, purity approximately 80% by NMR) and concentrated HCl (50 ml) were stirred at 100° for 1.5 hr, treated with C, and filtered. The solution was evaporated under reduced pressure and the residue was dissolved in 2 *N* NaOH and extracted with $CHCl_3$. The aqueous solution was then acidified (pH 2) with concentrated HCl and extracted with $CHCl_3$. The organic extracts were dried ($NaSO_4$) and evaporated to yield a solid which was recrystallized from EtOH–H_2O. This gave pure **8** (1.0 g, 29%): mp 123°. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

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A Lapachol Derivative Active against Mouse Lymphocytic Leukemia P-388

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Lapachol [2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone] and its analogs [2-(3,7-dimethyl-2,6-octadienyl)-3-hydroxy-1,4-naphthoquinone and 2-(3,3-dibromo-2-propenyl)-3-hydroxy-1,4-naphthoquinone] have been described, among almost a hundred synthesized analogs, as active against rat tumor Walker 256 carcinosarcoma. The acetylglucosylation of lapachol results in a compound which extends lapachol activity becoming effective against mouse lymphocytic leukemia P-388. When mice inoculated with 10^6 leukemic cells were treated with the drug during 9 days, their life span increased 80% over the control animals. Identification spectral data (uv, ir, ^1H NMR, and MS) of the compound obtained by synthesis are given.

It is well known that activity of a drug depends upon its reaching the site of action and that derivatives, referred to sometimes as "prodrugs",[1] which reach this site more efficiently and are there degraded to the active compound, may be therapeutically more effective. In a recent publication, Segal and coworkers[2] showed that the activity of saponin is due to the aglycone. The hemolytic effect of a particular saponin will depend on its degree of adsorption by the cell and on the presence of specific glycosidases on the cell wall. The present paper describes a modification of lapachol by glycosidation which extends and enhances its antitumor activity.

Lapachol, 2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone (**1**), occurs in the wood of several species of the family Bignoniaceae[3] and is presently commercialized in Brazil as an antitumor drug. Experimentally, lapachol is