and Mr. Nelson Major for providing expert technical assistance.

References and Notes

(1) J. S. Cox, J. E. Beach, A. M. J. N. Blair, A. J. Clarke, J. King, T. B. Lee, D. E. E. Loveday, G. F. Moss, T. S. C. Orr, J. T. Richie, and P. Sheard, *Adv. Drug Res.*, **5**, 115 (1970).
(2) J. Goose and A. M. J. W. Blair, *Immunology*, **16**, 749 (1969).
(3) C. M. Hall, H. G. Johnson, and J. B. Wright, *J. Med. Chem.*, **17**, 685 (1974).
(4) The Upjohn Co., Belgian Patent 808 898 (1973).
(5) J. B. Wright, U.S. Patent 3 852 324 (1974).
(6) J. H. Sellstedt, C. J. Guinosso, A. J. Begany, S. C. Bell, and M. Rosenthale, *J. Med. Chem.*, **18**, 926 (1975).
(7) H. G. Johnson and C. A. VanHout, *Proc. Soc. Exp. Biol. Med.*, **143**, 427 (1973).

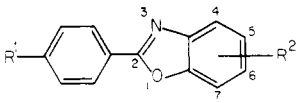
Synthesis and Antiinflammatory Activity of Some 2-Substituted 4- and 7-Benzoxazoleacetic and α-Methylacetic Acids

Delme Evans, Christine E. Smith, and W. R. Nigel Williamson*

Organic Chemistry Department, Lilly Research Centre Limited, Erl Wood Manor, Windlesham, Surrey, England.
Received February 2, 1976

4- and 7-benzoxazoleacetic and α-methylacetic acids substituted in the 2 position with phenyl and substituted phenyl groups have been synthesized and tested on the carrageenan-induced rat paw edema assay. The only compound found to have significant activity, albeit of a low order, was 2-phenyl-α-methyl-7-benzoxazoleacetic acid.

2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetic acid, benoxaprofen [1, R^1 = Cl; R^2 = 5-$CH(CH_3)CO_2H$], was found to be a potent inhibitor of carrageenan-induced edema[1] and adjuvant arthritis in rats and is undergoing clinical trials as a new nonsteroidal antiinflammatory agent. It was therefore of interest to determine the effect



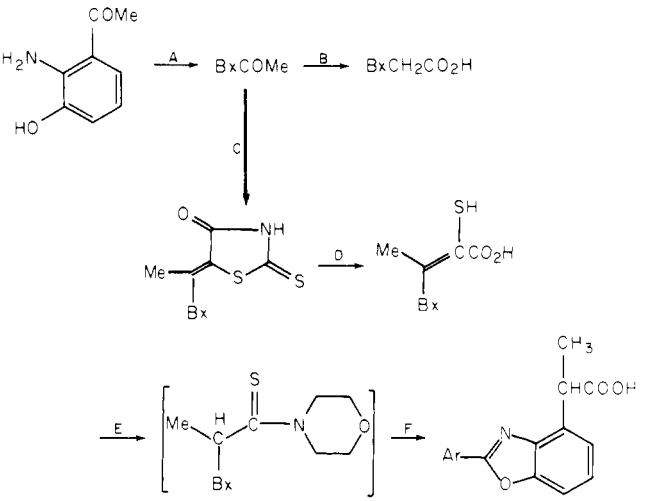
on pharmacological activity of moving the side chain R^2 onto other positions of the benzoxazole system and this paper reports the synthesis and results from pharmacological assay of compounds in which the benzoxazole system was substituted in the 4 and 7 positions with acetic acid and α-methylacetic acid side chains.

Chemistry. Compounds in the series having substituents in the 4 and 7 positions were prepared according to the routes indicated in Schemes I and II. Further details are given in Table I and the Experimental Section. The sequence C to F is an adaptation of the method of Moreau and Durand-Henchoz.[2] Examination of the product from method D by NMR spectroscopy showed that it had an α-mercaptocinnamic acid structure in solution, rather than the thiopyruvic acid tautomer. The latter was expected from the paper by Moreau and Durand-Henchoz. However, the α-mercaptocinnamic acid structure does agree with the findings of Campaigne and Cline who examined the uv spectra of some α-mercaptocinnamic acids[3] and of Nishio and Ho, who used NMR spectroscopy and reached the same conclusion for α-mercaptocinnamic acid.[4] Our product from method D had a strong ir band at 1690 cm^{-1} (in KBr), so in the solid state the compound probably also exists as an α-mercaptocinnamic acid.

Antiinflammatory Activity. The results of antiinflammatory testing against carrageenan-induced foot edema of Winter et al.[5] in rats, modified as indicated in ref 1, are reported in Table I. Only one compound, **5**, showed significant reduction of swelling at 2 × 100 mg/kg po compared with controls, but the magnitude of the result compared with those obtained using the control compounds, hydrocortisone and phenylbutazone, did not encourage further development of the compound.

Two correlations emerge from Table I. (i) In the 7-substituted series, compound **6**, having *p*-chloro substitution in the 2-phenyl ring, was inactive, while its unsubstituted analogue (**5**) was active. This is the opposite of the situation in the benoxaprofen series,[1] where para substitution with chlorine increased the activity of the unsubstituted analogue. (ii) Compound **3**, in the series having the side chain in the 4 position of the benzoxazole nucleus, was inactive although its equivalent **5** in the 7-substituted series was active. Such a difference between the activities is surprising as the only difference between the compounds lies in the positions of the isosteric oxygen and nitrogen atoms. Differences in metabolism, shape, and/or physicochemical parameters could be responsible for this difference[6] but an examination of the pK_a and partition coefficients (cf. Table I) shows that the pK_a is not involved since all of the measured values were very close to each other. It is possible, however, that the amount of difference in the *p* values of **3** and **5** could contribute to their difference in activity.

Scheme I. Preparation of 2-Arylbenzoxazole-4-alkanoic Acids[a]

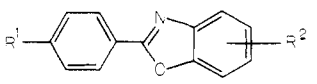


[a] Reagents for method A, ArCOCl-pyridine, heat; B, (1) S + H-c-$N(CH_2CH_2)_2O$, (2) concentrated HCl; C, 2-thioxo-4-thiazolidinone, NaOAc; D, 0.33 N NaOH; E, as B (1); F, concentrated HCl and AcOH; Bx = 4-substituted 2-arylbenzoxazole.

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by Mr. G. Maciak and associates, Eli Lilly & Co., Indianapolis,

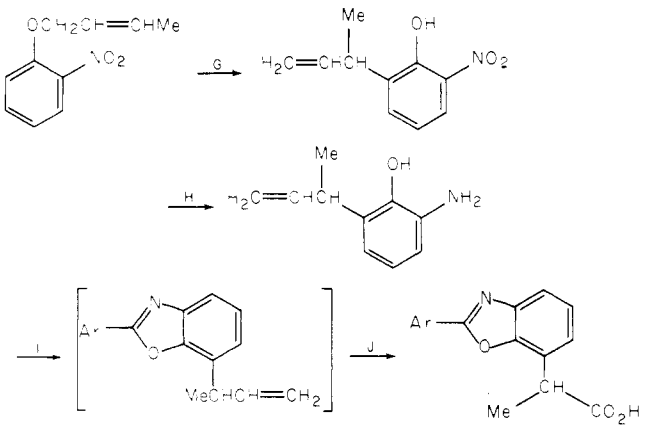
Table I. 4- and 7-Substituted 2-Arylbenzoxazoles



No.	R^1	R^2	Mp, °C	Method	Yield, %	Purifn procedure[a]	Formula	Analyses	Antiinflam act. vs. carrageenan: Dose, mg/kg po × 2	Antiinflam act. vs. carrageenan: % redn[b]	Approx LD_{50} in mice, mg/kg po	p^i	pK_a^j
1	H	4-CH_2CO_2H	176-177	B	19	I	$C_{15}H_{11}NO_3$	C, H, N	100	28[c]	400	1.03	6.30
2	Cl	4-CH_2CO_2H	199-200	B	10	II	$C_{15}H_{10}ClNO_3$	C, H, N	100	8[c]	600	9.28	6.10
3	H	4-CH(Me)CO_2H	140-144	F	3[d]	III	$C_{16}H_{13}NO_3$	C, H, N	50	1[e]	N.T.[f]	6.93	
4	H	4-	253-255	C	8	I	$C_{18}H_{12}N_2O_2S_2$	C, H, N, S	100	9[g]	>1600		
5	H	7-CH(Me)CO_2H	163-164	J	33	II	$C_{16}H_{13}NO_3$	C, H, N	100 50	44*[c] 26**[e]	1200	3.66	6.20
6	Cl	7-CH(Me)CO_2H	198-199	J	16	II	$C_{16}H_{12}ClNO_3$	C, H, N	100	16[c]	1200	16.90	6.25
7	Me	7-CH(Me)CO_2H	202-203	J	14	II	$C_{17}H_{15}NO_3$	C, H, N	100	10[h]	>1600	8.94	6.20

[a] I, recrystallization from C_6H_6-dioxane; II, recrystallization from aqueous MeOH; III, purified by preparative TLC (eluent 10% AcOH in $CHCl_3$) on PLC silica gel 60 F_{254} plates (E. Merck) and precipitation by acid from solution in aqueous $NaHCO_3$. [b] * = result significant on Student's t test at $p < 0.01$; ** = $p < 0.001$. [c] Control compound hydrocortisone gave 57% reduction of edema at 2 × 50 mg/kg per os ($p < 0.001$). [d] Overall yield for steps E and F. [e] Hydrocortisone control: 33% reduction at 2 × 50 mg/kg po ($p < 0.001$). Phenylbutazone control: 59% reduction at 2 × 50 mg/kg po ($p < 0.001$). [f] N.T. = not tested. [g] Phenylbutazone control: 52% reduction at 2 × 33 mg/kg po ($p < 0.001$). [h] Control compound and result as for *e*, but $p < 0.01$. [i] p = partition coefficient between octanol and water (not measured for 4). [j] pK_a measurements were in 75% EtOH (not measured for 3 and 4), values were ±0.025.

Scheme II. Preparation of 2-Arylbenzoxazole-7-alkanoic Acids[a]



[a] Reagents for method G, heat at 170-200 °C for 5 h under N_2; H, Zn-NH_4Cl; I, ArCOCl-pyridine, heat; J, KIO_4-$KMnO_4$ in aqueous Me_2CO.

Ind., and microanalytical results were within ±0.4% of the theoretical values. Ir (Perkin-Elmer 457 spectrophotometer) and NMR (Varian A-60A spectrometer) spectra were obtained for all of the compounds and were consistent with the given structures. Typical examples of the various methods are given below. Further details of compounds 1–7 are noted in Table I.

Method A. 2-Amino-3-hydroxyacetophenone hydrochloride[7] (7.55 g, 0.04 mol) in pyridine (112 ml) was treated with benzoyl chloride (6.2 g, 0.04 mol) and heated at 100 °C for 2 h. The pyridine was evaporated under reduced pressure and the liquid residue heated at 220 °C for 5 min. The cooled residue was dissolved in Et_2O and washed with 2 N NaOH, the Et_2O evaporated, and the residual oil (7.49 g) crystallized from EtOH to give a solid. This was further purified by heating in 2 N HCl (200 ml) for 0.5 h, filtering, washing with H_2O, and recrystallizing from DMF–H_2O to give 4-acetyl-2-phenylbenzoxazole (0.85 g, 9%) as yellow crystals, mp 108 °C. Anal. ($C_{15}H_{11}NO_2$) C, H, N. Similarly, 4-acetyl-2-(4-chlorophenyl)benzoxazole, mp 192 °C, was prepared (49%) and purified by sublimation [160–180 °C (5 mm)]. Anal. ($C_{15}H_{10}ClNO_2$) C, H, Cl, N.

Method B.[8] (1) 4-Acetyl-2-phenylbenzoxazole (6.65 g, 0.03 mol), S (2.16 g, 0.07 g-atom), and morpholine (4.74 g, 0.052 mol) were mixed and stirred at 140 °C for 2 h. The solution was poured into boiling EtOH (30 ml) and cooled in ice to yield a gum. (2) The excess of EtOH was decanted and the residual gum was refluxed with concentrated HCl (50 ml) for 2 h. The HCl was decanted from resinous material, diluted with H_2O to give a solid purified as in Table I, to give **1**.

Method C. 4-Acetyl-2-phenylbenzoxazole (13.7 g, 0.058 mol), 2-thioxo-4-thiazolidinone (6.66 g, 0.05 mol), and NaOAc (4.73 g, 0.058 mol) were mixed and stirred at 120–140 °C overnight. The mixture solidified. It was cooled, ground up, washed with H_2O, filtered, and purified as in Table I to give 2-thioxo-5-(α-methyl-2-phenyl-4-benzoxazolylidene)-4-thiazolidinone (**4**).

Method D.[9] Compound **4** (0.2 g, 0.6 mmol) was stirred with a solution of NaOH (0.24 g, 6 mmol) in H_2O (2.4 ml) at 60 °C for 0.5 h. The material did not dissolve appreciably during this time so sufficient EtOH (5–10 ml) was added to dissolve the solid and stirring was continued for another 0.5 h. The EtOH was evaporated off, H_2O added, and the solution acidified with dilute HCl to give 2-mercapto-3-(2-phenyl-4-benzoxazolyl)-2-butenoic acid (0.15 g, 93%): mp 159–162 °C; NMR [10% $(CD_3)_2SO$ in $CDCl_3$] δ 2.52 (3 H, s, Me), 7.0–7.7 (6 H, m, Ar), 8.25 (2 H, m, Ar), and two exchangeable protons. Anal. ($C_{16}H_{13}NO_3S$) C, H, N, S.

Method E. The above mercaptobutenoic acid (4.27 g, 0.0142 mol), S (0.44 g, 0.0137 g-atom), and morpholine (8.63 ml) were mixed, stirred, and heated at 140 °C for 1.25 h. Evaporation of the morpholine left a dark gum which was substantially 1-morpholino-1-thioxo-2-(2-phenyl-4-benzoxazolyl)propane: ir (film) 1620, 1565, 1495, 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (3 H, d, Me), 4.7–5.2 (1 H, q, CH), 2.8–4.3 (8 H, m, morpholino H's), 7.2–7.6 (6 H, m, Ar), 8.0–8.5 (2 H, m, Ar); mass spectrum m/e 352 (M^+).

Method F. The above morpholino product was refluxed in concentrated HCl (100 ml) and AcOH (50 ml) for 5 h, evaporated to dryness, and purified as in Table I.

Method G. (a) A solution of Na (1.6 g, 0.06 g-atom) in EtOH (55 ml) was treated with 2-nitrophenol (8.8 g, 0.063 mol) and 1-chloro-2-butene (5 g, 0.055 mol) gradually added with stirring. The stirred solution was refluxed for 4.5 h, then further 1-chloro-2-butene (1 g, 0.0112 mol) and some KI were added, and refluxing was continued overnight. The EtOH was evaporated off under reduced pressure; the residue was treated with H_2O and extracted with Et_2O. The ethereal solution was washed with 2 N NaOH solution and with H_2O, dried (Na_2SO_4), filtered, and evaporated to give 1-(2-butenyloxy)-2-nitrobenzene (8 g, 67%), bp 111 °C (0.08 mm). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

(b) 1-(2-Butenyloxy)-2-nitrobenzene (3 g, 9.6 mmol) was heated at 170–200 °C for 5 h. The cooled reaction mixture was dissolved in Et_2O and extracted with 2 N NaOH. The alkaline solution was stirred with C, filtered through Supercel, acidified with HCl, and extracted with Et_2O. The ethereal solution was dried, treated with C, filtered, and evaporated to give 2-(1-buten-3-yl)-6-nitrophenol (1.85 g, 62%), bp 88 °C (0.35 mm). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

Method H. 2-(1-Buten-3-yl)-6-nitrophenol (27.17 g, 0.14 mol) in 90% MeOH (344 ml) with NH_4Cl (20.64 g, 0.39 mol) was stirred at 60 °C and Zn powder (86 g, 1.3 g-atom) added over 40 min. The mixture was stirred and refluxed for 2.5 h and filtered through Supercel. The solution was evaporated, treated with H_2O, and extracted with $CHCl_3$ and the $CHCl_3$ was extracted with 2 N HCl. The HCl was neutralized with $NaHCO_3$ and the product extracted with $CHCl_3$, dried (Na_2SO_4), filtered, and evaporated to give 2-hydroxy-3-(1-buten-3-yl) aniline (14.17 g, 62%) as golden plates, mp 47–48.5 °C, from petroleum ether (bp 40–60 °C). Anal. ($C_{10}H_{13}NO$) C, H, N.

Method I. 2-Hydroxy-3-(1-buten-3-yl)aniline (14.17 g, 0.087 mol) in pyridine (45 ml) with benzoyl chloride (11.4 ml, 0.096 mol) when subjected to conditions of method A gave a 65% pure sample of 2-phenyl-7-(1-buten-3-yl)benzoxazole (15.82 g): NMR (CCl_4) δ 1.53 (3 H, d), 3.98 (H, m), 4.9–5.3 (2 H, m), 5.78–6.5 (H, m), 6.95–7.8 (6 H, m), 8.12–8.50 (2 H, m).

Similarly were prepared 2-(4-methylphenyl)- and 2-(4-chlorophenyl)-7-(1-buten-3-yl)benzoxazoles.

Method J. The 65% pure 2-phenyl-7-(1-buten-3-yl)benzoxazole (15.8 g) in Me_2CO (350 ml) with KIO_4 (105 g, 0.46 mol) was stirred and treated with $KMnO_4$ (10 g, 0.063 mol) in H_2O (500 ml) at 5–10 °C under N_2 while Me_2CO (500 ml) was added simultaneously. The mixture was stirred overnight and then filtered. The filtrate was evaporated and the residue treated with H_2O and extracted with $CHCl_3$. The $CHCl_3$ was extracted with 2 N NaOH and, after acidification of the aqueous phase, the product was extracted with $CHCl_3$, which was dried (Na_2SO_4), filtered, and evaporated to yield 2-phenyl-α-methyl-7-benzoxazoleacetic acid, which was then purified as in Table I.

Acknowledgment. We thank Dr. D. M. Rackham and Mr. R. C. Harden for the determination and assistance with interpretation of spectral results and Mr. C. H. Cashin and Miss E. A. Kitchen for the carrageenan edema results. Miss S. E. Cowdrey determined the partition coefficients.

References and Notes

(1) C. H. Cashin, D. W. Dunwell, D. Evans, T. A. Hicks, and E. A. Kitchen, *J. Med. Chem.*, **18**, 53 (1975).
(2) R. Moreau and S. Durand-Henchoz, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **271** (14), 862 (1970).
(3) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32 (1956).
(4) M. Nishio and T. Ho, *Agric. Biol. Chem.*, **29**, 1119 (1965).
(5) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(6) Cf. G. Redl, R. D. Cramer III, and C. E. Berkoff, *Chem. Soc. Rev.*, 273 (1974).
(7) A. Spada and E. Casini, *Gazz. Chim. Ital.*, **80**, 642 (1950).
(8) Cf. M. Carmack and M. A. Spielman, *Org. React.*, **3**, 85 (1946).
(9) Cf. T. H. Haskell, *J. Med. Chem.*, **13**, 697 (1970).

Butyrophenones from the Isomeric 2-Amino-5-phenylbicyclo[3.3.1]nonanes

Daniel Lednicer

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001. *Received April 28, 1976*

The preparation of 5-phenylbicyclo[3.3.1]nonan-2-one is described starting from the ketal of 4-phenyl-4-(2-carbethoxyethyl)cyclohexan-1-one. The ketone was then taken on to the butyrophenone derivatives of *endo*- and *exo*-5-phenylbicyclo[3.3.1]nonyl-2-amine. CNS screening results of these compounds are described.

Piperidines bearing a *p*-fluorobutyrophenone moiety on nitrogen and an aromatic ring in the vicinity of the 4 position have proven an unusually rich source for neuroleptic agents.[1] It is of interest that wide structural latitude maintains as to the nature of the attachment of the aryl group. We have shown that environment about nitrogen can be similarly modified; butyrophenones of 4-phenylcyclohexylamine exhibit good psychotropic activity.[2] Both piperidines and cyclohexylamines possess conformational freedom; it was of some interest to ascertain the biological activity of analogues containing nitrogen attached to a rigid cyclohexyl fragment.

Chemistry. Internal alkylation provided access to the requisite intermediate 5-phenylbicyclo[3.3.1]nonan-2-one (**4**). Thus, reduction of ester ketal **1**[3] gave the corresponding alcohol **2**; this was then converted to the mesylate and hydrolyzed to give the ketone **3**. Treatment of that intermediate with *t*-BuOK in THF afforded the desired bicyclic ketone **4** in 78% yield.

Reduction of the ketone by means of $NaBH_4$ gave a single alcohol, in contrast to the observation on the corresponding 4-arylcyclohexanones.[2] This is assigned the configuration **5** based on the known propensity of this reaction to give equatorial alcohols. The NMR spectrum of the mesylate **6** (carbinyl H, seven-line pattern centered at δ 5.0) supports this assignment. The mesylate was then taken on to the axial butyrophenone (**9**) by standard manipulations.

Preparation of the epimer started by conversion of the ketone to the oxime **10**; reduction of the corresponding acetate **11** by means of diborane gave a primary amine **12** clearly different from **8**. This was then taken on to the butyropheone **13**.

Pharmacology. The effects of the compounds on overt behavior as well as nicotine toxicity in mice were determined using procedures described earlier.[4] The results are listed in Table I.

The present compounds show a great diminution in activity from the corresponding cyclohexylamines[2] using nicotine antagonism as an index of potency. The relative configuration of the amine and nitrogen seems to have little effect on the biological activity of these compounds.