2-Benzodioxinylaminoethanols: A New Class of β-Adrenergic Blocking and Antihypertensive Agents

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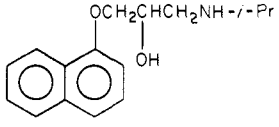
Various 2-benzodioxinylaminoethanol derivatives were synthetized and investigated for β-adrenergic blocking activity. Most compounds demonstrated a β-blocking activity of a competitive type when evaluated in guinea pig atrial and tracheal preparations. Three compounds were more potent than practolol and propranolol. All compounds demonstrated antihypertensive properties in spontaneously hypertensive rats. The most active compound was 1-(1,4-benzodioxin-2-yl)-2-[N^4-(2-methoxyphenyl)piperazino]ethanol (11), which at 2.5 mg/kg iv lowered blood pressure by 41%.

The β-adrenergic antagonist drug propranolol (1)[1] and a number of other (aryloxy)propanolamines, such as practolol,[2] metoprolol,[3] and atenolol,[4] have been shown to be effective in humans for the treatment of hypertension.



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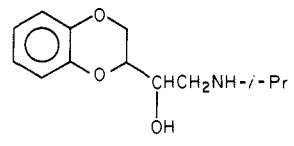
Moreover, other compounds, such as benzodioxanylethanolamines 2[5] and 3[6] and benzofuranylethanolamines 4[7] and 5[8] which are ring-closed, ortho-substituted (aryloxy)propanolamines, are β blockers and exhibit antihypertensive properties.

It was, therefore, interesting to prepare the closely related benzodioxinylaminoethanols 6–13 to evaluate their specificity for β_1 and β_2 receptors and their antihypertensive activity. Indeed, the flattening of the molecule as a result of the introduction of a double bond could influence both the pharmacological properties and metabolic pathways. Furthermore, the insertion of the ethylenic bond will eliminate one of the chiral centers and, consequently, the difficult separation of diastereoisomers.[9]

Chemistry. Compounds 6–13 were prepared as indicated in Scheme I and are listed in Table I. Treatment of the starting 2-carbethoxy-1,4-benzodioxan (14)[10] with



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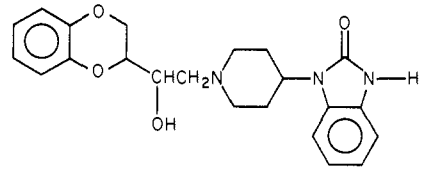

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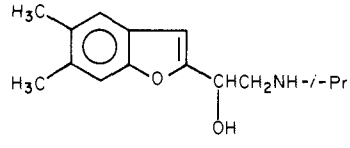

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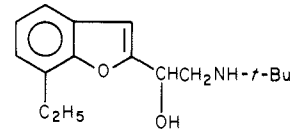

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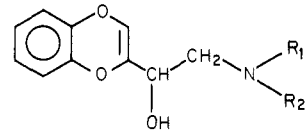

6-13

N-bromosuccinimide (NBS) in carbon tetrachloride, followed by sodium iodide in acetone, gave 2-carbethoxy-1,4-benzodioxin (16) with almost quantitative yield.[11] The corresponding acid 17 was obtained after saponification by 8% sodium hydroxide for 1 h at 95 °C (85–95% yield).

Either more prolonged or more vigorous treatment led to a decreased overall yield. The chloromethyl ketone 19 was prepared in 75–83% yield from the acid chloride 18 by action of diazomethane, followed by hydrogen chloride. Reduction of the chloro ketone 19 to chloro alcohol 20 with $LiAlH_4$ was preferred to $NaBH_4$. Finally, the aminoethanols 6–13 were obtained via nucleophilic substitution

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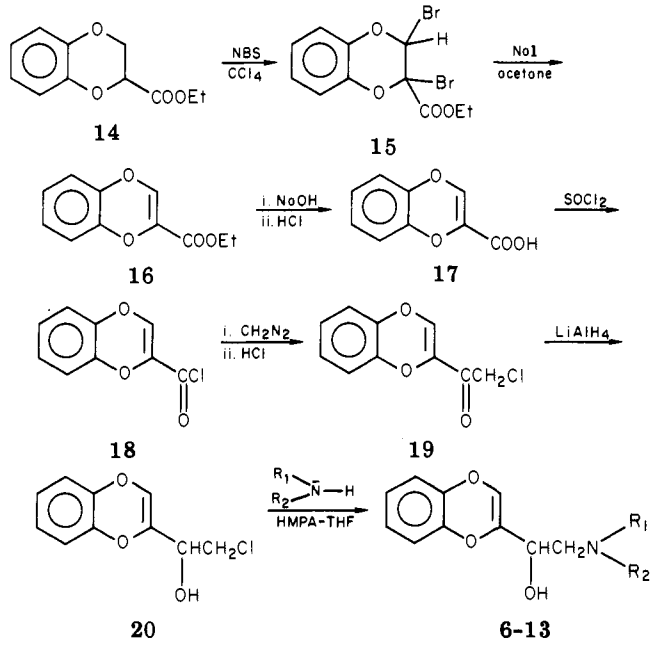
Scheme I



of the chloro alcohol **20** (or of the corresponding epoxide formed in situ) with amines, generally using hexamethylphosphoramide (HMPA)–tetrahydrofuran (THF) as solvent. The yields of this last step varied between 48 and 78%. The procedure involving the direct attack of the chloro ketone **19** by the amino compounds failed. Likewise, the epoxide was not available from the chloro alcohol **20** under more classical conditions.

Pharmacological Results and Discussion

In order to determine the affinity of the compounds for β_1 and β_2-adrenoceptor subtypes, studies were carried out using pharmacological models showing receptor specificity, i.e., isolated guinea pig left atria (β_1) and isolated guinea pig trachea (β_2).

Table I shows the pharmacological results obtained with compounds derived from 2-benzodioxinylaminoethanols. All the compounds, except compound **12**, showed β_1-blocking activity of the competitive type. The most interesting examples were **6**, **7**, and **10**. After comparison with reference drugs, these representatives were significantly (Student's t test) more potent than practolol, while compound **10** was significantly more potent than propranolol. In addition to their competitive type of interaction, i.e., a parallel shift of the cumulative log dose–response curves to the right, compounds **7**, **11**, and **13** also induced a reduction in the slope of the curves and the maximum contraction. This means that these compounds have mixed competitive and noncompetitive (dualistic) antagonist activity, which is characterized by their pA_2 and pD_2' values.

Both compound **7** and propranolol were equipotent on the trachea (β_2). The β_2-blocking activity decreased for compounds **6**, **10**, **8** and **9**, while the three others, **11**–**13**, were inactive up to doses of 10^{-4} M.

Compound **10** is characterized by high cardioselectivity ($\beta_1/\beta_2 = 90$) in comparison to compound **6** ($\beta_1/\beta_2 = 10$); this is in agreement with Hoefle et al.,[12] who pointed out equivalent cardioselectivity in the case of other substrates bearing the homoveratrylamine moiety. All compounds were tested on isolated rat vas deferens for possible interaction with α-adrenergic receptors. None of the 2-benzodioxinylaminoethanols tested in this model were as active as α-adrenoceptor antagonists.

An evaluation of the antihypertensive activities was carried out in spontaneous hypertensive rats (SHR). Since the initial work of Prichard and Gillam in 1964,[13] it is currently accepted that most β-blocking agents possess antihypertensive properties. This activity is difficult to establish, since there is a lack of a consistent and predictable response to these drugs in a convenient animal model. Some investigators reported that these drugs have no effect on the blood pressure of SHR;[14-16] others showed that the agents caused a further increase in arterial pressure,[17-19] whereas in some studies varying degrees of a depressor effect were shown, depending on the age and the sex of the animal, the drug and dosage used, the route of administration, and the duration of the treatment.[16,17,20,21]

The compounds were administered intravenously to anesthetized, spontaneously hypertensive rats (SHR). Some β-adrenergic blocking agents have already been tested in this model, i.e., propranolol and alprenolol,[22] practolol and propranolol (present study), and pindolol and sotalol (unpublished results). All these β-adrenergic blocking agents at high doses induce antihypertensive effects. This fall in blood pressure cannot be ascribed to intrinsic β-agonist activity, since propranolol and sotalol are active in this system but have no partial agonist activity.[23]

The results are presented in Table II. The doses listed in this table are the minimal dose levels giving an antihypertensive effect for at least 20 min. All the compounds tested in the 2-benzodioxinylaminoethanol series revealed antihypertensive properties. The most active compound was 1-(1,4 benzodioxin-2-yl)-2-[N^4-(2-methoxyphenyl)-piperazino]ethanol (**11**), which at 2.5 mg/kg decreased blood pressure by 41%, with activity lasting more than 45 min. Compounds **6**, **10**, and **13** also had equipotent or even higher antihypertensive activity than propranolol. The doses used for the reference drugs were higher than those described in the literature for inducing clear blockade of β receptors in vivo. In order to compare β-blocking activity and antihypertensive potency, experiments were carried out with chloralose-anesthetized dogs, using the most frequently studied 2-benzodioxinylaminoethanol and reference drugs propranolol and practolol. β-Blocking potency was evaluated from the ability of the drugs to inhibit the hypotension, tachycardia, and positive ventricular in-

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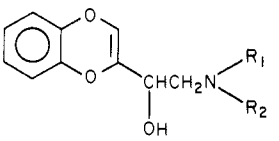
(23) Frishman, W.; Silverman, R. *Am. Heart J.* **1979**, *97*, 797–807.

Table I. Physical Properties and β-Blocking Activities of 2-Benzodioxinylaminoethanols



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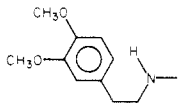
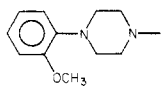
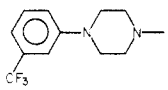
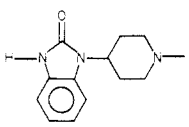
no.	R_1, R_2	yield,[a] %	mp, °C	salt	mol. formula[b]	apparent pA_2 and pD_2'[c] atrium[d]	trachea[e]
6		58	178	HCl	$C_{13}H_{18}ClNO_3$	$pA_2 = 7.81 \pm 0.12$ (4)	$pA_2 = 6.79 \pm 0.17$ (4)
7		78	163	HCl	$C_{14}H_{20}ClNO_3$	$pA_2 = 8.07 \pm 0.31$ (4) $pD_2' = 4.8$	$pA_2 = 7.09 \pm 0.68$ (5)
8		53	208	HCl	$C_{15}H_{20}ClNO_3$	$pA_2 = 6.21 \pm 0.16$ (3)	$pA_2 = 5.87 \pm 0.30$ (4)
9		47	186	HCl	$C_{16}H_{22}ClNO_3$	$pA_2 = 5.93 \pm 0.84$ (4)	$pA_2 = 4.77 \pm 0.16$ (3)
10		43	105	base	$C_{20}H_{23}NO_5$	$pA_2 = 8.70 \pm 0.31$ (5)	$pA_2 = 6.75 \pm 0.08$ (3)
11		56	102	base	$C_{21}H_{24}N_2O_4$	$pA_2 = 6.58 \pm 0.55$ (3) $pD_2' = 4.84 \pm 0.39$ (3)	*f* *f*
12		42	140	base	$C_{21}H_{21}F_3N_2O_3$	*f*	*f*
13		42	197	base	$C_{22}H_{23}N_3O_4$	$pA_2 = 6.84 \pm 0.19$ (5) $pD_2' = 4.89 \pm 0.25$ (4)	*f*
propranolol						$pA_2 = 8.06 \pm 0.045$ (54)	$pA_2 = 7.36 \pm 0.168$ (19)
practolol						$pA_2 = 6.76 \pm 0.092$ (15)	*f*

[a] Yield based on the last step. [b] All compounds were analyzed for C, H, and N. [c] pA_2 and pD_2' values ± SD, with the number of experiments in parentheses. [d] Antagonism of the isoprenaline-induced positive inotropic effect. [e] Antagonism of the isoprenaline-induced relaxations. [f] Inactive at 10^{-4} mol/L.

Table II. Antihypertensive Action of 2-Benzodioxinylaminoethanols on SH Rats

compd	dose, mg/kg iv	max blood pressure change,[a] % dia-stolic	sys-tolic	duration of action, min
placebo		−9	−12	
6	5	−60	−49	>45
7	10	−57	−50	25
8	20	−78	−66	20
9	10	−57	−44	20
10	2,5	−37	−33	>25
11	2,5	−41	−41	>45
12	20	−83	−65	20
13	2,5	−43	−38	>25
propranolol	5	−64	−54	30
practolol	20	−31	−32	45

[a] A Student's *t* test was carried out. All compounds induced a significantly different diastolic and systolic blood pressure change from measurements on controls ($p < 0.05$).

otropism induced by isoprenaline (0.5 μg/kg iv). The doses required to induce at least 50% inhibition of the isoprenaline-induced effects were 0.25 mg/kg iv for propranolol, 1 mg/kg iv for compounds **7**, **10**, and **13**, 2.5 mg/kg iv for practolol, and 10 mg/kg iv, for compounds **9** and **12**. This demonstrated that the compounds exert β-blocking activity in vivo at lower doses than those needed to induce an antihypertensive effect in anesthetized SHR (see Table II). Compound **11** is at variance with these results, since doses higher than 5 mg/kg iv were necessary to induce 50% inhibition of the isoprenaline-induced effects in vivo, whereas doses of 2.5 mg/kg iv were sufficient to induce a marked and long-lasting antihypertensive effect. This difference is probably due to the dualistic character of **11** shown in vitro (Table I) and demonstrated that no clear relationship exists between β blockade and antihypertensive activity.

Experimental Section

Chemistry. Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were taken on a Perkin-Elmer 257 and the ^1H NMR spectra on a Perkin-Elmer R 12 with tetramethylsilane as internal standard. All compounds were analyzed for C, H, and N and are within ±0.4% of the theoretical values.

2-Carbethoxy-1,4-benzodioxan (14). This compound was obtained according to the method of Koo[10] in 80% yield.

2-Carbethoxy-1,4-benzodioxin (16). A mixture containing 62.4 g (0.3 mol) of 2-carbethoxy-1,4-benzodioxan (**14**) 120 g (0.66 mol) of NBS, and 2 g of benzoyl peroxide in 300 mL of dry CCl_4 was refluxed for 6–7 h. After the mixture was cooled and filtered, the solvent was evaporated in vacuo; crude 2-carbethoxy-2,3-dibromo-1,4-benzodioxan (**15**; mp 88 °C) was dissolved in 600 mL

of dry acetone. After the addition of 180 g of dry NaI and agitation for 1.5 h at room temperature, acetone was evaporated. Water, ether and, hyposulfite were added. The organic layer was separated, washed with hyposulfite and water, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure 59 g (95% yield) of 2-carbethoxy-1,4-benzodioxin (**16**) was collected: mp 39–40 °C (pentane); IR (neat, NaCl) 1735 (CO), 1675 (C=C) cm^{-1}; NMR (CCl_4) δ 7.00–6.40 (br s, 5 H, aromatic and ethylenic), 4.15 (q, J = 7.3 Hz, 2 H, CH_2), 1.29 (t, J = 7.3 Hz, 3 H, CH_3). Anal. ($C_{11}H_{10}O_4$) C, H.

2-Carboxy-1,4-benzodioxin (17). The crude ester **16** (38 g, 0.18 mol) was saponified at 95 °C by 8% NaOH for 1 h. After cooling, the acid was precipitated by the addition of concentrated HCl; 30 g (93% yield) of 2-carboxy-1,4-benzodioxin (**17**) was collected after filtration: mp 176 °C (benzene); IR (KBr) 3500–2800 (OH), 1715 (CO) 1670 (C=C) cm^{-1}; NMR (Me_2CO-d_6) δ 9.30 (s, 1 H, OH), 7.10 (s, 1 H, ethylenic), 7.20–6.60 (br s, 4 H, aromatic). Anal. ($C_9H_6O_4$) C, H.

2-(Chlorocarbonyl)-1,4-benzodioxin (18). A mixture of 2-carboxy-1,4-benzodioxin (**17**; 5 g, 28 mmol) and thionyl chloride (10 g, 85 mmol) in anhydrous benzene (250 mL) was refluxed during 6 h. The 2-(chlorocarbonyl)-1,4-benzodioxin (**18**; 5.5 g) was obtained quantitatively after removal of excess benzene and thionyl chloride under vacuo: mp 106–107 °C; IR (KBr) 1740 (CO), 1665 (C=C) cm^{-1}; NMR (CCl_4) δ 7.25 (s, 1 H, ethylenic), 7.00–6.50 (br s, 4 H, aromatic). Anal. ($C_9H_5ClO_3$) C, H, Cl.

Chloromethyl 1,4-Benzodioxin-2-yl Ketone (19). The acid chloride **18** (16.50 g, 84 mmol) dissolved in anhydrous ether (350 mL) was added slowly at −10 to −20 °C to a solution of diazomethane prepared from nitrosomethylurea[24] (28 g). After the solution stirred for 30 min at −10 to −20 °C and then for 14 h at room temperaure, a saturated solution of HCl in ether was rapidly added and, after the end of the reaction (2 h, verified by TLC), the ether layer was washed with a saturated solution of $NaHCO_3$. After the solvents were dried over Na_2SO_4 and evaporated under reduced pressure, the crude product was dissolved in benzene–petroleum ether (1:4) (400 mL). The solution obtained after filtration was evaporated, and the solid was washed with 75 mL of ether–petroleum ether (1:2). The product weighed 12.7–14.2 g (74–83% yield): mp 91–92 °C; IR (KBr) 1720 (CO), 1660 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.20–6.50 (br s, 5 H, aromatic and ethylenic), 4.27 (s, 2 H, CH_2). Anal. ($C_{10}H_7ClO_3$) C, H, Cl.

1-(1,4-Benzodioxin-2-yl)-2-chloroethanol (20). The chloro ketone **19** (5.25 g, 25 mmol) was reduced by an excess of $LiAlH_4$ in anhydrous ether (250 mL) at 20 °C for 1 h to give **20** as a colorless oil (5.30 g, 100%); IR (neat, NaCl) 3400 (OH), 1710 (C=C) cm^{-1}; NMR (CCl_4) δ 6.95–6.44 (br s, 4 H, aromatic), 5.99 (s, 1 H, ethylenic), 4.29–3.95 (m, 1 H, CH), 3.83–3.30 (m, 2 H, CH_2) 3.19 (s, 1 H, OH). Anal. ($C_{10}H_9ClO_3$) C, H, Cl.

1-(1,4-Benzodioxin-2-yl)-2-aminoethanol (6–13). 1-(1,4-Benzodioxin-2-yl)-2-(isopropylamino)ethanol (6). The chloro alcohol **20** (3.50 g, 16.6 mmol) dissolved in isopropylamine (15 mL) and hexamethylphosphoramide (HMPA; 50 mL) was heated for 15 h at 80 °C. After the mixture cooled, an excess of 20% HCl was added. The organic layer containing the starting chloro alcohol **20** was taken up in Et_2O. The acidic aqueous solution was made basic with 20% NaOH and then extracted with ether. After washing (H_2O), the ether layer was dried ($MgSO_4$) and evaporated under reduced pressure to yield **6** (2.30 g, 58%): mp 97–98 °C (petroleum ether–benzene); IR (KBr) 3600–2500 (OH, NH, CH), 1710 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 6.95–6.45 (m, 4 H, aromatic), 5.99 (s, 1 H, ethylenic), 3.97 (t, J = 6 Hz, 1 H, C*H*OH), 3.15–2.46 (m, 5 H, OH, NH, CH_2, CHN), 1.08 (d, J = 5.65 Hz, 6 H, CH_3). Anal. ($C_{13}H_{17}NO_3$) C, H, N.

1-(1,4-Benzodioxin-2-yl)-2-(*tert*-butylamino)ethanol (7). The chloro alcohol **20** (1.80 g, 8.6 mmol) dissolved in *tert*-butylamine (15 mL) and HMPA (10 mL) was heated for 24 h at 55 °C to yield **7** (1.65 g, 78%) after treatment as described for **6**: mp 74–75 °C (petroleum ether); IR (neat, NaCl) 3600–2500 (OH, NH, CH), 1705 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 6.90–6.50 (m, 4 H, aromatic), 6.03 (s, 1 H, ethylenic), 4.01 (t, J = 6 Hz, 1 H, C*H*OH), 3.35 (s, 2 H, OH and CH), 2.77 (d, J = 6 Hz, 2 H, CH_2), 1.10 (s, 9 H, CH_3). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

1-(1,4-Benzodioxin-2-yl)-2-piperidinoethanol (8). The chloro alcohol **20** (5.50 g, 26 mmol) and piperidine (6.80 g, 80 mmol) were dissolved in THF (15 mL) and HMPA (30 mL). The solution was stirred at 85 °C for 15 h to yield **8** (3.40 g, 53%) after treatment as described for **6**: mp 88–89 °C (benzene–petroleum ether); IR (neat, NaCl) 3600–2500 (OH, NH, CH), 1705 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 6.95–6.45 (m, 4 H, aromatic), 6.00 (s, 1 H, ethylenic) 4.15–3.84 (m, 1 H, C*H*OH), 3.76 (s, 1 H, OH), 2.90–2.15 (m, 6 H, CH_2N), 1.85–1.25 (br s, 6 H, CH_2). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

1-(1,4-Benzodioxin-2-yl)-2-homopiperidinoethanol (9). As described above for **8**, 3.30 g of **9** (47%) was obtained from homopiperidine (8 g, 80 mmol) and **20** (5.50 g, 26 mmol): mp 68–69 °C (benzene–petroleum ether); IR (KBr) 3600–2500 (OH, NH, CH), 1705 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 6.97–6.47 (m, 4 H, aromatic), 6.00 (s, 1 H, ethylenic), 3.86 (t, J = 6.65 Hz, 1 H, C*H*OH), 3.34 (s, 1 H, OH), 2.90–2.53 (m, 6 H, CH_2N), 1.93–1.40 (m, 8 H, CH_2). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

1-(1,4-Benzodioxin-2-yl)-2-[[(3,4-dimethoxyphenyl)ethyl]amino]ethanol (10). The chloro alcohol **20** (4.20 g, 20 mmol) and homoveratrylamine (9 g, 50 mmol) were dissolved in THF (15 mL) and HMPA (30 mL). The solution was stirred at 85 °C for 6 h and yielded 2 g (47%) of unchanged starting material (**20**) and 2.9 g (43%) of **10** after the usual treatment: mp 105 °C (methanol); IR (KBr) 3600–2500 (OH, NH, CH), 1705 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.95–6.50 (m, 7 H, aromatic), 5.97 (s, 1 H, ethylenic) 3.97 (t, J = 6 Hz, 1 H, C*H*OH), 3.81 (s, 6 H, OCH_3), 3.13–2.51 (br s, 8 H, CH_2, OH and NH). Anal. ($C_{20}H_{23}NO_5$) C, H, N.

1-(1,4-Benzodioxin-2-yl)-2-[N^4-(2-methoxyphenyl)piperazino]ethanol (11). As described above for **8** and after heating for 30 h, 5 g (56%) of **11** was obtained from *N*-(2-methoxyphenyl)piperazine (15 g, 80 mmol) and **20** (5.50 g, 26 mmol): mp 102 °C (benzene): IR (KBr) 3600–2500 (OH, NH, CH), 1710 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.15–6.55 (m, 8 H, aromatic), 6.06 (s, 1 H, ethylenic), 4.21–3.88 (m, 1 H, C*H*OH), 3.85 (s, 3 H, OCH_3), 3.41 (s, 1 H, OH), 3.30–2.50 (m, 10 H, CH_2). Anal. ($C_{21}H_{24}N_2O_4$) C, H, N.

1-(1,4-Benzodioxin-2-yl)-2-[N^4-[3-(trifluoromethyl)phenyl]piperazino]ethanol (12). As described above for **8** and after heating for 40 h, 4.2 g (42%) of **12** was obtained from *N*-[3-(trifluoromethyl)phenyl]piperazine (16 g, 80 mmol) and **20** (5.50 g, 26 mmol): mp 140 °C (benzene); IR (KBr) 3600–2500 (OH, NH, CH), 1705 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.50–6.52 (m, 8 H, aromatic), 6.10 (s, 1 H, ethylenic), 4.26–3.93 (m, 1 H, C*H*OH), 3.46 (s, 1 H, OH), 3.35–2.50 (2 br s, 10 H, CH_2). Anal. ($C_{21}H_{21}F_3N_2O_3$) C, H, N.

1-[1-[2-(1,4-Benzodioxin-2-yl)-2-hydroxyethyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (13). The chloro alcohol **20** (5.25 g, 25 mmol) and 4-(2-keto-1-benzimidazolinyl)piperidine (10.8 g, 50 mmol) were dissolved in THF (15 mL) and HMPA (30 mL). After 5 h at 85 °C with stirring and then the usual treatment, 2.1 g (45%) of unchanged starting material **20** and 4.1 g (42%) of **13** were obtained: mp 197 °C (EtOH); IR (KBr) 3600–2500 (OH, NH, CH), 1705–1700 (CO, C=C) cm^{-1}; NMR (Me_2SO-d_6) δ (7.40–6.00 (m, 10 H, aromatic, NH, OH), 6.28 (s, 1 H, ethylenic), 4.40–3.85 (br s, 2 H, C*H*OH and C*H*N), 3.30–1.40 (m, 10 H, CH_2). Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

Pharmacology. Pharmacological Tests of β-Adrenergic Blocking Activity. β_1-Adrenergic and β_2-adrenergic blocking activities were determined on the atria and trachea of guinea pigs. The antagonism of isoprenaline-induced positive inotropism was measured on electrically stimulated left atria according to Labrid.[25] The preparations were suspended in a Krebs solution at 37 °C and aerated with a mixture of 95% O_2 and 5% CO_2. Contractions were recorded isotonically. The resting tension was set at 0.5 g. The preincubation time of the antagonists was 15 min before the next cumulative dose–response curve with isoprenaline was

(24) Arndt, F. in "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 165.

(25) Labrid, C.; Grosset, A.; Dureng, G.; Mironneau, J.; Duchene-Marullaz, P. *J. Pharmacol. Exp. Ther.* **1979**, *211*, 546–554.

performed. β_2-Adrenergic blocking activity was estimated with spirally cut tracheal segments. The segment of trachea was placed in a Krebs solution at 37 °C and gassed with 5% CO_2 in O_2. Contractions were recorded isotonically with a 2-g preload. The preincubation time of the antagonists was 3 min. Calculation of the classical parameters indicating possible activity (pA_2, pD_2') was performed according to the technique of Van Rossum.[26]

SHR Test for Antihypertensive Activity. Thirty-one spontaneously hypertensive male rats, 35 to 39 weeks of age, were used. They were anesthetized with pentobarbital (45 mg/kg intraperitoneally). Blood pressure was measured in the carotid artery and was recorded with a Statham pressure transducer. The drugs were injected intravenously in increasing doses until an antihypertensive effect of at least 20-min duration was observed. A 60-min period was observed between two consecutive doses. The maximal variations of both diastolic and systolic blood pressure under the influence of the drugs are calculated in percentages of the initial values before treatment. Since usually three rats were used in each group, no statistical evaluation was performed.

(26) Van Rossum, J. M. *Arch. Int. Pharmacodyn. Ther.* **1963**, *143*, 299-330.

Notes

2-(Arylmethyl)arylacetic Acids as Potential Antiinflammatory Agents

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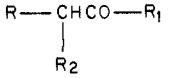
Received August 4, 1980

The title compounds **2** have been synthesized and tested for antiinflammatory activity. The synthetic method, consisting of the chemical sequence 3-aryl-1*H*-indenes (**4**) → 2-(aroyl)arylacetic acids (**5**) → **2**, appears to be of value because of its simplicity and generally acceptable yields. The synthesized compounds showed low pharmacological activity.

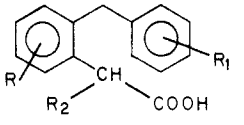
A research area of continuous and ever-growing development is that of nonsteroidal antiinflammatory agents. Derivatives of arylacetic acids[2a] of formula **1** probably



1, R = aryl, heteroaryl; R_1 = OH, NHOH, NH_2; R_2 = H, alkyl

represent the class in which the greatest research effort has occurred. This class has produced many pharmacologically interesting compounds, several of which have been clinical candidates.[2b]

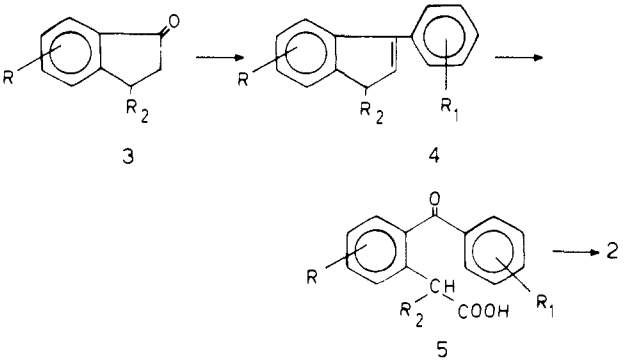
Therefore, we were interested in synthesizing a new series of 2-(arylmethyl)arylacetic acids (**2**), in order to investigate their antiinflammatory properties.



2, R = H, Cl, CH_3, OCH_3; R_1 = H, Cl, CH_3, OCH_3; R_2 = H, CH_3

Chemistry. 2-(Arylmethyl)arylacetic acids (**2**) can be prepared by the procedures of Leonard et al.[3] and Rigaudy and Nedelec.[4] These methods, however, are rather troublesome, require the use of carefully handled reagents, and, therefore, are unsuitable for large-scale preparations. We have prepared compounds **2** by the reaction sequence shown in Scheme I.

Scheme I



The starting indanones, **3**, were treated with the appropriate Grignard reagent, and the resulting alcohols were dehydrated to the indenes. Previously unreported compounds are reported in Table IV.

The substituted 3-aryl-1*H*-indenes **4** were oxidized to the corresponding 2-(aroyl)arylacetic acids **5**, which in turn could be reduced to the expected 2-(arylmethyl)arylacetic acids **2**. The conversion[5] of **4** into **5** was usually accomplished by $K_2Cr_2O_7$ in H_2SO_4 solution at 55 °C.

(1) Consorzio Regionale Farmaceutico Ospedaliero Via Manzoni 249, Napoli, Italy.

(2) (a) P. F. Juby in "Antiinflammatory Agents", Vol 1, R. A. Scherrer and M. W. Whitehouse, Eds., Academic Press, New York, 1974, p 91. (b) P. F. Juby, ref 2a, p 99. *Drugs Today*, **15**, 43 (1979); **15**, 91 (1979). *Drugs Future*, **3**, 924 (1978); **4**, 373 (1979).

(3) N. J. Leonard, A. J. Kresge, and M. Oki, *J. Am. Chem. Soc.*, **77**, 5078 (1955).

(4) J. Rigaudy and L. Nedelec, *Bull. Soc. Chim. Fr.*, 638 (1959).

(5) C. F. Koelsch and C. D. Le Claire [*J. Org. Chem.*, **6**, 516 (1941)] reported the oxidation of 1,1-dimethyl-3-phenylindene to 2-benzoyl-α,α-dimethylbenzeneacetic acid. However, it must be noted that this last compound, in contrast to compounds of structure **5**, is resistant to further oxidation.

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