α-(2-Pyridine)benzyl Aryl Ketones as Potential Hypocholesteremic Agents

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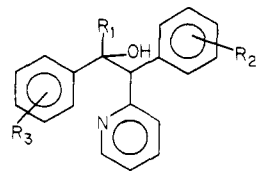
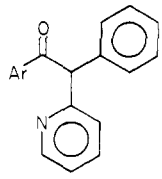
A series of α-(2-pyridine)benzyl aryl ketones were prepared as potential hypocholesteremic agents. The synthesis of these compounds was by conversion of 2-benzylpyridine to its anion with *n*-butyllithium and condensation of the anion with selected aromatic esters. The ketones were tested for their hypocholesteremic activity in rats, and those compounds showing activity were further tested for estrogenicity. Only those aryl ketones with substituents in the ortho position showed a statistically significant reduction in serum cholesterol. Of these compounds the *tert*-butyl derivative had the most favorable hypocholesteremic to estrogenic ratio.

A large number of derivatives of generic structure I were



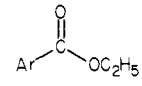
I



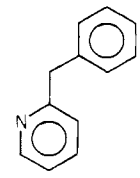
II

prepared by Burckhalter et al.[1] as potential hypocholesteremic agents having minimal estrogenic activity. Several of the compounds exhibited significant serum cholesterol lowering activity in rats with only slight estrogenic effect. However, compound I (R_1 = CH_3; R_2 = H; R_3 = *m*-Cl) failed to lower serum cholesterol both in monkeys and in a human clinical trial.[1] Efforts to find effective agents among structurally related substances have resulted in the synthesis of the series of α-(2-pyridine)-benzyl aryl ketones, II, given in Table I.

Ketones of type II were prepared by conversion of 2-benzylpyridine (IV) to the anion with butyllithium, followed by condensation with the appropriate aromatic ester, III. In general, a 1:1 ratio of reactants was employed. However, in some cases, as observed by Levine and Raynolds,[3] a 2:1 ratio of benzylpyridine anion to ester gave optimal yields. Three of the aryl ketones (**2**, **5**, and **10**)



III



IV

Table I. α-(2-Pyridine)benzyl Aryl Ketones II

compd no.	aryl group	yield,[a] %	mp, °C	hypocholesteremic activity[b] serum cholesterol,[c] mg/100 mL	hypocholesteremic activity[b] change in cholesterol, %	p[d]	estrogenicity[e]
1	phenyl	69	119-121	73.0 ± 1.0	+2.5	ns	
2	2-bromophenyl	56	143-144	32.7 ± 8.5	-54.1	0.001	0.87
3	3-bromophenyl	74	110-112	76.3 ± 8.5	+6.7	ns	
4	4-bromophenyl	46	96-98.5	55.0 ± 5.7	-22.8	ns	
5	2-chlorophenyl	72	145-147	30.7 ± 9.1	-56.9	0.001	0.80
6	3-chlorophenyl	62	106-107.5	71.3 ± 5.9	0.0	ns	
7	4-chlorophenyl	12	95-98	68.7 ± 4.7	-3.5	ns	
8	2-fluorophenyl	53	112-113	50.0 ± 4.4	-30.0	0.025	0.45
9	4-fluorophenyl	43	128-129.5	70.3 ± 4.5	-1.3	ns	
10	2-iodophenyl	42	146-147	16.3 ± 5.8	-77.1	0.001	0.70
11	4-iodophenyl	26	104-105	71.5 ± 3.6	0.0	ns	
12	2-methylphenyl	32	142-144.5	25.0 ± 8.5	-64.9	0.001	0.82
13	3-methylphenyl	22	74-76.5	82.0 ± 2.6	+13.2	ns	
14	4-methylphenyl	33	97.5-99	72.3 ± 4.0	+1.5	ns	
15	2-*tert*-butylphenyl	42	116.5-118	18.4 ± 7.1[f]	-42.0	0.005	0.29
16	4-*tert*-butylphenyl	21	127-129	32.5 ± 6.0[f]	0.0	ns	
17	4-methoxyphenyl	21	104-105	60.0 ± 1.7	-15.7	ns	
18	3-bromo-4-methoxyphenyl	24[g]	128-129.5	80.3 ± 2.5	+11.3	ns	
19	3,4-dimethoxyphenyl	40	96.5-98	76.0 ± 3.5	+6.3	ns	
20	3,4-(methylenedioxy)phenyl	35	119.5-121	76.0 ± 7.5	+6.3	ns	
21	2-phenoxyphenyl	70	104-105.5	60.3 ± 4.5	-15.0	ns	
22	3-(benzyloxy)phenyl	49	86.5-88	81.0 ± 1.1	+12.1	ns	
23	4-(benzyloxy)phenyl	35	139-140.5	78.5 ± 3.5	+9.3	ns	
24	3-pyridyl	13	104-106	69.7 ± 6.7	-2.1	ns	
25	2-naphthyl	31	105-107	71.3 ± 2.3	0.0	ns	
26	7-chloro-2-phenyl-4-quinolyl	17[g]	162.5-163.5	74.0 ± 1.6	+3.8	ns	

[a] Purified yield. All compounds were recrystallized from ethanol or methanol; both work equally well. [b] Dose: 25 mg/kg in 200-g rats for 7 days. As a control, 10 rats were dosed with vehicle only and resulted in an average serum cholesterol of (71.2 ± 8.4 mg)/100 mL. Recorded as the mean ± standard deviation. [c] See ref 4 for method of determination. [d] Student's *t* test. ns = not significant. [e] The micrograms of 17β-estradiol that produce an estrogenic response equivalent to that produced by 25 mg of the test compound. [f] This compound was run later in a different group. The control for this group was 31.6 ± 4.98. [g] These two compounds could not be purified by crystallization because of contamination with the starting ester. They were purified by silica gel chromatography with benzene-ethyl acetate (9:1) as the eluant. Fractions containing colorless esters came off the column first followed by the yellow ketone base.

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were found to have been prepared previously by DeWald et al.[2] by a different route.

The ketones of Table I have been evaluated for hypocholesteremic effects using rats dosed orally with (25 mg of compounds/kg of body weight)/day for 7 days. Control rats were dosed in the same manner with vehicle only. At the end of 7 days, rats were killed and serum cholesterol assays were performed.[4] For each compound, three rats were used initially and positive results were confirmed with a second group of three rats.

It would appear that there is a steric effect but little electronic effect by the substituents, since only substituents in the ortho position led to statistically significant ($p < 0.005$) hypocholesteremic effects[4] (see Table I). Exceptions to this are the fluoro derivative 8 which had but moderate hypocholesteremic effect and the phenoxy derivative **21** which had no hypocholesteremic effect. The size of the ortho substituent alone appears not to control the magnitude of the effect, as the *tert*-butyl derivative **15** was not the most potent compound.

As the related carbinol compounds have varying degrees of estrogenicity[1] and as it is our object to develop hypocholesteremic agents with limited estrogenicity, the ortho-substituted ketones were further tested for estrogenicity using a modified version of an estrogen assay described by Dorfman and Dorfman.[5] The Br, Cl, I, and Me compounds show a higher degree of estrogenicity than the F and *t*-Bu ketones (see Table I). It is this difference in estrogenicity that may explain the increased cholesterol lowering effects of the ortho Br, Cl, I, and Me ketones over those of the F and *t*-Bu ketones. Of the compounds evaluated the *t*-Bu ketone has the most promise with its significant hypocholesteremic effect and minimal estrogenicity.

Experimental Section

Melting points were determined with a Mel-Temp apparatus; they are uncorrected. Boiling points are also uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. The *n*-butyllithium was a commercial 2 M solution in hexane (Alfa).

α-(2-Pyridine)benzyl Aryl Ketones (Table I). General Method. α-(2-Pyridine)-α-phenyl-2-phenoxyacetophenone (21). To a solution of 4.72 g (0.022 mol) of 2-benzylpyridine in 150 mL of dry ether cooled in a dry ice–acetone bath at −78 °C and kept under a N_2 atmosphere, 19.1 mL of 1.54 M butyllithium in hexane was added over a period of 15 min. The deep red mixture was allowed to stand at −78 °C for 1 h before a solution of 5.35 g (0.022 mol) of ethyl 2-phenoxybenzoate in 20 mL of ether was added in one portion. The resulting yellow solution was allowed to warm to 0 °C, and 2.5 mL of 38% HCl in 20 mL of water was added. The mixture was stirred for 0.5 h, the ether layer separated, and the aqueous layer neutralized with $NaHCO_3$ solution and extracted with ether. The combined ether extracts were dried over K_2CO_3, the ether was removed, and the gummy residue was crystallized by treatment with hexane, giving 5.2 g (70%) of yellow crystalline **21**, mp 101–103 °C. Recrystallization from ether gave 3.6 g, mp 104–105.5 °C.

Biological Evaluation. Male Sprague–Dawley rats of approximately 200-g weight were supplied Purina Mouse Chow and water ad libitum. Rats (three to six animals per experimental group) were administered aqueous suspensions of the α-(2-pyridine)benzyl aryl ketones (25 mg/kg) by oral intubation tube daily for 7 days and then exsanguinated by closed-chest cardiac puncture 24 h after the last administration of drug and analyzed for cholesterol by the method of Block et al.[4]

Estrogenicity was determined by the following modification of the estrogen assay described by Dorfman and Dorfman.[5] Female Sprague–Dawley rats (21 days old) of approximately 35 g were ovariectomized. After 7 days and for the next consecutive 7 days these rats were administered aqueous suspensions of the ketones (25 mg/kg, seven rats per drug group) by oral intubation. On day 8 uteri were removed and freed of surrounding tissue. The uteri were weighed after pressing out the intrauterine fluid on blotting paper, and results were expressed as weight of the uterus in milligrams per gram of body weight times 100. Additional rats were treated in a similar manner following subcutaneous injections of 17β-estradiol in peanut oil for preparation of a standard curve.

Acknowledgment. This research was supported by Grant GM 19815 from the National Institutes of Health, Bethesda, MD.

References and Notes

(1) J. H. Burckhalter, W. D. Dixon, M. L. Black, R. D. Westland, L. M. Werbel, H. A. DeWald, J. R. Dice, G. Rodney, and D. H. Kaump, *J. Med. Chem.*, **10**, 565 (1967).
(2) H. A. DeWald, R. D. Westland, and J. D. Dice, U.S. Patent 3 157 666 (1964); *Chem. Abstr.*, **62**, 4011 (1965).
(3) R. Levine and S. Raynolds, *J. Org. Chem.*, **25**, 530 (1960).
(4) W. D. Block, K. J. Jarrett, Jr., and J. A. Levine, *Clin. Chem. Winston-Salem, N.C.*, **12**, 681 (1966).
(5) R. I. Dorfman and A. S. Dorfman, *Endocrinology*, **55**, 65 (1954).

Additions and Corrections

1978, Volume 21

Michael J. Umen* and A. Scarpa: New Synthetic Calcium Selective Ionophores. Design, Synthesis, and Transport Properties.

Page 505. In Table I, the entry in column R^1R^2N for compound **2d** should read as follows: 10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl.

P. S. Portoghese,* D. L. Larson, J. B. Jiang, A. E. Takemori, and T. P. Caruso: 6β-[*N*,*N*-Bis(2-chloroethyl)amino]-17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan (Chlornaltrexamine), a Potent Opioid Receptor Alkylating Agent with Ultralong Narcotic Antagonist Activity.

Page 598. The name chlornaltrexamine is incorrectly spelled in the title of the paper. The correct spelling is chlornaltrexamine.

Mitsugi Yasumoto,* Ichiro Yamawaki, Teruyoshi Marunaka, and Sadao Hashimoto: Studies on Antitumor Agents. 2. Syntheses and Antitumor Activities of 1-(Tetrahydro-2-furanyl)-5-fluorouracil and 1,3-Bis(tetrahydro-2-furanyl)-5-fluorouracil.

Page 741. In the left column, the ε values in lines 26 and 27 should read as follows: (ε 13 000) → (ε 6500), (ε 17 400) → (ε 8700), and (ε 12 900) → (ε 6450). Also in the left column, the ε value in line 54 should read (ε 12 900 in MeOH) → (ε 6450 in MeOH).