interacts with its bioreceptor only significantly as a monomer, this extensive aggregation must lower its effective concentration and activity. This could account in part for the relatively high dose level required for coralyne to reach significant activity.[6]

Propylcoralyne dimerizes slightly less than coralyne ($K \approx 10^5$ at $I = 0.02$) and does not seem to have the marked tendency that coralyne has to form higher aggregates. Analysis of Corey–Pauling–Kolthum molecular models reveals that coralyne can exist as an essentially flat molecule with the methoxy groups rotated into the plane of the aromatic ring system. The propyl group of Ic, because of steric hinderance, cannot be rotated into the plane of the aromatic ring system. This bulky group apparently does not greatly hamper dimerization but does inhibit higher aggregation. This could not occur if the propyl groups (and positive charges) point in opposite direction in the dimer. In higher aggregates, however, at least two propyl groups must point in the same direction, giving the potential for unfavorable steric interactions if the hydrophobic interactions are to be maximized, as the large dimerization constant would suggest. Propylcoralyne will form higher aggregates but only at higher concentration and/or higher ionic strength than coralyne.

NMR experiments on acridine orange,[11] actinomycin,[13] and ellipticine[18] have indicated that the "inverted stack" type of association is favored by these molecules and may be a general feature of self-association of planar aromatic compounds. This type complex with acridine orange, ellipticine, and coralyne would be favored because it allows maximum overlap of the aromatic ring systems with minimum charge repulsion.

It is difficult to see how these results relate to the dramatically different activity of coralyne and propylcoralyne. The propyl compound does undergo higher aggregation less well than coralyne, but the ethyl derivative Ib is closer to Ic than Ia in this respect (not shown). In the same manner, Ia and Ic do not show any striking differences in their interaction with DNA. The aggregation of these compounds can lead to their precipitation under physiological conditions, and this has been reported to occur after interperitoneal injection of coralyne in mice.[14] Even here, however, we have qualitatively not observed any dramatic precipitation differences among Ia, Ib, and Ic. The dramatic differences, between the closely related Ib and Ic, in in vivo activity would seem to require a bioreceptor with higher selectivity than apparently exists in DNA for these two compounds.

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Potential Antiinflammatory Compounds. 2.[1a] Acidic Antiinflammatory 1,2-Benzisoxazoles

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A number of 1,2-benzisoxazoles, substituted in the 3 position with 4-substituted phenyl groups and in the 5–7 positions with acetic and propionic acid residues, have been synthesized and tested in the rat carrageenan foot edema assay. Activity has been found in the 6- and 7-substituted acids.

The leads provided by indomethacin and ibufenac in the nonsteroidal antiinflammatory field have stimulated workers to synthesize considerable numbers of substituted acetic and propionic acids.[1b] These compounds have had nuclei chosen from a wide range of substituted aromatic and heterocyclic systems. Among the more significant systems which have been exploited in the last few years are 1-phenylnaphthalene[2] and 2-phenylbenzoxazole.[3]

In seeking a molecule which combined, as nearly as possible, the structural features of the 1-phenylnaphthalenes and the 2-phenylbenzoxazoles, we decided to investigate the effect on biological activity of placing

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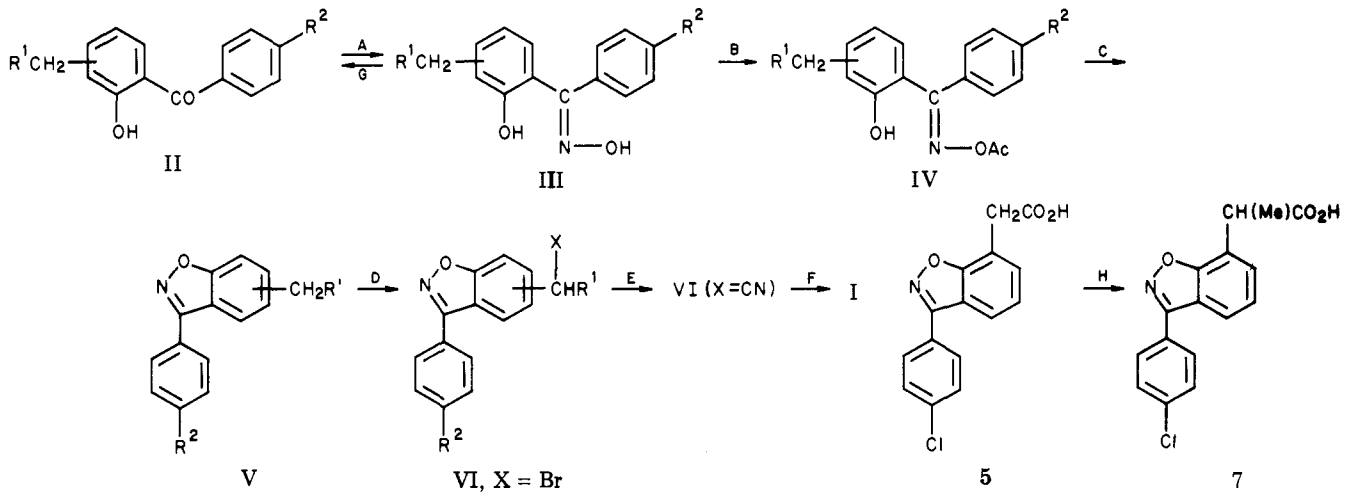
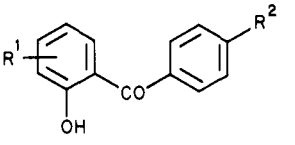
Scheme I[a]



[a] Reagents: A = NH_2OH, HCl, KOH; B = Ac_2O; C = Na_2CO_3 in refluxing triglyme; D = *N*-bromosuccinimide, UV; E = NaCN, NaI/DMF; R = concentrated HCl, HOAc/80 °C; G = $Na_2S_2O_5$; H = *n*-BuLi, MeI, $(Me_2N)_3PO$.

Table I. Benzophenones II

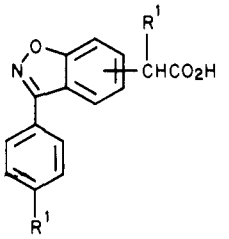


II

no. of corresp acid	R^1	R^2	mp or bp (mm), °C	method	yield, %	purifn[a] proced	formula	anal.
1	5-Me[b]	Cl	168-174 (0.1)		78	II	$C_{14}H_{11}ClO_2$	
2	5-Et	Cl	41.5-43.5					
			147-150 (0.09)		72	I	$C_{15}H_{13}ClO_2$	C, H, Cl
3	4-Et	Cl	52	G	83	IV	$C_{15}H_{13}ClO_2$	C, H, Cl
4	4-Et	F	44-48		5	III	$C_{15}H_{13}FO_2$	C, H, F
5	3-Me[c]	Cl	61-63		47	V	$C_{14}H_{11}ClO_2$	C, H, Cl
			148-152 (0.5)					
6	3-Et[d]	H	123-126 (0.4)		58	II	$C_{15}H_{14}O_2$	C, H
7[e]	3-Et	Cl	72-73		31	VI	$C_{15}H_{13}ClO_2$	C, H, Cl

[a] I = recrystallization from *n*-hexane; II = distilled; III = chromatographed on PLC silica gel 60 F_{254} plates (E. Merck), $CHCl_3$ eluent; IV = chromatographed on silica gel, $CHCl_3$ eluent; V = recrystallized from EtOH; VI as V but using light petroleum (bp 40-60 °C). [b] Reference 8 gives mp 66.9-67.6 °C. [c] Reference 8 gives mp 61.5-62 °C. [d] Reference 9 gives bp 165-167 °C (3 mm). [e] The carboxylic acid 7 was prepared by methylation of acid 5.

acetic and propionic acid groupings on the 3-phenyl-1,2-benzisoxazole nucleus of I.

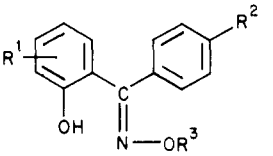


I

Chemistry. The compounds were prepared according to Scheme I. The route employed for the preparation of the alkyl-substituted 1,2-benzisoxazole V was essentially a standard one,[4] but improvements were made in the published method for cyclizing the hydroxyacetates IV to the 1,2-benzisoxazoles V. In general, the final acids I were made by hydrolysis of the crude nitriles VI, but acid **7** was prepared by methylation of the acid **5**. Details of the intermediates to the acids and of the acids themselves are listed in the Tables I–IV. The benzophenones II were prepared by standard procedures: the 4- and 5-alkyl substituted compounds by means of Friedel–Crafts reactions between the appropriately substituted alkylphenols and benzoyl chlorides, while for the 3-alkyl substituted compounds the appropriately substituted salicyloyl chlorides were reacted with benzene or chlorobenzene.

Antiinflammatory Activity. The results of antiinflammatory testing against the carrageenan-induced foot edema of Winter et al.,[5] modified as indicated in ref 3, are reported in Table IV. The 5-substituted compounds were inactive or very weakly active, while the 6- and 7-substituted compounds showed activities comparable to each other and, except for compounds **4** and **5**, they were somewhat more active than the control compounds hydrocortisone and phenylbutazone. The 6- and 7-substituted compounds were also tested in the adjuvant arthritis assay in rats.[6] Compound **7** was the most active in this test, being several times more active than phenylbutazone and considerably more active than its analogue in the 6-substituted series. The finding of activity in the 7-substituted series, which has a comparable orientation to that of 5-phenylnaphthalene-1-acetic acid, can be considered as evidence in favor of the active-site theories of Shen and

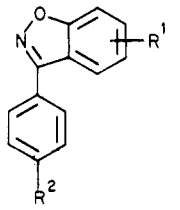
Table II. Benzophenone Oximes (III) and Oxime Acetates (IV)



no. of corresp acid	R^1	R^2	R^3	mp or bp (mm), °C	method	yield, %	purifn[a] proced	formula	anal.
1	5-Me	Cl	H	157-160	(*E*) A	63	I	$C_{14}H_{12}ClNO_2$	C, H, Cl, N
				145-147	(*Z*) A	1	I	$C_{14}H_{12}ClNO_2$	C, H, Cl, N
1	5-Me	Cl	Ac[b]				III	$C_{16}H_{14}ClNO_3$	
2	5-Et	Cl	H	117	A	64	II	$C_{15}H_{14}ClNO_2$	C, H, Cl, N
2	5-Et	Cl	Ac	105	B	77.5	III	$C_{17}H_{16}ClNO_3$	C, H, Cl, N
3	4-Et	Cl	H	159-161	A	59	II	$C_{15}H_{14}ClNO_2$	
3	4-Et	Cl	Ac[b]		B	84	III	$C_{17}H_{16}ClNO_3$	
4	4-Et	F	H	130-132	A	48	II	$C_{15}H_{14}FNO_2$	C, H, F, N
4	4-Et	F	Ac[b]		B	67	III	$C_{17}H_{16}FNO_3$	
5	3-Me	Cl	H	178	A	68	I	$C_{14}H_{12}ClNO_2$	C, H, Cl
5	3-Me	Cl	Ac	154-156	B	79	III	$C_{16}H_{14}ClNO_3$	C, H, Cl
6	3-Et	H	H	146-148	A	100	IV	$C_{15}H_{15}NO_2$	C, H, N
6	3-Et	H	Ac	63-65	B	80	III	$C_{16}H_{17}NO_3$	(NMR)

[a] I = recrystallized from C_6H_6; II = recrystallized from C_6H_6-light petroleum (bp 60-80 °C); III = crystallized from reaction mixture, filtered, and washed with light petroleum; IV = filtered and dried. [b] Compound used in next stage of synthesis without complete characterization.

Table III. 1,2-Benzisoxazoles V and VI (X = Br)



V, R^1 = CH_3 or CH_2CH_3
VI, R^1 = CH(X)R

no. of corresp acid	R^1	R^2	mp or bp (mm), °C, or *n*	method	yield, %	purifn[a] proced	formula	anal.
1	5-Me	Cl	95	C	63	I	$C_{14}H_{10}ClNO$	C, H, Cl, N
1	5-CH_2Br	Cl	142	D	54.5	II	$C_{14}H_9BrClNO$	C, H, Br, Cl, N
2	5-Et	Cl	42-45	C	53	III	$C_{15}H_{12}ClNO$	C, H, Cl, N
2	5-CH(Me)Br	Cl	111-116	D	70	II	$C_{15}H_{11}BrClNO$	C, H, Br, Cl, N
3	6-Et	Cl	78-79	C	19	III	$C_{15}H_{12}ClNO$	C, H, Cl, N
3	6-CH(Me)Br	Cl[b]		D	66	II	$C_{15}H_{11}BrClNO$	
4	6-Et	F[b]		C	58	V	$C_{15}H_{12}FNO$	
4	6-CH(Me)Br	F[b]		D	88	IV	$C_{15}H_{11}BrFNO$	
5	7-Me	Cl	97-99	C	78	I	$C_{14}H_{10}ClNO$	C, H, Cl, N
5	7-CH_2Br	Cl	117-120	D	82	VI	$C_{14}H_9BrClNO$	N
6	7-Et	H	129-130 (0.3)	C	85	VII	$C_{15}H_{13}NO$	C, H, N
6	7-CH(Me)Br	H	n^{23}_D 1.6280	D	95	VIII	$C_{15}H_{12}BrNO$	(NMR)

[a] Recrystallization solvents were: I, EtOH; II, PhMe-light petroleum (bp 60-80 °C); III, MeOH-H_2O; IV, reaction mixture; V, EtOH-H_2O; VI, light petroleum (bp 60-80 °C)-CCl_4; VII, distilled; VIII, solvent evaporated. [b] Compound used in next stage of synthesis without complete characterization.

Scherrer, Winder, and Short.[7]

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by Mr. G. Maciak and associates, Eli Lilly and Co., Indianapolis, 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 the compounds are noted in Tables I–IV.

2-Hydroxy-5-ethyl-4′-chlorobenzophenone [II(2)]. Aluminium chloride (267 g, 2 mol) was added in portions during 20 min to a stirred solution of 4-ethylphenol (122.1 g, 1 mol) and 4-chlorobenzoyl chloride (192.5 g, 1.1 mol) in $Cl_2CHCHCl_2$ (800 mL). The temperature rose to 50 °C. The mixture was heated and stirred at 105 °C for 22 h. It was cooled, treated with ice (600 g) and concentrated HCl (300 mL) (**vigorous reaction!**), and extracted with $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$), filtered, and evaporated to give the benzophenone as an oil, which was distilled.

Method A.[4] 2-Hydroxy-5-methyl-4′-chlorobenzophenone Oxime [III(1)]. 2-Hydroxy-5-methyl-4′-chlorobenzophenone (192 g, 0.78 mol) was melted and poured into a stirred solution of KOH (500 g) in H_2O (2 L). To this cooled (ice), stirred suspension, NH_2OH·HCl (200 g, 2.9 mol) was added in portions over 1 h. The mixture was stirred for 48 h at room temperature. Ice was added with 5 N HCl to give a thick white precipitate, which was filtered, washed, dried, and recrystallized from C_6H_6 to give the *E* form of the oxime (corresponding to Blatt's syn form of 2-hydroxy-5-methylbenzophenone oxime) (129.4 g). Slow evaporation of the C_6H_6 yielded two further crops of crystals, the second of which

Table IV. 5-, 6-, and 7-Substituted 3-Phenyl-1,2-benzisoxazoleacetic and -propionic Acids I

no.	R¹	R²	mp, °C	method	yield, %	purifn proced[a]	formula	anal	antiinflam act. vs. carrageenan dose, mg/kg po	antiinflam act. vs. carrageenan % redn[b]	antiinflam act. of control dose, mg/kg po	antiinflam act. of control % redn[c]	ca. LD_{50} in mice, mg/kg po
1	5-CH_2CO_2H	Cl	189	F	73	III	$C_{15}H_{10}ClNO_3$	C, H, Cl, N	50[d]	22*	50[d]	36* (P)	600
2	5-CH(Me)CO_2H	Cl	137–139	F	57	I	$C_{16}H_{12}ClNO_3$	C, H, N	50	18	50	38** (H)	800
3	6-CH(Me)CO_2H	Cl	176–179	F	17	III	$C_{16}H_{12}ClNO_3$	C, H, Cl, N	50	46**	50	38** (H)	600
4	6-CH(Me)CO_2H	F	151–154	F	12.5	III	$C_{16}H_{12}FNO_3$	C, H, F, N	50	37*	50	57** (P)	400
5	7-CH_2CO_2H	Cl	198–200	F	11	II	$C_{15}H_{10}ClNO_3$	C, H, Cl, N	50	36*	50	49** (P)	600
6	7-CH(Me)CO_2H	H	99–101	F	3	IV	$C_{16}H_{13}NO_3$	C, H, N	50	42**	50	32* (P)	1600
7	7-CH(Me)CO_2H	Cl	136–138	H	18	IV	$C_{16}H_{12}ClNO_3$	C, H, Cl, N	25	46**	50	48* (P)	200

[a] Recrystallization solvents: I, toluene; II, 50% EtOH–H_2O; III, precipitated from Na_2CO_3 solution with 5 N HCl; IV, chromatographed in PLC silica gel 60 F_{254} plates (E. Merck) (organic solvent from $CHCl_3$, MeOH, H_2O in 75:25:10 ratio as eluent). [b] An asterisk indicates that the result was significant on Student's t test at $p < 0.01$; a double asterisk indicates that the result was significant on Student's t test at $p < 0.001$. [c] H = hydrocortisone; P = phenylbutazone. [d] Rats were dosed orally with the stated dose 3 h and again 0.5 h prior to the injection of carrageenan; hence, the total dose given was twice that stated above (see previous paper).

(1.9 g) was the *Z* form (corresponding to Blatt's anti form of 2-hydroxy-5-methylbenzophenone oxime; oxime OH adjacent to phenolic OH). The structures of the oxime *O*-acetates were identified by aqueous hydrolysis of the corresponding *O*-acetates according to Blatt's method, and identification of the products was confirmed by comparison with authentic samples, obtained as above, on TLC. In the preparation of the other oximes (III), only the *E* form was isolated and used for subsequent reactions.

Method B.[4] **2-Hydroxy-5-ethyl-4′-chlorobenzophenone Oxime *O*-Acetate [IV(2)].** 2-Hydroxy-5-ethyl-4′-chlorobenzophenone oxime (22 g, 0.08 mol) was dissolved in preheated acetic anhydride (45 mL) and as soon as complete solution had occurred was cooled in an ice bath; scratching caused precipitation of the product.

Method C. 3-(4-Chlorophenyl)-5-ethyl-1,2-benzisoxazole [V(2)]. (*E*)-2-Hydroxy-5-ethyl-4′-chlorobenzophenone oxime acetate (19 g, 0.06 mol) was refluxed with anhydrous Na_2CO_3 (13.3 g, 0.125 mol) in triethylene glycol dimethyl ether (200 mL) for 0.5 h and, after cooling, poured into water (1 L). An oil separated and was extracted with Et_2O (3 × 250 mL). The Et_2O was washed with water (3 × 200 mL), dried ($MgSO_4$), filtered, and evaporated to give the benzisoxazole (16.4 g).

Method D. 3-(4-Chlorophenyl)-5-(1-bromoethyl)-1,2-benzisoxazole [VI(2)]. 3-(4-Chlorophenyl)-5-ethyl-1,2-benzisoxazole (12.3 g, 0.048 mol) and *N*-bromosuccinimide (8.5 g, 0.048 mol) were refluxed together for 2.5 h in CCl_4 (200 mL) in the presence of UV light. On cooling, the mixture was filtered and the filtrate evaporated to dryness. The solid bromoethyl-1,2-benzisoxazole (11.3 g) was recrystallized.

Method E. 2-[3-(4-Chlorophenyl)-1,2-benzisoxazol-5-yl]-propionitrile. Sodium cyanide (1.47 g, 30 mmol) was added to a cooled (0 °C), stirred solution of 3-(4-chlorophenyl)-5-(1-bromoethyl)-1,2-benzisoxazole (9 g, 26.7 mmol) and NaI (0.42 g, 3 mmol) in dry $CHONMe_2$ (75 mL), and the mixture (after stirring for 21 h at room temperature) was poured into H_2O (600 mL). It was extracted with ether, washed with H_2O (2 × 200 mL), dried ($MgSO_4$), filtered, and evaporated to leave the crude nitrile as an oil [yield 6.4 g; IR ν_{max} 2250 cm^{-1} (CN); NMR δ 1.68 (3 H, d), 4.02 (1 H, q), 7.4–7.9 (7 H, m)] which was used in the next stage without further purification.

Method F. 2-[3-(4-Chlorophenyl)-1,2-benzisoxazol-5-yl]-propionic Acid [I(2)]. The above nitrile (6.4 g, 22.6 mmol) was stirred with concentrated HCl (60 mL) and AcOH (30 mL) at 80 °C for 4 h. It was cooled, poured into H_2O (500 mL), and extracted with Et_2O (3 × 200 mL). The Et_2O was extracted with 10% Na_2CO_3 (3 × 100 mL) and the latter was acidified with 5 N HCl. The product was extracted with Et_2O (3 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to give the carboxylic acid I(2).

Method G. 2-Hydroxy-4-ethyl-4′-chlorobenzophenone [II(3)]. 2-Hydroxy-4-ethyl-4′-chlorobenzophenone was obtained crude by the standard method and converted to its pure oxime. The oxime (5.5 g, 0.02 mol) was refluxed with $Na_2S_2O_5$ (7.6 g, 0.04 mol) in EtOH (30 mL) and H_2O (30 mL) for 40 h. The EtOH was evaporated off, 2 N HCl was added to the residue, and the latter was extracted with $CHCl_3$. The $CHCl_3$ was washed with 10% Na_2CO_3, dried (Na_2SO_4), filtered, and evaporated to give the product, which was purified (see Table I).

Method H. Methyl(3-*p*-chlorophenyl-1,2-benzisoxazol-7-yl)acetic Acid [I(7)]. *n*-BuLi (31 mL, 46 mmol of 1.5 M) was cooled to −30 °C under N_2 with stirring and treated with a solution of *i*-Pr_2NH (4.65 g, 6.52 mL, 46 mmol) in tetrahydrofuran (THF; 38 mL). Cooling was applied to keep the temperature at −30 to −50 °C. A solution of the carboxylic acid **5** (4.5 g, 15.64 mmol) in THF (38 mL) and $(Me_2N)_3PO$ (38 mL) was added dropwise (immediate formation of purple anion) and the solution was stirred at −30 to −40 °C for 1.5 h. It was then transferred under N_2 pressure to a solution of MeI (35.5 g, 15.4 mL, 250.26 mmol) in THF (150 mL) at 5 °C. It was stirred at ca. 5 °C for 1.5 h, a little concentrated HCl was added, and the THF was evaporated. The residue was diluted with H_2O (500 mL) and extracted with $CHCl_3$. The $CHCl_3$ was washed with enough $NaHCO_3$ solution to remove mineral acid and then with H_2O, dried, filtered, and evaporated to leave a product which contained some methyl ester (NMR and mass spectrum). This material was hydrolyzed by refluxing for 4 h with AcOH (30 mL) and concentrated HCl (60 mL). The solution was diluted with water and extracted with $CHCl_3$ as

before, and the product of evaporation was purified as in Table IV.

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References and Notes

(1) (a) For Part 1, see: T. A. Hicks, C. E. Smith, E. H. Day, and W. R. N. Williamson, *J. Med Chem.*, **22**, first paper in a series of three in this issue (1979); (b) For collected references, see T. Y. Shen, *Angew. Chem., Int. Ed. Engl.* 11, 460 (1972).
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Optical Resolution of Some Homobenzomorphan Derivatives and Their Pharmacological Properties

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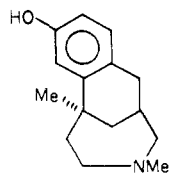
Racemic 1,4-dimethyl- (1), 1,4,12α-trimethyl- (2), and 1,4,12β-trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (3) have been optically resolved. The analgesic potency and physical-dependence capacity of the optical isomers and their racemic parents were determined. The levo isomers of compounds 2 and 3 were analgesically much more potent than the dextro isomers and were equipotent with morphine. Optical resolution gave no effect on the analgesic activity of compound 1. None of the optical isomers and the racemates suppressed the morphine-withdrawal syndrome in the monkey.

In the previous paper,[1] we described the synthesis and analgesic activity of derivatives of 10-hydroxy-4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (homobenzomorphan), including compounds which had the potency of morphine. Since it has been shown that in the 6,7-benzomorphan analgesics optical resolution produces one isomer (levo) that is analgesically potent and without physical-dependence capacity in rhesus monkeys,[2] it appeared interesting to resolve the racemic homobenzomorphans and to evaluate their pharmacological properties. We have resolved 1,4-dimethyl- (1), 1,4,12α-trimethyl- (2), and 1,4,12β-trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (3)



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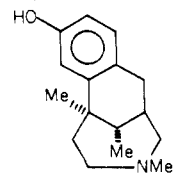

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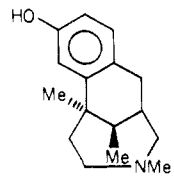

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and have examined their analgesic potency and their ability to suppress the withdrawal syndrome in physically dependent monkeys, as compared with their parent racemic compounds.

The racemates 1 and 2 were resolved by treatment with *d*- and *l*-mandelic acids and fractional crystallization of the mandelate salts from methanol–acetone to constant rotation. Resolution of compound 3 was achieved by treatment with *d*- and *l*-tartaric acids and fractional crystallization of the tartrate salts from methanol to constant rotation. In all cases, both (+) and (−) rotamers were obtained.

Pharmacology. The resolved compounds were tested for analgesic activity by the method of pressure stimuli on the mouse tail[3,4] and the Eddy hot-plate test.[5,6] Table I shows the analgesic ED_{50} values of these compounds and the parent racemates when administered sc. In the case of compounds 2 and 3, virtually all of the analgesic activity is exhibited by levo isomers. These results are similar to those of the 6,7-benzomorphan series.[2] Compound (−)-3 was found to be the most potent of the group, being about two times as potent as morphine. On the contrary, it was observed that in compound 1 there was no effect of resolution on analgesic activity. In the precipitated withdrawal test in monkey, compounds 1, (+)-1 and (−)-1 appeared to be strong depressants.[7] Their depressant properties may be suggested as a possible reason for the peculiar results observed in the analgesic tests. Perhaps, when a compound has both analgesic and depressant properties, odd results are obtained in the analgesic test in mice. The racemic compound 1 and the levo isomer (−)-1, potent analgesics comparable with morphine, appeared to have some narcotic antagonist activity (mouse tail-flick test).[7]

Table I also indicates the acute toxicities of compounds 1–3, (+)-1, and (−)-1.[4] The racemates showed toxicity at 30 mg/kg iv in mice. It is interesting that the levo isomer (−)-1 is much less toxic than the dextro isomer (+)-1.

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