yield of α-fenchylhydrazine, isolated as the hydrochloride, mp 283–288°, was obtained. Tlc and ir were identical with those of an authentic sample.

2,3,3-Trimethyl-2-norcamphanylhydrazine.—1-(2,3,3-Trimethyl-2-norcamphanyl)-1,2-diazaspiro[2.5]octane (2.4 g, 0.01 mol) was added to 50 ml of boiling 10% aqueous $(COOH)_2$ solution and refluxed for 5 min, then made basic and the product extracted into Et_2O. This was dried ($MgSO_4$) and the product precipitated with dry HCl. The weight of product obtained was 1.1 g, mp 288–288.5° (melting point bath preheated to 280°). Recrystallization from *i*-PrOH gave 0.8 g of material, mp 291.5–292°.

***N*-Nitroso-*N*-benzyl-α-fenchylamine.**—A mixture of 15.3 g (0.1 mol) of α-fenchylamine and 11.1 g of benzaldehyde in 200 ml of C_6H_6 was refluxed for 2.5 hr with a Dean–Stark trap, 1.6 ml out of a theoretical 1.8 ml of H_2O being collected. The solvent was removed and the crude Schiff base was dissolved in 200 ml of MeOH and reduced with 8 g of $NaBH_4$ added portionwise over 15 min. After stirring for 30 min 100 ml of H_2O was added and the product was extracted with $CHCl_3$, washed (H_2O), and dried ($MgSO_4$). Removal of solvent left 23 g of crude *N*-benzyl-α-fenchylamine. It was an extremely weak base, being insoluble in cold dilute H_2SO_4, HCl, CF_3COOH, and *p*-TsOH. It dissolved in dilute H_2SO_4 on boiling, and remained in solution on cooling.

N-Benzyl-α-fenchylamine (16 g, 0.066 mol) was dissolved in 800 ml of H_2O and 10 ml of concentrated H_2SO_4 by boiling for a short time. The solution was then cooled and 7 g of $NaNO_2$ in 50 ml of H_2O were added at about 0°. The mixture was allowed to warm to room temperature overnight with stirring, then was filtered and the solid washed with H_2O. The weight of crude product was 14.5 g, mp 87–88°. Recrystallization from 29 ml of hexane gave 9.7 g, mp 92–92.5°.

1-(2,3,3-Trimethyl-2-norcamphanyl)-1,2-diazaspiro[2.5-]octane.—2,3,3-Trimethyl-2-norcamphanylamine (15.4 g, 0.1 mol) and 15.5 ml of cyclohexanone in 40 ml of C_6H_6 were refluxed with either 10 drops of $BF_3 \cdot Et_2O$ or 0.2 g of anhydrous $ZnCl_2$ for 96 hr using a Dean–Stark trap. The amount of H_2O collected was 1.4 ml. The solvent was removed under vacuum and the crude base was dissolved in 60 ml of MeOH. To this was added 15.4 g of 2,3,3-trimethyl-2-norcamphanylamine, and, after cooling to 0°, 18.0 g of 63% hydroxylamine-*O*-sulfonic acid was added over 15 min and the mixture stirred at 0° for 2 hr then allowed to warm to room temperature over 1 hr. The reaction mixture was poured into 300 ml of H_2O and extracted with Et_2O. The Et_2O was washed with H_2O and K_2CO_3 solution and dried (K_2CO_3). Removal of the solvent left 6 g of crude product which was chromatographed on 1000 g of SiO_2, using $CHCl_3$ as the eluent. There was thus obtained 2.4 g of analytically pure product.

1,1-Dimethylthiourea.[12]—Me_2NH (450 g, 10 mol) in 2350 ml of H_2O was neutralized to brom phenol blue with about 900 ml of concentrated HCl. KSCN (970 g, 10 mol) was then added and the mixture stirred until complete solution occurred. The H_2O was removed on a Rotovap and the dimethylammonium thiocyanate was extracted from the KCl with EtOH (2 × 1000 ml). The EtOH solution was taken to dryness on a Rotovap and the residue heated at 150–160° for 72 hr, cooled to 100°, and diluted with 3000 ml of H_2O. The very dark solution was extracted four times with 250 ml of $CHCl_3$, which does not remove the product, and the resulting amber aqueous layer was filtered with a little Celite. Salt (700 g), 2000 ml of THF, and 500 ml of EtAc was added to the filtrate and the mixture was stirred for 1 hr. It was then continuously extracted with EtAc (2 l. of EtAc in pot) for 65 hr. The extract was cooled and the product filtered off and washed with EtAc; wt, 78 g; mp 161–164°. The filtrate and washings were concentrated to about 500 ml on a Rotovap and yielded another 33 g of product, mp 161–163°.

(12) W. A. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

Nonsteroidal Antiinflammatory Agents. I. 6-Substituted 2-Naphthylacetic Acids[1]

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Some 6-substituted 2-naphthylacetic acids and derivatives are shown to be potent systemic antiinflammatory agents.

The clear need[4] for better antirheumatic drugs has led us to develop a series of novel systemic nonsteroidal antiinflammatory agents. The program was based on our supposition that some of the side effects inherent in certain clinically important agents can be ascribed to the presence of N heteroatoms in these compounds.

Analysis and interpretation of the structure–activity relationship among antiinflammatory compounds, in which N is not required for biological activity, led us to conclude that arylacetic acids, as well as certain aryl-substituted enols and phenols, might provide a fertile area for synthetic work. Accordingly, a number of compounds incorporating these structural features were screened in the well-recommended carrageenin-induced rat paw edema assay,[5] as well as an antipyretic assay. Among the compounds showing biological activity 2-naphthylacetic acid showed the most significant response and led us to study this unexplored series more fully.[6]

The antiinflammatory activity of our primary lead compound, 2-naphthylacetic acid (**9**, series B, Table I), is 0.6 times phenylbutazone and is enhanced by substitution of small lipophilic groups (Cl, OCH_3, SCH_3, etc.) at the 6-position. Substitution of Me, α to CO_2H also enhanced activity (compare series A and B, Table I), most of the activity arising from the D-enantiomer. An antiinflammatory potency about 11 times that of phenylbutazone (55 times aspirin) was observed for D-2-(6-methoxy-2-naphthyl)propionic acid (**1**, Ta-

(1) Publication No. 369 from the Institute of Organic Chemistry. For publication No. 368 see P. Boyle, J. A. Edwards, and J. H. Fried, "Photochemical Cycloadducts. Part V. Photochemical Addition of Olefins to the Steroidal 1-en-3-one System," submitted for publication.

(2) Department of Bioassay, Institute of Hormone Biology, Syntex Research.

(3) Department of Pharmacology, Institute of Clinical Medicine, Syntex Research.

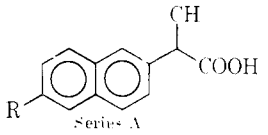
(4) H. J. Sanders, *Chem. Eng. News*, **46** (34), 46 (1968).

(5) Modification of the method described by C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

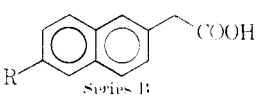
(6) Our assay indicated that 1-naphthylacetic acid had only weak antiinflammatory activity (<0.1 times phenylbutazone). For structure–activity correlations in this series see G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **9**, 603 (1966). Substantial activity was also noted with 1,4-naphthoquinone and many other quinones with similar oxidation potentials.

TABLE I

ANTIINFLAMMATORY, ANALGETIC, AND ANTIPYRETIC ACTIVITY OF 2-NAPHTHYLACETIC AND 2-NAPHTHYLPROPIONIC ACIDS



Series A



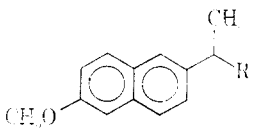
Series B

No.	R	Antiinflammatory act.[a] (rat paw edema, phenylbutazone = 1): Series A (enantiomer)[b]		Series B	Analgetic act. (mouse writhing, aspirin = 1): Series A (enantiomer)[b]		Series B	Antipyretic act. (rat, aspirin = 1): Series A (enantiomer)[b]		Series B
1	CH_3O	11	(D)		7	(D)		22	(D)	
2	CH_3O	4		3	4			9		
3	CH_3S	4		1				16		~3
4	CH_3	4		0.5			~0.4			3
5	CHF_2O	3								
6	Cl	2		1	~3			~5		
7	$(CH_3)_2CH$			1.3						~1
8	C_2H_5			0.8			~0.7			
9	H	1	(D)	0.6			0.6			~2
10	CH_3O	0.4	(L)					~1.5	(L)	
11	C_2H_5O	0.3								
Aspirin		0.2			1 (standard)			1 (standard)		
Phenylbutazone		1 (standard)			0.8			~3		

[a] More than 140 rats were used for the antiinflammatory assay of compounds **1** and **2**, series A; less than 75 rats for all other compounds. [b] Racemate except where D or L enantiomer is indicated.

TABLE II

DERIVATIVES OF 2-(6-METHOXY-2-NAPHTHYL)PROPIONIC ACID



No.	R	Antiinflammatory act., (rat paw edema, phenylbutazone = 1)	Mp, °C	$[\alpha]D$,[a] deg	Formula	Analyses[b]
1	COOH	11	152–154	+66 ($CHCl_3$)	$C_{14}H_{14}O_3$	C, H, O
12	COONa	10	244–246	−11 (CH_3OH)	$C_{14}H_{13}O_3Na$	
13	$COOCa_{1/2}$	10	255–265 dec	−37 (DMSO)	$C_{14}H_{14}O_3Ca_{0.5}$	
14	CH_2OH	12	88–89	−18 ($CHCl_3$)	$C_{14}H_{16}O_2$	C, H, O
15	CHO	4		(DL)		[c]
16	$COOCH_3$	2	88	+77 ($CHCl_3$)	$C_{15}H_{16}O_3$	C, H, O

[a] All compounds have the same absolute configuration. [b] Satisfactory elemental analyses were not obtained; however, acidification gave the free acid with correct melting point and $[\alpha]D$. [c] See G. Stork and J. W. Schulenburg, *J. Amer. Chem. Soc.*, **84**, 284 (1962), for physical data and preparation of this compound.

ble I).[7,8] Activity was observed in the Randall–Selitto oral analgetic assay[9] at 25 mg/kg (*cf.* 90 mg/kg for phenylbutazone) and also in the mouse writhing analgetic[10] (7 times aspirin) and antipyretic[11] (22 times aspirin) assays. The derived metal salts, aldehyde, and carbinol were biologically equivalent to the carboxylic acid, while esters were generally of lower activity (Table II).

Attempts to further increase the antiinflammatory activity by increasing the planar surface of the ring system or by substituents at other positions of the naphthalene ring were generally less rewarding. Results of these studies will be the subject of a subsequent report. The structural requirements for maximal activity in the naphthylacetic acid series appear to be defined by a suitably positioned acidic group (or group readily converted to an acid), an aromatic system, and a small lipophilic group at the 6-position. It is to be noted that very active compounds were obtained without resort to nitrogenous systems.

Chemistry.—The substituted 2-naphthylacetic acids III (Scheme I) were prepared by acylation[12] of the 6-substituted naphthalenes I by AcCl, forming the 2-acetyl derivative II, followed by a Wilgerodt–Kindler reaction.[13] Esterification and alkylation[14] of the acid III gave, after

(7) We wish to thank Dr. O. Halpern, Dr. F. S. Alvarez, Dr. N. H. Dyson, and Mr. A. Prince for the preparation of additional quantities of this compound.

(8) Toxicological, pharmacological, and efficacy studies in experimental animals and in humans are in progress and will be reported elsewhere.

(9) L. O. Randall and J. J. Selitto, *Arch. Int. Pharmacodyn. Ther.*, **111**, 409 (1957).

(10) Modification of the method described by L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1959).

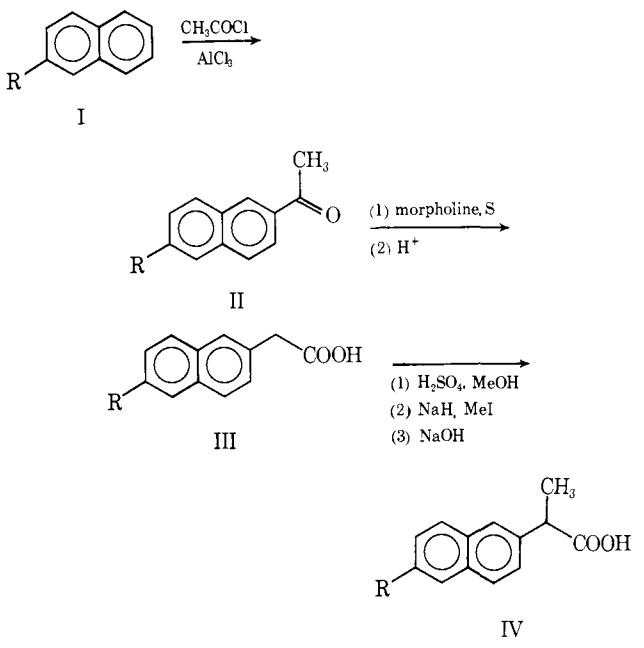
(11) Pyrexia was induced in rats by subcutaneous injection of baker's yeast suspended in saline. Compounds were administered by gavage.

(12) P. H. Gore, *Chem. Rev.*, **55**, 229 (1955).

(13) M. Carmack and M. A. Spielman, *Org. Reactions*, **3**, 83 (1946).

(14) W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 2937 (1965).

SCHEME I

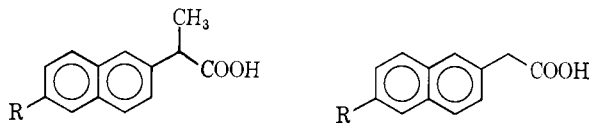


hydrolysis, the naphthylpropionic acid IV. Resolution of 2-(6-methoxy-2-naphthyl)propionic acid (IV, R = OCH_3) was readily achieved by crystallization of the cinchonidine salt, the salt of the more potent D enantiomer having the lower solubility.

Experimental Section

Melting points were determined on a Fisher–Johns hot-stage and are corrected. Physical properties are listed in Tables II and III. Where analyses are indicated only by symbols of the

TABLE III



Series A Series B

No.	R[a]	Series	Enantiomer	Mp. °C[b]	[α]D, [c] deg	Formula	Analyses
10	CH_3O	A	L	150–152	−66	$C_{14}H_{14}O_3$	C, H, O
2	CH_3O	A	DL	150–151		$C_{14}H_{14}O_3$	C, H, O
3	CH_3S	A	DL	140		$C_{14}H_{14}O_2S$	C, H, S
4	CH_3	A	DL	147		$C_{14}H_{14}O_2$	C, H, O
5	CHF_2O	A	DL	83–86		$C_{14}H_{12}F_2O_3$	M+ 266
6	Cl	A	DL	140–141		$C_{13}H_{11}ClO_2$	C, H, Cl
6	Cl	B		147–175		$C_{12}H_9ClO_2$	C, H, Cl
7	$(CH_3)_2CH$	B		128		$C_{15}H_{16}O_2$	C, H, O
8	C_2H_5	B		150		$C_{14}H_{14}O_2$	C, H, O
11	C_2H_5O	A	DL	148–150		$C_{13}H_{16}O_3$	M+ 244

[a] For unlisted compounds **2**, series B, **3**, series B, **4**, series B and **9**, series A, see reference 15a–d. [b] Compounds were crystallized from Me_2CO–hexane. [c] Measured in $CHCl_3$.

elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

DL-2-(6-Methoxy-2-naphthyl)propionic Acid (2, Series A).—A solution of 30 g of 6-methoxy-2-naphthylacetic acid[15a] in 500 ml of EtOH containing 20 ml of concentrated H_2SO_4 was heated under reflux for 17 hr. The solution was diluted with H_2O and the product extracted by C_6H_6. Washing of the C_6H_6 solution with $NaHCO_3$ solution followed by evaporation *in vacuo* gave the Et ester. Alkylation[14] of this ester with MeI and NaH in dimethoxyethane followed by hydrolysis with alcoholic KOH gave, after crystallization from Me_2CO–hexane, 18.1 g (57%) of the acid **2**, series A. *Anal.* ($C_{14}H_{14}O_3$) C, H, O. Other 6-substituted 2-naphthylpropionic acids listed in Table I were prepared by analogous methods from starting materials listed in Table III and ref 15a–d.

D- and L-2-(6-Methoxy-2-naphthyl)propionic Acid (1 and 10, Series A).—Hot solutions of 1.15 g of **2**, series A, in a mixture of 20 ml of MeOH and 5 ml of Me_2CO and 1.50 g of cinchonidine in 15 ml of MeOH and 10 ml of Me_2CO were mixed and allowed to cool to room temperature. The resulting salt was filtered and recrystallized twice from MeOH–Me_2CO and the free acid liberated from the salt by shaking with a mixture of dilute HCl and C_6H_6. Evaporation of the C_6H_6 layer and crystallization of the residue from Me_2CO–hexane gave 279 mg (49%) of the D-enantiomer **1**. *Anal.* ($C_{14}H_{14}O_3$) C, H, O. Addition of dilute HCl to the mother liquors from the above crystallization of the cinchonidine salt gave acid enriched in the L-enantiomer **10**, series A. Pure material [*Anal.* ($C_{14}H_{14}O_3$) C, H] was obtained *via* crystallization of the D-1-(1-naphthyl)ethylamine salt.

L-2-(6-Methoxy-2-naphthyl)propanol (14).—A solution of B_2H_6 in THF was slowly added to a solution of 60 g of the acid **1** in 750 ml of THF until tlc indicated reduction was complete. The mixture was evaporated to dryness and distributed between C_6H_6 and H_2O. The C_6H_6 layer was evaporated and the product recrystallized from Me_2CO–hexane yielding 49 g (87%) of **14**. *Anal.* ($C_{14}H_{16}O_2$) C, H, O.

L-Sodium 2-(6-Methoxy-2-naphthyl)propionate (12).—A solution of 15 g of **1** in 250 ml of MeOH was titrated with a 3% solution of NaOMe in MeOH. Evaporation of most of the solvent and addition of 700 ml of Me_2CO induced crystallization. Filtration gave 15.5 g of the salt **12**.

L-Calcium 2-(6-Methoxy-2-naphthyl)propionate (13).—Solutions of 2.5 g of the Na salt **12** in 20 ml of H_2O and 0.56 g of $CaCl_2$ in 10 ml of H_2O were mixed. Filtration of the precipitate gave 1.3 g of the Ca salt **13**.

D-Methyl 2-(6-Methoxy-2-naphthyl)propionate (16).—A mixture of 17 g of the Na salt **12** and 12 g of MeI in 200 ml of DMF was stirred for 24 hr. Dilution with H_2O and extraction with C_6H_6 gave, after evaporation of the solvent and crystallization from Me_2CO–hexane, 14.9 g (84%) of the ester **16**. *Anal.* ($C_{15}H_{16}O_3$) C, H, O.

2-(6-Difluoromethoxy-2-naphthyl)propionic Acid (5).—A solution of 0.6 g of **2**, series A, in a mixture of 5 ml of AcOH and 5 ml of 48% HBr was heated under reflux for 1 hr. The solution was diluted with H_2O and the product extracted with EtOAc. Evaporation followed by removal of AcOH by codistillation with toluene gave crude 2-(6-hydroxy-2-naphthyl)propionic acid which was converted into the difluoromethyl ether by treatment with $CHClF_2$ and NaOH in aqueous dioxane.[16] Purification by partition chromatography on silica gel containing 40% H_2O (elution with C_6H_6–Et_2O), followed by crystallization from Me_2CO–hexane, gave 60 mg (8%) of **5**.

2-(6-Ethyl-2-naphthyl)acetic Acid (8).—A mixture of 7 g of 2-acetyl-6-ethylnaphthalene,[17] 1.7 g of S, and 4.6 g of morpholine was heated under reflux for 18 hr. Excess morpholine was removed *in vacuo* and the residue heated under reflux with 35 ml of concentrated HCl and 35 ml of AcOH for 4 hr. The mixture was poured into H_2O and the products extracted into Et_2O. The acidic product was then extracted from the Et_2O layer into dilute NaOH which was separated. Acidification and Et_2O extraction gave, after crystallization from Me_2CO–hexane, 2.1 g (26%) of **8**. *Anal.* ($C_{14}H_{14}O_2$) C, H, O. Other 6-substituted 2-naphthylacetic acids were prepared by methods indicated in footnotes to Table III and from 2-acetyl-6-chloronaphthalene.[18]

Acknowledgment.—We wish to thank Dr. R. I. Dorfman and Dr. R. K. Richards for helpful discussions and Dr. L. J. Throop and his associates for the determination of physical constants.

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(19) G. Stork, and J. W. Schulenburg, *J. Amer. Chem. Soc.*, **84**, 284 (1962).