Fenbufen, a New Anti-Inflammatory Analgesic: Synthesis and Structure–Activity Relationships of Analogs

RALPH G. CHILD ˣ, ARNOLD C. OSTERBERG, ADOLPH E. SLOBODA, and ANDREW S. TOMCUFCIK

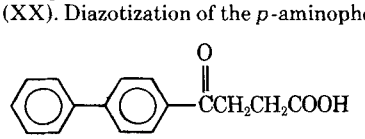
Abstract □ One hundred analogs of fenbufen were prepared and tested using the carrageenan, polyarthritis, and UV erythema anti-inflammatory tests and the 2-phenyl-1,4-benzoquinone writhing and inflamed paw pressure analgesic tests. Only three retained the same full spectrum of activity as fenbufen: *dl*-4-(4-biphenylyl)-4-hydroxybutyric acid, *dl*-4-(4-biphenylyl)-1,4-butanediol, and 4-biphenylacetic acid. Fenbufen had the same spectrum of activity as aspirin, phenylbutazone, and indomethacin in the five tests. In addition, dose–response derived potencies show fenbufen more potent than aspirin and at least as potent as phenylbutazone in all five tests. Two related compounds were generally similar.

Keyphrases □ Fenbufen—and various analogs, synthesized and evaluated for anti-inflammatory and analgesic activity □ Anti-inflammatory activity—evaluated in fenbufen and various analogs □ Analgesic activity—evaluated in fenbufen and various analogs □ Structure–activity relationships—fenbufen and various analogs, evaluated for anti-inflammatory and analgesic activity

While designing and synthesizing compounds for an immunosuppressive program, fenbufen (I) (1) was prepared as an intermediate potentially capable of imparting anti-inflammatory activity. Although fenbufen was uninteresting as an immunosuppressive, its activity in the ancillary anti-inflammatory tests (2) and its recognition as belonging to the well-known arylaliphatic carboxylic ("arylalkanoic") acid class of anti-inflammatory analgesics (3–5) prompted its full testing in this area. The biological testing program supporting this effort included the carrageenan-induced edema of the rat paw (6) and the guinea pig erythema (7) as anti-inflammatory tests, the polyarthritis test in rats as a model of chronic inflammation (8, 9), and the 2-phenyl-1,4-benzoquinone writhing (10) and paw pressure threshold (11) tests for analgesic action. When the preliminary screening data on I indicated activity in all five tests, a program was initiated to explore the structure–activity relationships of a series of analogs.

DISCUSSION

Chemistry—Most of the synthesized compounds were prepared by the Friedel–Crafts condensation of succinic anhydride with various aromatic compounds catalyzed by aluminum chloride. The reaction was described previously (12), and no unexpected difficulties were encountered. Twelve compounds were prepared by modification of preformed aryl keto acids. Thus, the benzylphenyl analog (VIII) was oxidized with chromic acid to the benzoylphenyl analog (XVI); similarly, the fluorene ring (III) gave the oxofluorene analog (XXV). Oxidation of the thioether (XIX) with peroxide gave the sulfoxide (XXI), whereas chromic oxide gave the sulfone (XX). Diazotization of the *p*-aminophenyl analog (13) followed by coupling to 2,6-diaminopyridine gave the azo compound (XXVII), which was oxidatively cyclized to the triazolo analog (XXVIII). The same *p*-aminophenyl analog reacted with *p*-chlorobenzoyl chloride to give the benzamido derivative (X). Table I summarizes the physical and pharmacological properties of the 3-(4-arylcarbonyl)propionic acids synthesized.



I

In the miscellaneous group (Table II) of compounds not previously described, sodium borohydride reduction of 4-phenoxybenzoylpropionic acid (V) gave the 4-hydroxybutyric acid analog (XXXIII) and bromination of 4-benzylbenzoylpropionic acid (VIII) gave the 3-bromopropionic acid analog (XXXIV).

The compounds listed in Table III consist of variations in the alkyl chain with the biphenyl moiety kept constant. The procedures used to modify the acid function of I or to replace it with various terminal substituents included esterification of I with ethanol and sulfuric acid to give the ester (XXXVIII) (Scheme I, R_1 = biphenylyl). The 4-hydroxy acid hydrazide (LXXII) came from the lactone (LX) (Scheme I) and hydrazine; the three polyols (XCI, C, and CI) were produced by reduction of the keto ester (XXXVIII), the diketone (XCVII), and the diketo ester (XCVI), respectively, with sodium bis(2-methoxyethoxy)aluminum hydride[1]. The chloro derivative (XLIV), obtained by Friedel–Crafts reaction of 3-chloropropionyl chloride and biphenyl, served as the intermediate for a number of products: the sodium sulfonate (L) *via* the acrylophenone (XLIII), the thioimidazoline (LI) from the corresponding imidazoline-2-thione, the nitrile (LII), and the *p*-tolylsulfinate (LIV).

The three amides (LXV, LXVI, and LXVII) were readily prepared directly from I and the corresponding amine at room temperature with the aid of the peptide-forming reagent, 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline[1] (CIII), in tetrahydrofuran (Scheme I, R_1 = biphenylyl). The procedure is simple, the by-products are volatile, and the yields are good.

Modifications to the carbonyl included the enol lactone (XXXIX) from I in boiling acetic anhydride (Scheme I, R_1 = biphenylyl). Reduction of I with excess sodium borohydride gave the *dl*-4-hydroxy analog (LV) (Scheme I). Resolution into the *d*- and *l*-isomers (LVI and LVII) was accomplished using the *d*- and *l*-isomers, respectively, of 2-aminobutanol. The *dl*-4-hydroxy acid (LV) cyclized readily in acid media to the lactone (LX) (Scheme I).

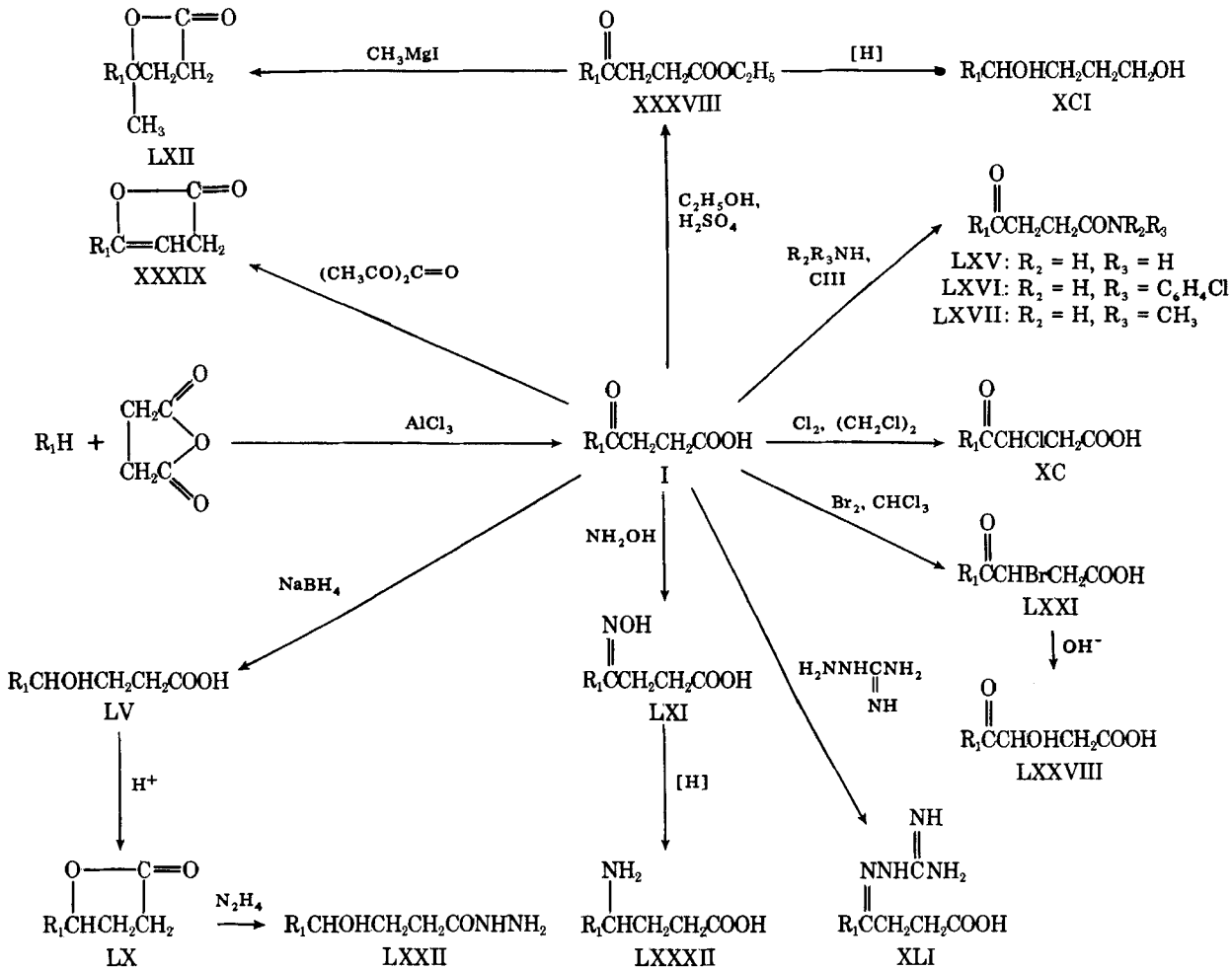
The keto group of I reacted with aminoguanidine to give the corresponding guanylhydrazone (XLI) and with hydroxylamine to give the oxime (LXI) (Scheme I, R_1 = biphenylyl). Reduction of the oxime with zinc and ammonium hydroxide afforded the 4-amino derivative (LXXXII). Methyl magnesium iodide added to the 4-carbonyl of the ester (XXXVIII), which subsequently lactonized by loss of ethanol to the lactone (LXII) (Scheme I). Dilute alkali opened the lactone to the corresponding 4-hydroxyvaleric acid analog (LXIII).

The Wittig reaction was employed in two instances to prepare biphenylbutenoic acids with the unsaturation conjugated to the biphenyl group. Thus, 4-acetylbiphenyl and the Wittig reagent, 2-carboxyethyltriphenylphosphonium chloride, yielded 4-(4-biphenylyl)-3-pentenoic acid (LXX). Similarly, 4-biphenylcarboxaldehyde yielded the 3-butenoic acid (XCIV).

The preparation of the sulfonyl (in place of carbonyl) analog of I required the preparation of 4-phenylthiophenol from diazotized 4-aminobiphenyl followed by condensation with 3-bromopropionic acid to give the thioether. This thioether was then oxidized *in situ* with peroxide to give the desired 3-(4-biphenylsulfonyl)propionic acid (LXXV).

The α,β-unsaturated chain analog of I was prepared directly from bi-

[1] Aldrich Chemical Co.

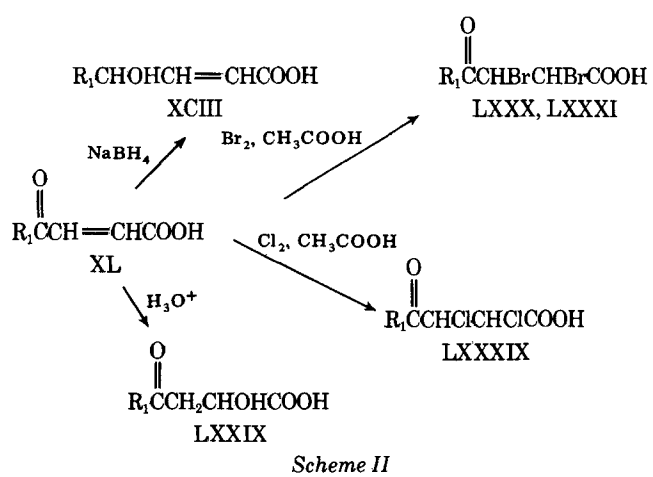


Scheme I

phenyl and maleic anhydride *via* the Friedel–Crafts reaction, giving 3-(4-biphenylylcarbonyl)acrylic acid (XL). On reduction with sodium borohydride, XL gave the unsaturated alcohol derivative (XCIII) (Scheme II, R_1 = biphenylyl).

The α,β-unsaturated analog (XL) was used to prepare a series of products by addition to the double bond. Thus, bromination in acetic acid gave one racemate isomer of the 2,3-dibromo analog (LXXX); bromination in chloroform gave the other 2,3-dibromo racemate (LXXXI) (Scheme II, R_1 = biphenylyl). Chlorination in acetic acid gave a 2,3-dichloro derivative (LXXXIX). Refluxing XL in dilute hydrochloric acid gave the 2-hydroxy analog (LXXIX) (Scheme II).

Bromination of I in ethanol-free chloroform gave the 3-bromo analog (LXXI) (Scheme I, R_1 = biphenylyl), which when stirred in dilute sodium carbonate solution, hydrolyzed to the 3-hydroxy derivative (LXXVIII). Similarly, chlorination of I in dichloroethane gave the 3-chloro analog (XC) (Scheme I).



Scheme II

Only the 2-methyl analog (XLVIII) was isolated from the Friedel–Crafts reaction of biphenyl and methylsuccinic anhydride. The 2-phenyl congener (XLIX) was prepared by hydrochloric acid hydrolysis in acetic acid of the corresponding nitrile (XLVII) which, in turn, was obtained by addition of hydrocyanic acid to 4′-phenylchalcone.

The Friedel–Crafts reaction of biphenyl and glutaric anhydride gave far lower yields than with succinic anhydride. Nevertheless, 4-(4-phenylbenzoyl)butyric acid (LXIX) was obtained in sufficient quantity and also brominated to the 4-bromo derivative (LXXVI). Finally, 4-biphenylcarboxaldehyde condensed smoothly with cyanoacetic acid in base to give good yields of 3-(4-biphenylyl)-2-cyanoacrylic acid (LXXXVIII).

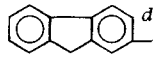
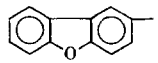
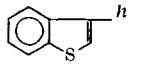
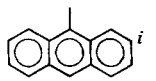
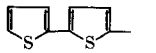
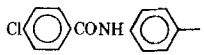
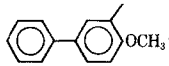
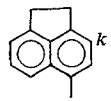
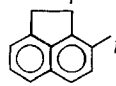
Biological Activity—All compounds were tested in the carrageenan anti-inflammatory and 2-phenyl-1,4-benzoquinone writhing analgesic tests. The decision to use the remaining three tests was dictated by the activity in the two basic tests and the availability of sufficient quantities of the compounds. These initial screening data were not designed to provide a comparison between compounds in any one test. The spectrum of activity over the range of all five tests using a standard large dose (250 mg/kg) provided a rapid initial evalution of a fairly large series of compounds, enabling selection of compounds for further study.

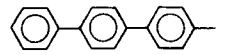
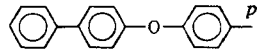
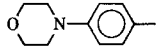
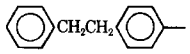
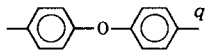
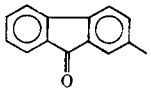
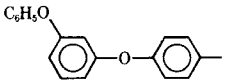
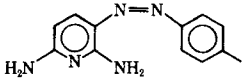
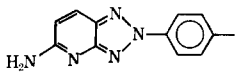
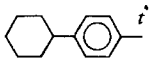
Table I lists the modifications to the biphenyl moiety or its replacement by other bulky groups and shows that all changes generally resulted in a reduced spectrum of activity. For example, substitution in the 4-position of the terminal phenyl group by chloro (II), methoxy (XI), phenyl (XVII), or fluoro (XXIX) groups decreased the carrageenan anti-inflammatory activity overall, and, where tested, there was a similar decrease in polyarthritis, UV erythema, and analgesic activity. In the single instance of a substituent on the ring adjacent to the alkyl chain, the 2-methoxy-5-phenyl analog (XII), there was complete loss of activity.

Separation of the two phenyl groups by oxygen, as in V, depressed

Table I—3-(4-Arylcarbonyl)propionic Acids

$RCOCH_2CH_2CO_2H$

Compound	R	Method	Reaction Solvent	Yield, %	Recrystallization Solvent	Melting Point	Formula	Analyses, % Calc.	Analyses, % Found	Carrageenan Edema, C/T, Paw Volume	Adjuvant Arthritis, % Inhibition	UV Erythema % Inhibition	2-Phenyl-1,4-benzoquinone, Number of Writhes	Paw Pressure Threshold, T/C
I	4-$C_6H_5C_6H_4$—[a]	A	$C_6H_5NO_2$	70	C_2H_5OH	185–187°	$C_{16}H_{14}O_3$	—	—	1.9	71	100	3	2.3
II	4-(4-ClC_6H_4)C_6H_4—[b]	A	CS_2	38	$CHCl_3$	185.5–186.5°	$C_{16}H_{13}ClO_3$	—	—	NA[c]	61	NA	16	1.8
III	 [d]	A	C_6H_6	80	—[e]	212–215°	$C_{17}H_{15}O_3$	—	—	NA	—	NA	NA	—
IV	 [f]	A	$(CHCl_2)_2$, $C_6H_5NO_2$	28	$CH_3COOC_2H_5$	185–187°	$C_{16}H_{12}O_4$	—	—	1.8	3.7	NA	NA	—
V	4-(C_6H_5O)C_6H_4—[g]	A	C_6H_6	67	—[e]	117–119°	$C_{16}H_{14}O_4$	—	—	1.9	NA	94	8	NA
VI	 [h]	A	$C_6H_5NO_2$	8	C_6H_6	133°	$C_{12}H_{10}O_3S$	—	—	NA	—	—	—	—
VII	 [i]	A	$C_6H_5NO_2$	43	C_2H_5OH	158–160°	$C_{18}H_{14}O_3$	—	—	NA	—	—	NA	—
VIII	4-($C_6H_5CH_2$)C_6H_4—[j]	A	$C_6H_5NO_2$	37	C_6H_6	125–127°	$C_{17}H_{17}O_3$	—	—	1.7	—	—	NA	—
IX		A	$C_6H_5NO_2$	10	C_6H_6	175–177°	$C_{12}H_{10}O_3S_2$	C 54.11 H 3.79 S 24.08	54.54 3.84 23.78	NA	NA	NA	NA	—
X		—	Aqueous NaOH	20	$CH_3OCH_2CH_2OH$	270–271°	$C_{17}H_{14}ClNO_4$	C 61.55 H 4.25 H 4.22 Cl 10.69	61.32 4.34 3.92 10.70	NA	NA	—	9	—
XI	4-($CH_3OC_6H_4$)C_6H_4—	A	$(CH_2Cl)_2$	9	—	201–202°	$C_{17}H_{16}O_4$	—	—	NA	—	—	8	NA
XII	 [j]	A	$(CHCl_2)_2$, $C_6H_5NO_2$	43	—	147–149°	$C_{17}H_{16}O_4$	—	—	NA	—	—	NA	—
XIII	 [k]	A	$C_6H_5NO_2$	90	—[l]	205–208°	$C_{16}H_{14}O_3$	—	—	NA	—	—	13	NA
XIV	 [k]	A	$C_6H_5NO_2$	1.4	—[m]	125–126°	$C_{16}H_{14}O_3$	—	—	NA	—	—	NA	—
XV	4-(*n*-C_4H_9O)C_6H_4—[n]	A	$C_6H_5NO_2$	82	—[d]	108–110°	$C_{14}H_{18}O_4$	—	—	NA	—	—	NA	—
XVI	4-(C_6H_5CO)C_6H_4—[o]	—	CH_3COOH	43	$(CH_2Cl)_2$, C_6H_{14}	125–127°	$C_{17}H_{14}O_4$	C 72.33 H 5.00	72.23 5.02	2.2	NA	NA	—	NA

XVII		A	$C_6H_5NO_2$	24	CH_3COOH	255–258°	$C_{22}H_{18}O_3$	C 79.98 80.63 H 5.49 5.54	NA	—	—	NA	—
XVIII	 [p]	A	C_6H_6	63	C_2H_5OH	185–187°	$C_{22}H_{18}O_4$	C 76.28 75.84 H 5.24 5.14	NA	—	—	NA	—
XIX	4-(C_6H_5S)C_6H_4—	A	C_6H_6	75	C_6H_6	143–145°	$C_{16}H_{14}O_3S$	C 67.12 67.30 H 4.93 4.87 S 11.18 11.21	1.7	40	NA	8	NA
XX	4-($C_6H_5SO_2$)C_6H_4—	—	CH_3COOH	65	Aqueous C_2H_5OH	157–159°	$C_{16}H_{14}O_5S$	C 60.08 59.79 H 4.42 4.33 S 10.05 10.31	NA	—	—	NA	—
XXI	4-(C_6H_5SO)C_6H_4—	—	$(CH_3)_2CO$	95	Aqueous C_2H_5OH	162–163°	$C_6H_{14}O_4S$	C 63.57 63.96 H 4.67 4.56 S 10.59 10.56	NA	—	—	NA	—
XXII		A	$(CHCl_2)_2$	6	H_2O	163–164°	$C_{14}H_{17}NO_4$	C 63.86 63.97 H 6.41 6.45 N 5.32 5.18	NA	—	—	NA	—
XXIII		A	$C_6H_5NO_2$	80	Aqueous C_2H_5OH	125–127°	$C_{18}H_{18}O_3$	C 76.57 76.48 H 6.43 6.28	NA	NA	—	NA	—
XXIV	 [q]	A	$(CHCl_2)_2$	22	—[r]	226–228°	$C_{20}H_{18}O_7$	— —	NA	—	—	NA	—
XXV		—	CH_3COOH	10	—[d]	—	$C_{17}H_{12}O_4$	C 72.85 72.09 H 4.32 4.43	NA	—	—	NA	—
XXVI		A	C_6H_6	16	C_6H_6	134–135°	$C_{22}H_{18}O_5$	C 72.92 73.18 H 5.01 5.11	NA	—	—	NA	—
XXVII		—	H_2O	54	—[r]	265–270°	$C_{15}H_{15}N_5O_3$	C 57.50 56.42 H 4.83 5.01 N 22.35 22.71	NA	NA	—	NA	—
XXVIII		—	C_5H_5N	17	—[s]	>300°	$C_{15}H_{13}N_6O_3$	N 22.50 22.66	NA	NA	—	11	—
XXIX	4-(4-FC_6H_4)C_6H_4—	A	CS_2	23	CH_3COOH	169–171°	$C_{16}H_{13}FO_3$	C 70.57 70.72 H 4.81 4.70 F 6.98 6.35	1.7	NA	NA	10	NA
XXX	 [t]	A	$C_6H_5NO_2$	66	C_6H_6	135–137°	$C_{16}H_{19}O_3$	— —	NA	—	—	NA	—

[a] Reference 1. [b] Reference 14. [c] NA = not active. [d] Reference 15. [e] Precipitates from sodium carbonate solution with hydrochloric acid. [f] References 16 and 17. [g] Reference 18. [h] Reference 19. [i] Reference 20. [j] Reference 21. [k] Reference 22. [l] Purified as the sodium salt and liberated with acid. [m] Purified *via* the methyl ester. [n] Reference 23. [o] Mass spectrum showed a mass ion of 282 and a strong 209 of $C_6H_5COC_6H_4CO$. [p] UV λ_{max} (methanol): 273 nm. Compound V λ_{max} (methanol): 268 nm; XI λ_{max} (methanol): 302 nm. [q] Reference 24. [r] Aqueous dimethylformamide. [s] Precipitated from ammonia solution with acetic acid. [t] Reference 25.

Table II—Miscellaneous Compounds

Compound	R	Method	Reaction Solvent	Yield, %	Recrystallization Solvent	Melting Point	Formula	Analyses, %		Carrageenan Edema, C/T, Paw Volume	Adjuvant Arthritis, % Inhibition	UV Erythema, % Inhibition	2-Phenyl-1,4-benzoquinone, Number of Writhes	Paw Pressure Threshold, T/C
								Calc.	Found					
XXXI	[a]	A	$(CH_2Cl)_2$	36	C_2H_5OH	87–90°	$C_{11}H_{10}OS_2$	—	—	NA[b]	—	—	14	NA
XXXII	[a]	A	$(CH_2Cl)_2$	32	C_2H_5OH	117–180°	$C_{14}H_{14}O_2S_2$	—	—	NA	NA	NA	—	—
XXXIII	4-$(C_6H_5O)C_6H_4CH(OH)CH_2CH_2CO_2H$	—	H_2O	88	—[c]	102–103°	$C_{16}H_{16}O_4$	C 70.57 H 5.92	70.22 5.82	2.2	NA	NA	12	1.8
XXXIV	4-$(C_6H_5CH_2)C_6H_4CO$-$CHBrCH_2CO_2H$[d]	—	$(CH_2Cl)_2$	43	C_6H_6	137–138°	$C_{17}H_{15}BrO_3$	C 58.81 H 4.26 Br 23.02	59.23 4.49 23.13	1.7	—	—	NA	—
XXXV	4-$(C_6H_5S)C_6H_4$-$(CH_2)_3CO_2H$[e]	—	—[f]	95	—[g]	66–67°	$C_{16}H_{16}O_2S$	—	—	2.3	NA	NA	NA	—

[a] Reference 26. [b] NA = not active. [c] See *Experimental*. [d] Mass spectrum showed a mass ion of 346 and a 195, 4-$(C_6H_5CH_2)C_6H_4CO$, indicative of bromination in the propionic acid chain. [e] Reference 27. [f] Triethylene glycol. [g] Precipitated from alkaline solution by addition of hydrochloric acid.

activity in all five tests; the addition of a dibenzofuran group (IV) reduced activity further.

Separation by sulfur (XIX) showed about the same order of reduction of activity as the oxygen analog (V). Oxidation of the sulfur in XIX to sulfoxide (XXI) and sulfone (XX) destroyed activity completely. In contrast, where the phenyl groups were separated by a methylene (VIII), oxidation to a carbonyl (XVI) caused a slight increase in the low order of activity. Again, addition of a fluorene (III) or 9-oxofluorene (XXV) reduced activity further.

Separation of the two phenyl groups by an ethylene (XXIII) resulted in total loss of activity. Similarly, separation by a carboxamide group (X) gave much lower activity when compared to the analogous II. With phenyl as a separating group in the terphenyl analog (XVII), activity was totally eliminated.

Replacement of the terminal phenyl group by various substituents such as butoxy (XV), morpholino (XXII), 3-phenoxyphenoxy (XXVI), diaminopyridylazo (XXVII), its cyclized triazolopyridyl (XXVIII), and cyclohexyl (XXX) likewise eliminated all activity.

None of the other various bulky aromatic groups such as VI, VII, IX, XIII, XIV, and XVIII showed any activity. The one case of a bis(carboxypropionic acid)-substituted diphenyl ether (XXIV) similarly was inactive.

With the miscellaneous compounds of Table II, reduction of the carbonyl of V to a carbinol (XXXIII) made no significant change, nor did the complete reduction of the carbonyl of XIX to a methylene (XXXV). Similarly, bromination of the chain in the 3-position of VIII giving XXXIV made no change in the activity spectrum.

Among the numerous changes to the alkyl chain moiety of I listed in Table III, only three retained the full spectrum of activity: the racemic 4-hydroxy analog (LV), the racemic 1,4-diol (XCI), and the acetic acid analog (CII). Although the full spectrum of tests was not carried out on the *d*-LVI and *l*-LVII isomers of LV, it appears that they were comparable.

Halogenation in the 3-position of I, *e.g.*, the 3-bromo product (LXXI), or its ester (LXIV) and the 3-chloro product (XC), retained the anti-inflammatory activity but reduced the analgesic activity. The 2,3-dichloro derivative (LXXXIX), as well as both racemates of the 2,3-dibromo analog (LXXX and LXXXI), showed minimal activity in both the anti-inflammatory and analgesic tests.

The effect of modifying the carboxylic acid group of I was dramatic and surprising in that only the 4-hydroxy acid hydrazide (LXXII) and the 1,4-diol (XCI) of 13 congeners retained anti-inflammatory activity. Unexpectedly, the ethyl ester (XXXVIII) and the three amides (LXV, LXVI, and LXVII) were devoid of carrageenan activity. Other substitutions for the carboxylic acid function that were inactive were the chloro (XLIV), the sodium sulfonate (L), the thioimidazole (LI), the nitrile (LII), the *p*-toluenesulfonate (LIV), the acetyl (XCVII), and the hydroxyethyl (C).

Modifications of the 4-carbonyl function of I, other than its reduction to a carbinol (LV), produced less active compounds. Thus, complete reduction to the methylene (XXXVI) eliminated the polyarthritis and paw pressure activity. The lactone (LX) of the 4-hydroxy acid (LV) showed only UV erythema and writhing activity, whereas the enol lactone (XXXIX) showed no activity. The oxime (LXI) and the 4-amino derivative (LXXXII) were completely inactive, yet the guanyl hydrazone ester (XLI) showed carrageenan activity. Reductive alkylation of the carbonyl to the 4-methyl-4-hydroxy analog (LXIII) and its lactone (LXII) also reduced overall activity. Replacement of the carbonyl by sulfonyl (LXXV) or oxygen (LXXIV) likewise reduced activity.

Unsaturation along the butyric acid chain at the 2,3-position as in XL or its ester (LXVIII) and XCIII eliminated anti-inflammatory activity, leaving minimal analgesic activity. However, unsaturation at the 3,4-position (XCIV) retained, except for the paw pain, a full spectrum of activity. Similarly, the 4-methyl 3,4-unsaturated analog (LXX) retained carrageenan activity but lost analgesic activity.

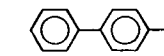
Aryl substitution as in the 2-phenyl (XLIX) and 3-phenyl (LXXVII) derivatives destroyed all activity. Alkyl substitution as in the 2-methyl (XLVIII) derivative retained only writhing activity.

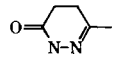
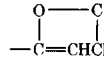
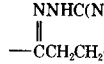
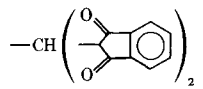
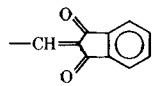
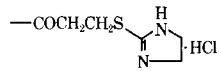
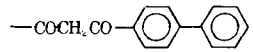
Lengthening the alkyl chain as in the valeric acid 5-oxo analog (LXIX) reduced anti-inflammatory activity and eliminated analgesic activity. The 4-bromo derivative (LXXVI) was completely inactive.

Both the 2- and 3-hydroxy-substituted analogs of I (LXXIX and LXXVIII, respectively) showed only carrageenan activity. The remaining miscellaneous substituted biphenyls of Table III were inactive.

Summary—The only modifications or analogs of I that, at best, did not reduce the spectrum of activity over the five tests were the reduction of the 4-carbonyl to a carbinol, giving *dl*-4-(4-biphenylyl)-4-hydroxy-

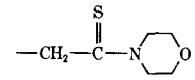
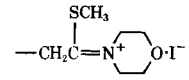
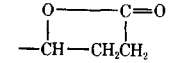
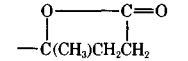
Table III—Substituted Biphenyls

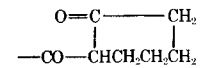
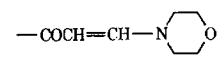
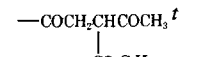
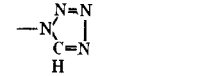


Compound	R	Yield, %	Recrystallization Solvent	Melting Point	Formula	Analyses, % Calc.	Analyses, % Found	Carrageenan Edema, C/T, Paw Volume	Adjuvant Arthritis, % Inhibition	UV Erythema, % Inhibition	2-Phenyl-1,4-benzoquinone, Number of Writhes	Paw Pressure Threshold, T/C
XXXVI	$-(CH_2)_3CO_2H$[a]	—	—	—	—	—	—	1.8	NA[b]	94	2	NA
XXXVII		33	—[c]	241–242°	$C_{16}H_{14}N_2O$	C 76.77 H 5.64 N 11.19	C 76.48 H 5.69 N 10.92	1.2	—	—	38	—
XXXVIII	$-CO(CH_2)_2CO_2C_2H_5$	31	C_2H_5OH	48–49°	$C_{18}H_{18}O_3$	C 76.57 H 6.43	C 76.65 H 6.32	NA	—	NA	10	NA
XXXIX		40	$(CH_3CO)_2O$	182–184°	$C_{16}H_{12}O_2$	C 81.33 H 5.12	C 80.91 H 5.03	NA	—	NA	NA	—
XL	$-COCH{=}CHCO_2H$[d]	35	CH_3COOH	172–175°	$C_{16}H_{12}O_2$	—	—	NA	—	NA	4	NA
XLI		44	C_2H_5OH	193–194°	$C_{17}H_{18}N_4O_2$	C 60.87 H 6.18 N 14.95	C 60.64 H 6.04 N 14.98	2.2[e]	—	NA	NA[f]	—
XLII	$-SO_2NH_2$[g]	55	—[h]	227–228°	$C_{12}H_{11}NSO_2$	—	—	NA	—	—	NA	—
XLIII	$-COCH{=}CH_2$[i]	23	C_2H_5OH	82–84°	$C_{15}H_{12}O$	—	—	NA	—	—	10	NA
XLIV	$-COCH_2CH_2Cl$[i]	70	C_6H_6	119–120°	$C_{15}H_{13}ClO$	—	—	NA	—	—	NA	—
XLV		50		188–190°	$C_{31}H_{20}O_4$	C 81.56 H 4.42	C 81.21 H 4.36	NA	—	—	NA	—
XLVI		54	CH_3COOH	167–169°	$C_{22}H_{14}O$	C 85.14 H 4.55	C 85.05 H 4.36	NA	—	—	NA	—
XLVII	$-COCH_2CH(C_6H_5)CN$	77	—[c]	175–176°	$C_{22}H_{17}NO$	C 84.86 H 5.50 N 4.50	C 85.68 H 5.45 N 4.30	NA	—	—	13	NA
XLVIII	$-COCH_2CH(CH_3)CO_2H$[j]	55	CH_3OH	212–215°	$C_{17}H_{16}O_3$	—	—	NA	NA	NA	4	NA
XLIX	$-COCH_2CH(C_6H_5)CO_2H$	63	—[k]	180–181°	$C_{22}H_{18}O_3$	C 79.78 H 5.49	C 79.78 H 5.45	NA	NA	NA	NA	—
L	$-COCH_2CH_2SO_3Na$	56	H_2O	278–280°	$C_{15}H_{13}NaO_4S$	C 56.18 H 4.37 S 10.00	C 56.72 H 4.36 S 9.44	NA	—	NA	NA	—
LI		27	C_2H_5OH	163–165°	$C_{18}H_{18}NOS{\cdot}HCl$	C 63.13 H 4.99 N 9.25 S 10.57	C 62.87 H 4.84 N 9.11 S 10.58	NA	—	—	NA	—
LII	$-COCH_2CH_2CN$[l]	75	C_2H_5OH	171–173°	$C_{16}H_{13}NO$	—	—	NA	—	—	NA	—
LIII		3	C_6H_6	132–133°	$C_{29}H_{24}O$	C 86.11 H 5.98	C 86.45 H 6.00	NA	—	—	NA	—
LIV	$-COCH_2CH_2SO_2C_6H_4$-4-CH_3	49	—[m]	179–180°	$C_{22}H_{20}O_3S$	C 72.50 H 5.53 S 8.80	C 72.39 H 5.41 S 8.83	NA	NA	NA	NA	—
LV	$-CH(OH)CH_2CH_2CO_2H$	97	—[n]	135–136°	$C_{16}H_{16}O_3$	C 74.98 H 6.29	C 74.67 H 6.32	1.8	52	100	3	1.4
LVI	d-$CH(OH)CH_2CH_2CO_2H$	10	C_2H_5OH	153–155°	$C_{16}H_{16}O_3$	C 74.98 H 6.29	C 74.70 H 6.45	2.1	61	92	—	—
LVII	l-$CH(OH)CH_2CH_2CO_2H$	10	C_2H_5OH	153–155°	$C_{16}H_{16}O_3$	C 74.98 H 6.29	C 74.73 H 6.42	2.2	—	82	12	NA

(continued)

Table III—*Continued*

Compound	R	Yield, %	Recrystallization Solvent	Melting Point	Formula	Analyses, % Calc.	Analyses, % Found	Carrageenan Edema, C/T, Paw Volume	Adjuvant Arthritis, % Inhibition	UV Erythema, % Inhibition	2-Phenyl-1,4-benzoquinone, Number of Writhes	Paw Pressure Threshold, T/C
LVIII		39	C_2H_5OH	138–140°	$C_{18}H_{19}NOS$	C 72.69 H 6.44 N 4.71 S 10.78	72.34 6.56 4.63 11.27	NA	NA	—	NA	—
LIX		97	$(CH_3)_2CO$	163–167°	$C_{19}H_{22}NOS$	C 51.94 H 5.05 N 3.19 S 7.30	52.02 5.12 3.12 7.56	NA	—	—	NA	—
LX		75	—[o]	105°	$C_{16}H_{14}O_2$	C 80.44 H 5.92	80.15 5.77	NA	NA	100	0	NA
LXI	—C(=NOH)$CH_2CH_2CO_2H$	60	C_2H_5OH	188–190°	$C_{16}H_{15}NO_3$	C 71.36 H 5.61 N 5.20	71.79 5.76 5.10	NA	—	—	NA	—
LXII		66	C_2H_5OH	107–110°	$C_{17}H_{16}O_2$	C 80.92 H 6.39	80.68 6.50	NA	34	—	NA	—
LXIII	—C(OH)$(CH_3)CH_2CH_2CO_2H$	61	—[n]	133–135°	$C_{17}H_{18}O_3$	C 75.03 H 6.71	74.85 6.67	NA	NA	—	NA	—
LXIV	—$COCHBrCH_2CO_2C_2H_5$	65	CH_3OH	77–78°	$C_{18}H_{17}BrO_3$	C 59.84 H 4.75 Br 22.12	59.96 4.87 21.97	2.3	58	91	NA	NA
LXV	—$COCH_2CH_2CONH_2$	47	C_2H_5OH	191–192°	$C_{16}H_{15}NO_2$	C 75.87 H 5.97 N 5.53	75.61 5.84 4.84	NA	—	—	6	NA
LXVI	—$COCH_2CH_2CONHC_6H_4$-4-Cl	55	C_2H_5OH	200°	$C_{22}H_{18}ClNO$	C 72.61 H 4.98 N 3.85	72.90 4.89 3.74	NA	—	—	NA	—
LXVII	—$COCH_2CH_2CONHCH_3$	40	C_2H_5OH	172–173°	$C_{17}H_{17}NO_2$	C 76.83 H 6.41 N 5.24	76.62 6.49 4.93	NA	—	—	NA	—
LXVIII	—$COCH{=}CHCO_2C_2H_5$	57	CH_3OH	87–88°	$C_{18}H_{16}O_3$	C 77.12 H 5.75	76.91 5.63	NA	—	—	NA	—
LXIX	—$COCH_2CH_2CH_2CO_2H$	3	CH_3COOH	160–161°	$C_{17}H_{16}O_3$	C 76.10 H 6.01	74.90 5.89	1.6	37	NA	NA	—
LXX	—$C(CH_3){=}CHCH_2CO_2H$	5	C_6H_6, C_6H_{14}	175–176°	$C_{17}H_{16}O_2$	C 80.92 H 6.39	79.86 6.29	2.0	—	—	NA	—
LXXI	—$COCHBrCH_2CO_2H$	60	C_6H_{14}	161–162°	$C_{16}H_{13}BrO_3$	C 57.67 H 3.94 Br 23.99	57.77 4.11 23.12	2.6	64	70	16	NA
LXXII	—$C(OH)HCH_2CH_2CONHNH_2$	36	C_2H_5OH	186–187°	$C_{16}H_{18}N_2O_2$	C 71.09 H 6.71 N 10.36	70.86 6.60 10.28	1.8	—	—	15	NA
LXXIII	—OCH_2CH_2CN[p]	30	$CH_2{=}CH_2CN$	130–131°	$C_{15}H_{13}NO$	—	—	NA	—	—	16	NA
LXXIV	—$OCH_2CH_2CO_2H$[p]	65	C_2H_5OH	174–175°	$C_{15}H_{14}O_3$	—	—	2.3	—	—	NA	—
LXXV	—$SO_2CH_2CH_2CO_2H$	25	C_2H_5OH, H_2O	174–176°	$C_{15}H_{14}O_4S$	S 11.04	11.25	NA	—	—	—	—
LXXVI	—$COCHBrCH_2CH_2CO_2H$	58	C_6H_6	163–164°	$C_{17}H_{15}BrO_3$	C 58.81 H 4.35 Br 23.03	58.85 4.25 23.32	NA	—	—	NA	—
LXXVII	—$COC(C_6H_5)HCH_2CO_2H$	6	CH_3COOH	175–177°	$C_{22}H_{18}O_3$	C 79.98 H 5.49	79.92 5.25	NA	—	—	NA	—
LXXVIII	—$COC(OH)HCH_2CO_2H$	78	—[q]	170–172°	$C_{16}H_{14}O_4$	C 71.10 H 5.22	71.25 5.02	1.8	NA	NA	NA	—
LXXIX	—$COCH_2C(OH)HCO_2H$	70	H_2O	174–175°	$C_{16}H_{14}O_4$	C 71.10 H 5.22	70.94 5.18	1.6	NA	NA	NA	—

LXXX	—COCHBrCHBrCO$_2$H(A)	30	C_6H_6	190–192°	$C_{16}H_{12}Br_2O_3$	C 46.63 46.81 H 2.94 2.87 Br 38.78 38.43	5.6	NA	NA	6	NA
LXXXI	—COCHBrCHBrCO$_2$H(B)	60	C_6H_6	181–182°	$C_{16}H_{12}Br_2O_3$	C 46.63 47.38 H 2.94 2.96 Br 38.78 38.43	4.2	NA	—	4	NA
LXXXII	—C(NH$_2$)HCH$_2$CH$_2$CO$_2$H	13	—[r]	182–184°	$C_{16}H_{19}NO_2$	C 75.27 75.48 H 6.71 6.80 N 5.48 5.31	NA	—	—	NA	—
LXXXIII		13	C_6H_6, C_7H_{16}	130–132°	$C_{19}H_{18}O_2$	C 81.99 81.70 H 6.52 6.31	NA	NA	—	NA	—
LXXXIV	—OCOCH=CHCO$_2$H	20	C_6H_6	218–219°	$C_{16}H_{12}O_4$	C 71.63 71.71 H 4.51 4.37	NA	—	—	9	NA
LXXXV	—COCH$_2$SCH$_2$CO$_2$C$_2$H$_5$	80	Aqueous C$_2$H$_5$OH	60–62°	$C_{18}H_{18}O_3S$	C 68.76 68.90 H 5.77 5.74 S 10.20 10.01	NA	—	—	NA	—
LXXXVI	—C(NNH$_2$)CH$_2$SCH$_2$CO$_2$C$_2$H$_5$	27	C$_2$H$_5$OH	78–79°	$C_{18}H_{20}N_2O_2S$	C 65.82 66.03 H 6.14 6.11 N 8.53 8.32 S 9.76 9.33	NA	—	—	NA	—
LXXXVII	—COCH$_2$SCH$_2$CO$_2$H	41	Aqueous C$_2$H$_5$OH	118–120°	$C_{16}H_{14}O_3S$	C 67.13 67.55 H 4.93 4.98 S 11.20 10.81	NA	NA	—	8	1.7
LXXXVIII	—CH=C(CN)CO$_2$H	77	—	243–245°	$C_{16}H_{11}NO_2$	C 77.09 77.15 H 4.45 4.40 N 5.62 5.78	1.8	NA	—	NA	—
LXXXIX	—COCHClCHClCO$_2$H	28	C_6H_6	180–184°	$C_{16}H_{12}Cl_2O_3$	C 59.46 59.52 H 3.74 3.66 Cl 21.94 22.05	4.8	NA	NA	15	NA
XC	—COCHClCH$_2$CO$_2$H	85	C_6H_6	158–159°	$C_{16}H_{13}ClO_3$	C 66.54 66.68 H 4.53 4.46 Cl 12.28 12.40	2.3	61	85	12	NA
XCI	—C(OH)HCH$_2$CH$_2$CH$_2$OH	50	Aqueous C$_2$H$_5$OH	79–80°	$C_{16}H_{18}O_2$	C 79.31 79.06 H 7.49 7.36	1.9	59	88	5	1.8
XCII		62	(CH$_3$)$_2$CO	191–193°	$C_{19}H_{19}NO_2$	C 77.79 77.71 H 6.53 6.68 N 4.77 4.66	NA	NA	—	NA	—
XCIII	—C(OH)HCH=CHCO$_2$H	43	Aqueous CH$_3$OH	155–157°	$C_{16}H_{14}O_3$	C 75.57 75.20 H 5.55 5.51	NA	NA	—	8	1.6
XCIV	—CH=CHCH$_2$CO$_2$H	25	C_6H_6	183–185°	$C_{16}H_{14}O_2$	C 80.64 81.01 H 5.92 5.92	1.8	50	85	9	NA
XCV	—COCH=CHNHC$_6$H$_5$	33	C_6H_6	220–222°	$C_{21}H_{17}NO$	C 84.25 83.95 H 5.72 5.37 N 4.68 4.50	NA	NA	—	NA	—
XCVI		65	C$_2$H$_5$OH	87–89°	$C_{20}H_{20}O_4$	— —	NA	NA	—	NA	—
XCVII	—COCH$_2$CH$_2$COCH$_3$[t]	41	C$_2$H$_5$OH	111–112°	$C_{17}H_{16}O_2$	— —	NA	NA	—	14	NA
XCVIII		54	C_6H_6, C_6H_{14}	161–162°	$C_{13}H_{10}N_4$	C 70.25 69.95 H 4.54 4.89 N 25.21 25.58	NA	NA	—	16	NA
XCIX	—COCHBrCH$_2$Br[i]	7	—[u]	84–86°	$C_{15}H_{12}Br_2O$	— —	NA	NA	NA	8	NA
C	—C(OH)HCH$_2$CH$_2$C(OH)-HCH$_3$	43	C_6H_6	106–107°	$C_{17}H_{20}O_2$	C 79.65 79.33 H 7.86 7.60	NA	NA	—	NA	—
CI	—C(OH)HCH$_2$C(CH$_2$OH)-HC(OH)HCH$_3$	80	—	Oil	$C_{18}H_{22}O$	C 75.49 76.26 H 7.74 7.50	NA	—	—	4	—
CII	—CH$_2$COOH[v]	—	—	—	—	— —	1.7	55	97	4	2.8

[a] Alfred Bader Chemicals, AB 3391. [b] NA = not active. [c] Ethanol–dimethylformamide (2:1). [d] Reference 28. [e] Toxic. [f] Dose was 5 mg/kg po. [g] Reference 29. [h] Dioxane–water (1:1). [i] Reference 30. [j] Reference 31. [k] Dimethylformamide–water (1:1). [l] Reference 32. [m] Ethanol–dimethylformamide (10:1). [n] Precipitated from solution with acetic acid. [o] Precipitated from acetic acid solution by dilution with water. [p] Reference 33. [q] Precipitated from sodium carbonate solution with acetic acid. [r] Dimethylformamide–2-methoxyethanol. [s] Reference 34. [t] Reference 35. [u] Cyclohexane–hexane. [v] Safron Laboratories.

Table IV—Potency Relative to Aspirin

Compound	Anti-Inflammatory			Analgesic	
	Carrageenan Edema	Adjuvant Arthritis	UV Erythema	2-Phenyl-1,4-benzoquinone-Induced Writhing	Paw Pain Pressure Threshold
Aspirin	1	1	1	1	1
Phenylbutazone	4.1	4.5	5.5	0.8	10.0
Indomethacin	25.0	118.0	9.2	119.0	20.0
Fenbufen (I)	4.2	6.3	6.3	3.7	10.0
4-Biphenylacetic acid (CII)	4.2	11.9	22.0	2.9	—
dl-4-(4-Biphenylyl)-4-hydroxybutyric acid (LV)	10.0	4.8	4.9	—	—

butyric acid (LV); the reduction of the carboxylic acid function to a carbinol, giving *dl*-4-(4-biphenylyl)-1,4-butanediol (XCI); and the acetic acid analog (CII).

From these data, I, CII, and LV were selected for dose–response studies. Table IV gives their relative potencies compared to aspirin, as the standard, along with phenylbutazone and indomethacin for comparison. The detailed pharmacological examination of fenbufen is the subject of a recent paper[2]; however, the long duration of action of this compound was noteworthy. It can be seen that all three compounds were considerably more potent than aspirin and at least as potent as phenylbutazone in the five test systems. Moreover, CII was more potent than indomethacin in the UV erythema test.

EXPERIMENTAL

Biological Tests—The carrageenan edema test was a modification of the test of Winter *et al.* (6). Drugs were administered by gavage at a dose of 250 mg/kg, except when resultant mortality required lower doses. Foot volume measurements were made 5 hr after drug administration (4 hr after carrageenan challenge). Results were expressed as a control (C)/treated (T) efficacy ratio (the ratio of mean edema volume of eight control rats over the mean edema volume of two treated rats). Compounds found to have activity were retested, and the final decision concerning such drugs was based on 32 control rats and eight treated rats.

The adjuvant-induced arthritis test was based on the procedures of Newbould (8) as well as Ward and Cloud (9). Test compound was administered orally at a dose of 50 mg/kg (occasionally lower because of toxicity) once daily on Days 0–13 postchallenge. On the 14th day postchallenge, the diameter of the injected paw (primary lesion) was measured with a micrometer caliper. From these measurements of inflamed paws, a determination was made of the rat paw volume. Results are expressed as the percent inhibition of inflamed control paw volume (mean volume of three treated rats compared with paw volume of 12 controls). Decisions of interesting activity were based on a minimum of 36 controls and nine treated rats.

The UV-induced erythema test followed that of Winder *et al.* (7). Groups of four albino guinea pigs received by gavage a 250-mg/kg dose (occasionally lower because of toxicity) 1 hr prior to UV exposure (−1 hr). At +1 and +4 hr after UV exposure, the degree of erythema for each of the three sites was assessed according to the following scoring system: 0, no erythema; 0.5, incomplete circle or faint erythema; and 1.0, complete circle of distinct erythema. In general, only compounds showing greater than 70% inhibition of erythema were considered of interest. The activity of compounds was confirmed with a second independent run; thus, the decision concerning activity was based on a minimum of 16 control guinea pigs and eight treated guinea pigs.

The 2-phenyl-1,4-benzoquinone test for analgesic activity was a modification of that described by Hindershot and Forsaith (10). The test compounds were administered orally at a dosage of 200 mg/kg to groups of two mice each 30 min before injection of 2-phenyl-1,4-benzoquinone. A compound was considered active if it reduced the total number of writhes in two test mice from a control value of approximately 30 per pair to 18 or less during a 3-min observation.

The inflamed paw pressure analgesic test was based on a modification of the method of Randall and Selitto (11). Pressure-pain thresholds were recorded 2 hr after the brewer's yeast injection. The agents being tested were given at the same time as the yeast at a dosage of 200 mg/kg. The ratios of treated (T)/control (C) reaction threshold were calculated as estimates of analgesic efficacy. A compound was considered an active analgesic if its T/C ratio was >1.5.

All results indicating activity were statistically significant ($p < 0.05$) by the t test.

Chemistry—Each analytical sample had an IR (potassium bromide) spectrum compatible with its assigned structure. Where deemed necessary, IR, mass, UV, and NMR spectral data are given. The melting points[3] of known compounds agreed with reported values within narrow limits.

General Method A: Friedel–Crafts Condensation of Succinic Anhydride and Aromatic Compounds—With the solvent listed in Table I in sufficient quantity to dissolve or suspend 0.2 mole of the aromatic compound and 0.21 mole of succinic anhydride at 0°, 0.42 mole of aluminum chloride was added portionwise with stirring. The reaction was allowed to warm to room temperature. It was stirred a few hours and then poured into 1 liter of ice water containing 125 ml of 12.2 *N* HCl. The solvents were removed by vacuum or steam distillation, and the residue was recrystallized from the solvent listed in Table I.

3-(4-Benzoylbenzoyl)propionic Acid (XVI)—A solution of 5.36 g (0.02 mole) of VIII in 150 ml of acetic acid and 1.9 ml of concentrated sulfuric acid was heated with 10.14 g (0.34 mole) of sodium dichromate and stirred at 40–60° for 4 hr. After standing at 20° for 2.5 days, the mixture was filtered. The filtrate was diluted with 1 liter of water, giving a crude product. This product was filtered, washed with water, and dried. Recrystallization gave 2.6 g of faintly green crystals. The mass spectrum showed *m/e* 282 and a strong 209 for 4-$(C_6H_5CO)C_6H_4CO$.

3-[4-(5-Amino-2H-triazolo[4,5-b]pyridin-2-yl)benzoyl]propionic Acid (XXVIII)—Eleven grams (0.035 mole) of XXVII was dissolved in 750 ml of refluxing pyridine. A solution of 32 g (0.2 mole) of copper sulfate in 250 ml of water was then added carefully (exotherm!). After the addition, refluxing was continued for a further 3 hr. Spot tests indicated complete conversion of the azo dye in about 30 min. The hot solution was added to 6 liters of water, and the suspension was treated with 12.2 *N* HCl until a clear solution was obtained. Solid sodium acetate was then added until the pH reached 4–5.

After cooling at 4° overnight, the precipitate was collected and extracted with 200 ml of boiling 12.2 *N* HCl. The insoluble portion was filtered off hot, washed with ethanol and ether, and dried. It was dissolved in 25 ml of hot water and 15 ml of concentrated ammonia, clarified with charcoal, and precipitated with 15 ml of acetic acid, giving 1.8 g of a bright-yellow product.

3-(4-Biphenylyl)-4,5-dihydro-6(1H)-pyridazinone (XXXVII)—A solution of 12.6 g (0.05 mole) of I in 300 ml of water containing 3.2 g (0.05 mole) of 85% KOH was treated with 2.5 ml of hydrazine hydrate (0.05 mole), and the mixture was stirred and heated on the steam bath for 4 hr. Acidification with 10 ml of acetic acid gave a precipitate, which was collected, washed with water, and dried. Recrystallization gave 4.1 g of pure product.

2,2′-[4-Biphenylylmethylene]bis(1,3-indandione) (XLV)—A mixture of 7.3 g (0.05 mole) of 1,3-indandione and 9.1 g (0.05 mole) of *p*-biphenylcarboxaldehyde in 125 ml of ethanol was refluxed for 3 hr and cooled. The formed solid was filtered off, washed well with ethanol, and dried, leaving 11 g of a pale-yellow solid. Recrystallization gave colorless crystals.

2-(4-Phenylbenzylidene)-1,3-indandione (XLVI)—A mixture of 4.4 g (0.03 mole) of 1,3-indandione and 5.5 g (0.03 mole) of *p*-biphenylcarboxaldehyde in 100 ml of acetic acid and 3 drops of concentrated sulfuric acid was heated on a steam bath for 2.5 hr and cooled. The formed bright-yellow plates were filtered and washed with acetic acid, water, and ethanol, yielding 5.0 g.

γ-Oxo-α-phenyl-4-biphenylbutyronitrile (XLVII)—A solution of 14.2 g (0.05 mole) of 4′-phenylchalcone, 700 ml of ethanol, 150 ml of di-

[2] See A. Sloboda and A. Osterberg, *Inflammation*, 1, 415 (1976).

[3] Melting points were taken on a Fisher-Johns block and are uncorrected.

methylformamide, and 3 ml of acetic acid at 55–60° was treated with 6.5 g (0.1 mole) of potassium cyanide in 25 ml of water during 15 min. The solution was stirred at 55–60° for an additional 5 hr and then at 20° for 2 days. The precipitate was collected, washed with water, dried, and recrystallized, giving 9.5 g of product. Concentration of the mother liquor to half-volume and cooling gave an additional 2.6 g with the same melting point. The total yield was 12.1 g.

1,4-Bis(4-biphenylyl)butane-1,4-dione (LIII)—An intimate mixture of 15.4 g (0.1 mole) of biphenyl and 11.4 g (0.1 mole) of glutaric anhydride was added portionwise to a cold (5°) solution of 28 g (0.21 mole) of aluminum chloride in 175 ml of nitrobenzene. The mixture was allowed to warm to 20° and was stirred for 4 days. After working up in the usual way, the crude product was precipitated from sodium carbonate solution with hydrochloric acid. After recrystallizing from acetic acid and benzene, 1.2 g of straw-yellow rods was obtained.

d-*4-(4-Biphenylyl)-4-hydroxybutyric Acid (LVI)*—A solution of 2.56 g (0.1 mole) of LV in 50 ml of warm ethanol was filtered, treated with 0.9 g (0.01 mole) of *d*-2-aminobutanol[1], and cooled. After 2 days at 5°, 1 g of colorless crystals was filtered off, mp 144–146°. Concentration of the mother liquor to half-volume gave a second crop (0.2 g, mp 144–148°). Two recrystallizations of the combined crops from ethanol gave 0.5 g (mp 152–153°) of the salt. Acidification of the salt in 50 ml of water with 5 *N* HCl to pH 2 gave a white precipitate. This precipitate was filtered, washed well with water, and dried, yielding the optically pure hydroxy acid, 0.2 g, $[\alpha]_D^{25}$ + 14.1 ± 0.18° (ethanol). The IR curve was identical to that of the racemic acid (LV).

l-*4-(4-Biphenylyl)-4-hydroxybutyric Acid (LVII)*—In the same manner as described for the previous resolution, *l*-2-aminobutanol[1] was used to separate the stereoisomeric salt (mp 150–152°) and yielded the optically pure hydroxy acid, $[\alpha]_D^{25}$ −14.1 ± 0.2° (ethanol). The IR curve was identical to that of the racemic acid (LV).

4-(4-Biphenylylthioacetyl)morpholine (LVIII)—A mixture of 29.4 g (0.15 mole) of 4′-phenylacetophenone, 8 g (0.25 mole) of sulfur, and 50 ml of morpholine was refluxed on steam for 8 hr and cooled. The reaction mass was triturated with 100 ml of ether; the insolubles were collected, washed with 100 ml of petroleum ether (bp 30–60°), and dried. Recrystallization gave 16.4 g.

4-[1-(4-Biphenylyl)-2-(methylthio)ethylidene]morpholinium Iodide (LIX)—A solution of 25.5 g (0.09 mole) of LVIII in 600 ml of acetone and 15 ml of methyl iodide was allowed to stand at 20° for 3 days. The crystalline precipitate was collected, washed with ether, and dried, giving 34.0 g.

4-(4-Biphenylyl)-4-valerolactone (LXII)—Grignard reagent, made in the usual way from 10 g (0.07 mole) of methyl iodide and 1.71 g (0.07 mole) of magnesium in ether, was added dropwise to a cold (5°) suspension of 14.1 g (0.05 mole) of the ester (XXXVIII) in 500 ml of ether (Scheme I, R_1 = biphenylyl). After stirring at 5° for 1.5 hr, the complex was decomposed with 15 ml of saturated ammonium chloride solution, allowed to warm to 20°, filtered, dried over calcium chloride, and concentrated to dryness. The residue was crystallized, yielding 10 g of lactone; IR (KBr): 5.65 μm.

Ethyl 3-Bromo-3-(4-phenylbenzoyl)propionate (LXIV)—A solution of 2.54 g (0.01 mole) of I in 300 ml of commercial grade chloroform containing ethanol was treated dropwise with 1.6 g (0.01 mole) of bromine in 25 ml of chloroform over 0.5 hr. The mixture was then refluxed for 4 hr and stripped to dryness. The residual oil was crystallized once from ether–hexane and finally from methanol, yielding 2.3 g; mass spectrum: *m/e* 360.

3-(4-Phenylbenzoyl)propionamide (LXV)—A saturated solution of ammonia in 75 ml of tetrahydrofuran was treated with 2.54 g (0.01 mole) of I (Scheme I). The resulting suspension of ammonium salt was treated with 2.96 g (0.012 mole) of CIII and stirred overnight at 20°. The mixture was stripped to dryness, and the residue was recrystallized, giving 1.2 g of colorless flakes.

Ethyl 3-(4-Phenylbenzoyl)acrylate (LXVIII)—A warm mixture of 2.7 g (0.045 mole) of acetic acid and 2.77 g (0.028 mole) of triethylamine in 100 ml of acetone was treated all at once with 1.805 g (0.005 mole) of LXIV and stirred for 2 hr. After cooling and filtering, the acetone solution was poured into two volumes of water. The formed solid was filtered, washed with water, dried, and recrystallized, yielding 0.8 g.

4-(4-Phenylbenzoyl)butyric Acid (LXIX)—Glutaric anhydride (12 g, 0.11 mole) was condensed with biphenyl (15.4 g, 0.1 mole) in tetrachloroethane by addition of aluminum chloride according to Carter *et al.* (36); 0.8 g of a yellow material was obtained.

4-(4-Biphenylyl)-3-pentenoic Acid (LXX)—By using the general procedure described by Corey *et al.* (37), 4-acetylbiphenyl (14.72 g, 0.075 mole) was condensed with the Wittig reagent, (2-carboxyethyl)triphenylphosphonium chloride, in the presence of sodium hydride. A pale-yellow solid (1 g) was obtained; UV λ_{max} (ethanol): 276 nm, consistent with an unsaturated alkyl conjugated with biphenyl.

3-(4-Biphenylylsulfonyl)propionic Acid (LXXV)—A solution of 7.2 g (0.04 mole) of crude 4-phenylthiophenol (38) in a mixture of 100 ml of water, 50 ml of ethanol, and 4.5 ml of 10 *N* NaOH was treated with a mixture of 6.3 g (0.04 mole) of 3-bromopropionic acid, 100 ml of water, and 4.5 g (0.04 mole) of sodium bicarbonate. The mixture was heated and stirred on the steam bath for 4 hr and then clarified. The filtrate was successively acidified (concentrated hydrochloric acid) and basified (concentrated ammonium hydroxide).

The insolubles in ammonia solution were removed by filtration, and the filtrate was reacidified with concentrated hydrochloric acid. The acid mixture was extracted with 250 ml of chloroform. Removal of the chloroform left 1.0 g of oily residue, which was taken up in acetic acid. Addition of 4 ml of 30% H_2O_2 and heating on steam for 5 hr, followed by dilution with 450 ml of cold water, produced a precipitate. This precipitate was collected, dried, and recrystallized, yielding 200 mg.

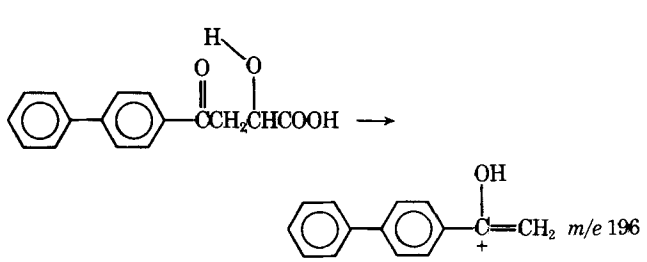
3-(4-Phenylbenzoyl)-3-phenylpropionic Acid (LXXVII)—A suspension of 13.6 g (0.05 mole) of benzyl biphenyl ketone (39) in 500 ml of absolute ethanol was treated with 1.2 g (0.05 mole) of sodium hydride followed by 8.35 g (0.05 mole) of ethyl bromoacetate. After refluxing for 20 min, the mixture was treated with 5 g of potassium hydroxide in 25 ml of water, refluxed for 2 hr more, and then poured into 1 liter of water. After filtering, acidification of the filtrate with concentrated hydrochloric acid gave a crude product. This product, when crystallized from acetic acid once and finally from benzene–hexane, gave 1 g of a colorless product.

3-Hydroxy-3-(4-phenylbenzoyl)propionic Acid (LXXVIII)—A mixture of 5 g (0.015 mole) of LXXI in 500 ml of 10% Na_2CO_3 was stirred at room temperature for 16 hr (33) (Scheme I). The formed peach-colored sodium salt was removed, suspended in water, and acidified with acetic acid, giving 3.2 g of colorless product; mass spectrum: *m/e* 270; $C_6H_5C_6H_4C{\equiv}O^+$, 181; and $C_6H_5C_6H_4^+$, 153.

2-Hydroxy-3-(4-phenylbenzoyl)propionic Acid (LXXIX)—A mixture of 5.7 g (0.023 mole) of XL and 100 ml of concentrated hydrochloric acid in 400 ml of water was refluxed for 20 hr and filtered hot, yielding 5.6 g of unreacted XL (Scheme II). On cooling, the filtrate yielded 0.2 g of a product whose IR curve indicated it to be a hydroxy keto acid. Boiling the unreacted material three times with large volumes of 1:4 diluted hydrochloric acid gave an accumulation of 5 g of crude product, mp 160–165°. Recrystallization gave 4.3 g of colorless product. A mixed melting point of this product with the 3-hydroxy analog (LXXVIII) was 150–155°; mass spectrum: *m/e* 270; $C_6H_5C_6H_4C{\equiv}O^+$, 181; $C_6H_5C_6H_4^+$, 153; and a 196 which results from a McLafferty rearrangement (40) of a β-hydroxy ketone (Scheme III). The α-hydroxy ketone (LXXVIII) described previously cannot undergo this fragmentation and does not show an *m/e* 196.

2,3-Dibromo-3-(4-phenylbenzoyl)propionic Acid (LXXX): Racemic Mixture A—In a manner similar to that described by Rice (41), 7.5 g (0.03 mole) of XL in 400 ml of acetic acid at 15° was treated dropwise with 4.8 g (0.03 mole) of bromine (Scheme II). The solution was then concentrated to dryness, and the residue was washed with water and dried. Recrystallization yielded 4.1 g of colorless grains.

4-Amino-4-biphenylbutyric Acid (LXXXII)—By using the general method of Tochims (42), 9.5 g (0.035 mole) of LXI was stirred into 500 ml of concentrated ammonium hydroxide, warmed, and held at 60–65° while 50 g of zinc dust was carefully added in small portions (Scheme I). After the addition, stirring at 60–65° was continued for 18 hr. The reaction mixture was clarified by filtration, and the filtrate was taken to dryness *in vacuo*. The residue was shaken with 500 ml of 0.1 *N* NaOH solution and clarified, and the filtrate was acidified with 10 ml of acetic acid. The semigelatinous precipitate was collected, washed with water, and dried. It was then extracted with 500 ml of boiling ethanol. The insoluble portion was recrystallized, giving 0.8 g of the amino acid. Con-



Scheme III

centration of the ethanol extract to 250 ml and cooling gave an additional 0.4 g; the total yield was 1.2 g.

2-(4-Phenylbenzoyl)cyclohexanone (*LXXXIII*)—4-Phenylbenzoyl chloride [formed from 19.8 g (0.1 mole) of 4-phenylbenzoic acid, benzene, and thionyl chloride under reflux for 1 hr] was dissolved in 250 ml of chloroform and added during 2 hr to a stirred mixture of 18.5 g (0.11 mole) of 1-morpholinocyclohexene, 18 ml (0.13 mole) of triethylamine, and 250 ml of chloroform at 30–35°. After stirring at 20° for 16 hr, 50 ml of water and 25 ml of concentrated hydrochloric acid were added; the mixture was then refluxed for 2 hr. The chloroform layer was separated, washed with water, dried over magnesium sulfate, and concentrated to dryness. The residual oil was dissolved in a hot mixture of 150 ml of benzene and 300 ml of *n*-heptane, decolorized with carbon, and cooled, yielding 3.6 g.

Maleic Acid Mono-4-biphenylyl Ester (*LXXXIV*)—A solution of 5.04 g (0.02 mole) of XL in 200 ml of acetic acid was treated with 12 ml of 30% H_2O_2 and heated at 60° for 24 hr. An additional 10 ml of hydrogen peroxide was added, and the reaction was stirred on steam overnight. Dilution of the clear yellow solution with 1.5 volumes of water gave a crude product. When this product was recrystallized, 1.0 g of colorless product was obtained. Hydrolysis of a sample of the product yielded 4-phenylphenol, mp 164–165°; mass spectrum: *m/e* 268; and $C_6H_5C_6H_4OH$, 170.

Ethyl 4-Phenylbenzoylmethylthioacetate (*LXXXV*)—A solution of 7.2 g (0.06 mole) of ethyl mercaptoacetate and 3.4 g (0.06 mole) of sodium methoxide in 500 ml of ethanol was treated with 13.8 g (0.05 mole) of 2-bromo-4′-phenylacetophenone. The mixture was stirred at 20° for 5 hr, refluxed for 4 hr, and then concentrated to a thick oil. Trituration with 250 ml of cold water left a solid, which was filtered, washed with water, and dried, yielding 19 g. Recrystallization gave 15 g of colorless crystals.

Ethyl 4-Phenylbenzoylmethylthioacetate Hydrazone (*LXXXVI*)—A solution of 7.0 g (0.022 mole) of LXXXV in 200 ml of boiling ethanol was treated with 1.1 ml (0.022 mole) of 100% $N_2H_4 \cdot H_2O$ and refluxed for 6 hr, clarified with carbon, filtered, and cooled, yielding 2 g of hydrazone.

3-(4-Phenylbenzoyl)-2,3-dichloropropionic Acid (*LXXXIX*)—A solution of 5 g (0.02 mole) of XL in 300 ml of acetic acid at 20° was treated with a steady stream of chlorine for 3 hr (Scheme II). The yellow solution was concentrated to dryness, and the residue was washed with water and dried. Two recrystallizations gave 1.8 g of colorless crystals.

3-Morpholino-4′-phenylacrylophenone (*XCII*)—A solution of 4.1 g (0.01 mole) of LXXX in 500 ml of boiling benzene was treated with 6 ml (0.07 mole) of morpholine. Extensive carbon dioxide evolution was detected by bubbling the evolved gas through barium hydroxide solution. After 8 hr of refluxing, the precipitate of morpholine salt was filtered off (3.2 g, 95%). The benzene filtrate was concentrated to 100 ml, diluted with 200 ml of petroleum ether (bp 30–60°), and cooled. The precipitate was collected and recrystallized, giving 1.5 g of product; IR (KBr): C=O, 6.08 (vinylogous amide); C=C, 6.5; *trans*-CH=CH, 10.1 μm; no COOH; mass spectrum: *m/e* 293.

3-Anilino-4′-phenylacrylophenone (*XCV*)—A mixture of 8.3 g (0.02 mole) of LXXX, 15 ml (0.16 mole) of aniline, and 500 ml of benzene was stirred under reflux for 16 hr. The precipitate of aniline salt was filtered from the hot suspension and washed with 100 ml of benzene. Concentration of the filtrate and wash to 150 ml and cooling to 20° gave a precipitate, which was washed with 100 ml of warm water and dried, giving 2.0 g.

1-(4-Biphenylyl)tetrazole (*XCVIII*)—A solution of 4.23 g (0.025 mole) of 4-aminobiphenyl in 180 ml of ethyl orthoformate was distilled slowly until the temperature reached 143° (3 hr). The remainder was evaporated to dryness, dissolved in 40 ml of acetic acid, treated with 6.5 g (0.1 mole) of sodium azide, and stirred at 20° for 24 hr. After addition of 100 ml of water, the solid was filtered off, washed with water, dried, and recrystallized (two times), giving pale-yellow crystals, 3.0 g.

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[x] To whom inquiries should be directed.