Bodanszky in "Peptides, Proceedings of the Fifth American Peptide Symposium", M. Goodman and J. Meienhofer, Ed., Wiley, New York, N.Y., 1977, p 1.
(7) V. Mutt and J. E. Jorpes, *Biochem. Biophys. Res. Commun.*, **26**, 392 (1967); *Eur. J. Biochem.*, **6**, 156 (1968); *Proc. Int. Union Physiol. Sci.*, **6**, 193 (1968); J. W. Jorpes, *Gastroenterology*, **55**, 157 (1968); V. Mutt and J. E. Jorpes, *Biochem. J.*, **125**, 57 (1971).
(8) A. Anastasi, V. Erspamer, and R. Endean, *Experientia*, **23**, 699 (1967).
(9) For a review on gastrin, cf. J. H. Walsh and M. I. Grossman, *N. Engl. J. Med.*, **292**, 1324 (1975).
(10) A. Anastasi, L. Bernardi, G. Bertaccini, G. Bosisio, R. deCastiglione, V. Erspamer, O. Goffredo, and M. Impicciatore, *Experientia*, 24, 771 (1968).
(11) (a) M. A. Ondetti, J. Pluŝĉec, E. F. Sabo, J. T. Sheehan, and N. Williams, *J. Am. Chem. Soc.*, **92**, 195 (1970); (b) M. A. Ondetti, B. Rubin, S. L. Engel, J. Pluŝĉec, and J. T. Sheehan, *Dig. Dis.*, **15**, 149 (1970).
(12) M. Bodanszky, N. Chaturvedi, D. Hudson, and M. Itoh, *J. Org. Chem.*, **37**, 2303 (1972).
(13) Y. S. Klausner and M. Bodanszky, *J. Org. Chem.*, **42**, 147 (1977).
(14) H. Yajima, Y. Mori, Y. Kiso, K. Koyama, T. Tobe, M. Setoyama, H. Adachi, T. Kanno, and A. Saito, *Chem. Pharm. Bull.*, **24**, 1110 (1976); Y. Mori and H. Yajima, *ibid.*, **24**, 2781 (1976); Y. Mori, K. Koyama, Y. Kiso, and H. Yajima, *ibid.*, **24**, 2788 (1976); H. Yajima, Y. Mori, K. Koyama, T. Tobe, M. Setoyama, H. Adachi, T. Kanno, and A. Saito, *ibid.*, **24**, 2794 (1976).
(15) Migration of the sulfate ester group with the concomitant formation of a tyrosine-3-sulfonic acid derivative was observed by Dr. M. A. Ondetti (personal communication).
(16) P. Dreyfuss, *J. Med. Chem.*, 17, 252 (1974).
(17) (a) M. Bodanszky and S. Natarajan, *J. Org. Chem.*, **40**, 2495 (1975); (b) S. Natarajan and M. Bodanszky, *ibid.*, **41**, 1269 (1976).
(18) M. Bodanszky, *Ann. N.Y. Acad. Sci.*, **88**, 655 (1960).
(19) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).
(20) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 98 (1957); F. C. McKay and N. F. Albertson, *ibid.*, **79**, 4686 (1957); G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).
(21) H. Medzihradszky-Schweiger and K. Medzihradszky, *Acta Chim. Acad. Sci. Hung.*, **50**, 339 (1966); H. Medzihradszky-Schweiger, *Ann. Univ. Sci. Budap. Rolando Eötvös Nominatae, Sect. Chim.*, **13**, 35 (1972); H. Medzihradszky-Schweiger, *Acta Chim. Acad. Sci. Hung.*, **76**, 437 (1973).
(22) A closed system was used with DMF containing DIEA (in the concentration present in the reaction mixture) in the gas buret and connecting tube.
(23) Hog kidney acylase from Nutritional Biochemicals Corp., Cleveland, Ohio.
(24) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids", Vol. 2, Wiley, New York, N.Y., 1961, p 1053.
(25) M. Itoh, D. Hayiwara, and T. Kamiya, *Tetrahedron Lett.*, 4393 (1975).
(26) H. C. Reitz, R. E. Ferrel, H. Fraenkel-Conrat, and H. S. Olscott, *J. Am. Chem. Soc.*, **68**, 1024 (1946); cf. also ref 11a.
(27) S. Ljungberg, *Acta Pharm. Suec.*, **6**, 599 (1969).
(28) J. D. Gardner, *Annu. Rev. Physiol.*, in press.
(29) W. König and R. Geiger, *Chem. Ber.*, **103**, 788 (1970).
(30) T. A. Hylton, G. Preston, and B. Weinstein, *J. Org. Chem.*, 31, 3400 (1966).
(31) J. M. Davey, A. H. Laird, and J. S. Morley, *J. Chem. Soc. C*, 555 (1966).
(32) F. Marchiori, R. Rocchi, and E. Scoffone, *Ric. Sci. Rend.*, **A2**, 647 (1962).
(33) M. Wilchek and A. Patchornik, *J. Org. Chem.*, **28**, 1874 (1963).
(34) M. Bodanszky, *Acta Chim. Hung.*, 10, 335 (1957).
(35) E. Scoffone, R. Rocchi, E. Vidali, V. Scatturin, and I. Marchiori, *Gazz. Chim. Ital.*, **94**, 743 (1964).
(36) M. Bodanszky and N. Chandramouli, unpublished work.
(37) L. Berlinguet and R. Gaudry, *J. Biol. Chem.*, **198**, 765 (1952).
(38) J. D. Gardner and M. J. Jackson, *J. Physiol.*, **270**, 439 (1977).
(39) M. Ceska, K. Birath, and B. Brown, *Clin. Chim. Acta*, **26**, 437 (1969).
(40) M. Ceska, B. Brown, and K. Birath, *Clin. Chim. Acta*, **26**, 445 (1969).
(41) V. Mutt, *Clin. Endocrinol.*, **5**, 175s (1976).

Synthesis and Antiinflammatory Activity of 6,11-Dihydro-11-oxodibenzo[*b,e*]thiepinalkanoic Acids and Related Compounds[1]

Jack Ackrell,* Yulia Antonio, Fidencio Franco, Rosita Landeros, Alicia Leon, Joseph M. Muchowski,*

Research Laboratories, Syntex, S.A., Apartado Postal 10-820, Mexico 10, D.F.

Michael L. Maddox, Peter H. Nelson, Wendell H. Rooks, Adolph P. Roszkowski, and Marshall B. Wallach

Syntex Research, Institutes of Biological Sciences, Organic Chemistry, and Pharmacology and Metabolism, Palo Alto, California 94304. *Received April 24, 1978*

Acetic acid derivatives of tricyclic systems, such as 6,11-dihydro-11-oxodibenzo[*b,e*]thiepin, 4,10-dihydro-4-oxothieno[2,3-c][1]benzothiepin, dibenzo[*b,f*]thiepin, dibenz[*b,f*]oxepin, etc., were synthesized and assayed for antiinflammatory activity. One of the compounds, 6,11-dihydro-11-oxodibenzo[*b,e*]thiepin-3-acetic acid (**52**), was chosen for evaluation in man on the basis of high antiinflammatory activity in both short- and long-term animal assays and a low gastric irritation liability in rats and dogs.

During the past 15 years a very large number of nonsteroidal antiinflmmatory agents, principally aryl- and heteroarylacetic and -propionic acids, have been synthesized[2] with the aim of finding substances with fewer side effects (especially gastric irritation) than phenylbutazone and indomethacin. Of the numerous compounds synthesized, only a few, including ibuprofen,[3] ketoprofen,[4] naproxen,[5] and tolmetin,[6] have met most of the above

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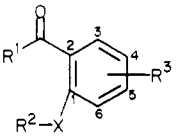
Table I. Substituted Phthalic Acids and Derivatives

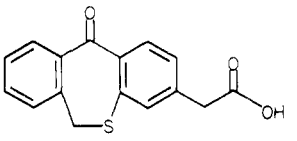


no.	R^1	R^2	X	R^3	mp or bp (mm), °C	% yield	recrystn solvent[a]	emp formula	analyses[b]
1	CH_3O	$C_6H_5CH_2$	S	6-$COOCH_3$	oil	84		$C_{17}H_{16}O_4S$	c
2	HO	$C_6H_5CH_2$	S	6-COOH	138-139	82	$CHCl_3$	$C_{15}H_{12}O_4S$	C, H
3	Cl	$C_6H_5CH_2$	S	6-COCl	37-38	79	hex	$C_{15}H_{10}Cl_2O_2S$	C, H, Cl
4	$(CH_3)_2CHO$	O_2	N	5-$COOCH(CH_3)_2$	oil	90		$C_{14}H_{17}NO_6$	C, H
5	$(CH_3)_2CHO$	$C_6H_5CH_2$	S	5-$COOCH(CH_3)_2$	70-71	91	pen	$C_{21}H_{24}O_4S$	C, H, S
6	HO	$C_6H_5CH_2$	S	5-COOH	299-300	92	*i*-PrOH	$C_{15}H_{12}O_4S$	C, H
7	Cl	$C_6H_5CH_2$	S	5-COCl	158	72	hex	$C_{15}H_{10}Cl_2O_2S$	*d*
8	CH_3O	$C_6H_5CH_2$	S	4-$COOCH_3$	73-74	90	C_6H_6	$C_{17}H_{16}O_4S$	C, H, S
9	$(CH_3)_2CHO$	$C_6H_5CH_2$	S	4-$COOCH(CH_3)_2$	105-107	80	C_6H_6-eth	$C_{21}H_{24}O_4S$	*e*
10	HO	$C_6H_5CH_2$	S	4-COOH	298-300	90	EtOH	$C_{15}H_{12}O_4S$	C, H, S
11	Cl	$C_6H_5CH_2$	S	4-COCl	99-100	90	C_6H_6-hex	$C_{15}H_{10}Cl_2O_2S$	*d*
12	CH_3O	$C_6H_5CH_2$	S	3-$COOCH_3$	70-70.5	65	MeOH	$C_{17}H_{16}O_4S$	C, H
13	O	$C_6H_5CH_2$	S	3-CO	160-162	84	C_6H_6	$C_{15}H_{10}O_3S$	C, H
14	HO	C_6H_5S	CH_2	5-COOH	272-273	80	MeOH	$C_{15}H_{12}O_4S$	C, H
15	Cl	C_6H_5S	CH_2	5-COCl	70	90	C_6H_6-hex	$C_{15}H_{10}Cl_2O_2S$	*d*
16	$(CH_3)_2CHO$	$C_4H_3SCH_2$	S	5-$COOCH(CH_3)_2$	57-58	88	MeOH-H_2O	$C_{19}H_{22}O_4S_2$	C, H
17	HO	$C_4H_3SCH_2$	S	5-COOH	280-282	97	MeOH	$C_{13}H_{10}O_4S_2$	C, H
18	Cl	$C_4H_3SCH_2$	S	5-COCl	80-81	90	CH_2Cl_2-hex	$C_{13}H_8Cl_2O_2S_2$	*f*
19	CH_3O	C_6H_5	S	5-$COOCH_3$	57-59	80	hex	$C_{16}H_{14}O_4S$	C, H, S
20	CH_3O	C_6H_5	S	4-$COOCH_3$	65-67	90	eth-hex	$C_{16}H_{14}O_4S$	C, H, S
21	CH_3O	C_6H_5	O	4-$COOCH_3$	170 (2)	72		$C_{16}H_{14}O_5$	*g*

[a] eth = ether; pen = pentane; hex = hexane. [b] Elements shown analyzed to within ±0.3% of the calculated values. [c] MS M^+ 316. [d] MS M^+ 326, 324. [e] MS M^+ 372. [f] MS M^+ 288, 286, 284. [g] MS M^+ 286.

requirements and reached the marketplace as well.

Recently Ueno et al.[7] and McFadden and co-workers[8] reported on the synthesis and antiinflammatory activity of several 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepins bearing acetic or propionic acid entities at carbons 1,[7] 2,[7,8] or 3.[8] In this paper we describe the synthesis and some of the pharmacological properties of the isoelectronic 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids.[9] The structure–activity relationships of the above compounds are discussed and compared with the isomeric 10,11-dihydro-10-oxodibenzo[*b*,*f*]thiepinacetic acids as well as with alkanoic acids in the 10,11-dihydro-10-oxodibenz[*b*,*f*]oxepin, 4,10-dihydro-4-oxothieno[2,3-*c*][1]benzothiepin, 10,11-dihydrodibenzo[*b*,*f*]thiepin, 10,11-dihydrodibenz[*b*,*f*]oxepin, dibenzo[*b*,*f*]thiepin, and dibenz[*b*,*f*]oxepin series. Based on the high degree of antiinflammatory activity and a low incidence of side effects in animals, 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-acetic acid (**52**)

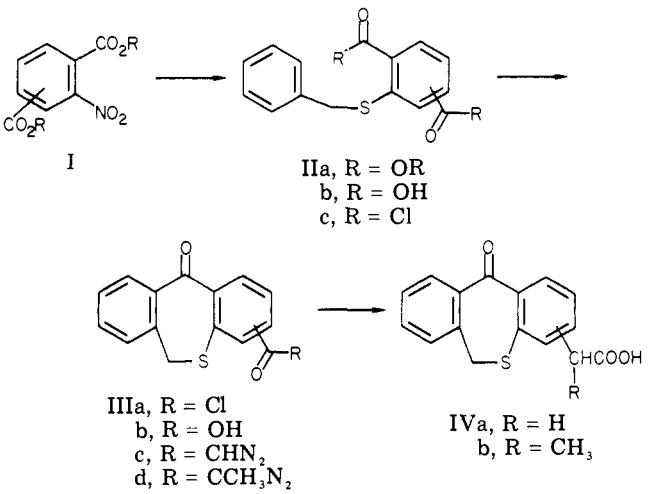


52

was selected for evaluation in man. [Compound **52** has been assigned the generic name "tiopinac".]

Chemistry. The 6,11-dihydro-11-oxodibenzo[*b*,*e*]-thiepinacetic acids were synthesized in the manner shown in Schemes I–III. Thus, the reaction of the appropriate dialkyl nitrobenzenedicarboxylates I with sodium benzyl mercaptide in dimethylformamide solution, at −30 °C to room temperature, gave the corresponding sulfides IIa in 65–91% yields (see Table I). Although the nucleophilic displacement of aromatic nitro groups no longer can be considered as unusual,[10] both the generality (see also below) and the ease with which the substitutions described herein took place, even with hindered substrates (e.g., dimethyl 2-nitroisophthalate), are remarkable. The proclivity of these compounds to undergo displacement of nitrite ion clearly must be a reflection of the combined effect of three strongly electron-attracting groups on the

Scheme I



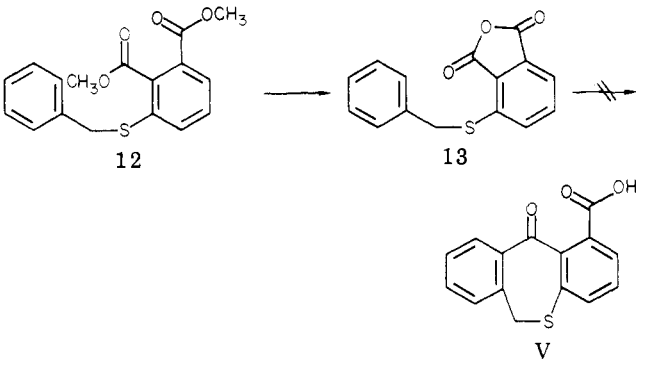
I

IIa, R = OR
b, R = OH
c, R = Cl

IIIa, R = Cl
b, R = OH
c, R = CHN_2
d, R = CCH_3N_2

IVa, R = H
b, R = CH_3

Scheme II



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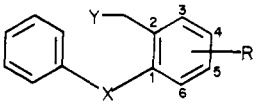
13

V

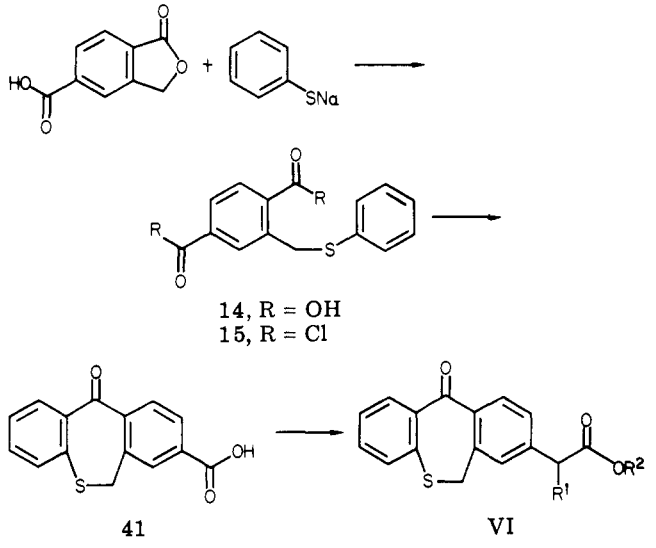
Table II. Precursors of Dibenzo[*b,f*]heteropins



no.	X	Y	R	mp or bp (mm), °C	% yield	recrystn solvent[a]	emp formula	analyses[b]
22	S	HO	5-CH_2OH	83-84	90	eth-hex	$C_{14}H_{14}O_2S$	C, H
23	S	HO	4-CH_2OH	68-69	88	C_6H_6	$C_{14}H_{14}O_2S$	C, H
24	O	HO	4-CH_2OH	73.5-74	90	C_6H_6	$C_{14}H_{14}O_3$	C, H
25	S	Cl	5-CH_2Cl	45-46	90	eth-hex	$C_{14}H_{12}Cl_2S$	C, H, Cl
26	S	Cl	4-CH_2Cl	168 (0.1)	92		$C_{14}H_{12}Cl_2S$	C, H, S
27	O	Cl	4-CH_2Cl	oil	95		$C_{14}H_{12}Cl_2O$	*c*
28	S	COOH	5-CH_2COOH	167-168	54	MeOH-H_2O	$C_{16}H_{14}O_4S$	C, H
29	S	COOH	4-CH_2COOH	176-180	60	MeOH-H_2O	$C_{16}H_{14}O_4S$	C, H
30	O	COOH	4-CH_2COOH	161-162	80	MeOH-H_2O	$C_{16}H_{14}O_5$	C, H

[a] See Table I for key to abbreviations. [b] Elements shown analyzed to within ±0.3% of the calculated values. [c] MS M^+ 270, 268, 266.

Scheme III



14, R = OH
15, R = Cl

41 VI

monocyclic aromatic systems.

With the exception of dimethyl 3-benzylthiophthalate (12), the diesters IIa were saponified and the dicarboxylic acids IIb, thus obtained, were converted into the acid chlorides IIc with thionyl chloride. The cyclization of these substances to the 6,11-dihydro-11-oxodibenzo[*b,e*]thiepincarbonyl chlorides IIIa (see Table III) was effected with the aluminum chloride–nitromethane complex[11] in dichloromethane solution. The carboxylic acid chlorides IIIa were transformed into the acetic and propionic acid derivatives IVa and IVb (see Table IV) by means of the Arndt–Eistert extension reaction.

To essay the synthesis of the 6,11-dihydro-11-oxodibenzo[*b,e*]thiepin-1-acetic acids, 3-benzylthiophthalic anhydride (13) was subjected to a varieity of Friedel–Crafts conditions. In no case was cyclization to the tricyclic carboxylic acid V (Scheme II) observed.

The 6,11-dihydro-11-oxodibenzo[*b,e*]thiepin-8-alkanoic acids VI (Scheme III) were prepared in a manner slightly different from that shown in Scheme I. Phthalide-4-carboxylic acid, upon treatment with potassium thiophenolate in boiling dimethylformamide, gave the dicarboxylic acid 14 in 80% yield. Cyclization to 41 was accomplished by heating the diacid chloride 15 in polyphosphoric acid[12] at 110–115 °C. The thiepin 41 was subsequently transformed into VI using the Arndt–Eistert procedure.

Members of the 4,10-dihydro-4-oxothieno[2,3-*c*][1]-benzothiepin-7-acetic acid series (e.g., **70**, Table IV)[14] were synthesized in a manner analogous to that shown in Scheme I commencing with diisopropyl 3-nitroterephthalate (4) (Table I) and sodium 2-thienylmethanethiolate.

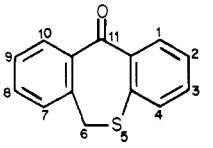
The 10,11-dihydro-11-oxodibenzo[*b,e*]thiepins bearing the alkanoic acid side chain at C-3 were found to be especially potent antiinflammatory agents (see below) and, therefore, the effect of slight structural modifications upon the activity of these substances was investigated. For example, reduction of the acetic acid **52** (Table IV) with sodium borohydride or with amalgamated zinc and hydrochloric acid gave the alcohol **59** or the deoxy compound **61**, respectively. In addition, the sulfoxide **62** and the sulfone **63** were obtained by oxidation of **52** with 1 or 2 equiv of *m*-chloroperbenzoic acid. Lastly, the butyric acid derivative **58** was prepared by alkylation of the sodium salt of the ester **51** with diethyl sulfate.

The resolution of *dl*-2-(6,11-dihydro-11-oxodibenzo-[*b,e*]thiepin-3-yl)propionic acid (**53**) was effected by chromatographic separation of the diastereomeric *l*-phenethylamides. Cleavage of the less polar *l*-phenethylamide with a mixture of concentrated hydrochloric acid and acetic acid gave the *d*-propionic acid **56**. Nitrosation of the more polar amide and subsequent rearrangement of the *N*-nitroso compound in hot benzene solution gave the phenethyl ester of the *l* acid from which the free *l* acid **55** was obtained upon treatment with trifluoroacetic acid.

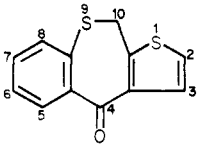
The dibenzothiepin- and dibenzoxepinacetic acids of the [*b,f*] series were prepared using the route shown in Scheme IV. Displacement of nitrite ion from the appropriate nitro diesters with sodium phenolate or thiophenolate gave the esters VII (Table I) which were converted into the diols VIIIa (Table II) by reduction with lithium aluminum hydride. The dichlorides VIIIb, derived from VIIIa and thionyl chloride, were treated with potassium cyanide in dimethyl sulfoxide to give the dinitriles VIIIc which were subsequently hydrolyzed to the diacetic acids IXa by means of a hot mixture of acetic and phosphoric (85%) acids. The diacid chlorides IXb, prepared from IXa by treatment with oxalyl chloride, were cyclized in a manner analogous to that described for IIc. In some cases it was more convenient to isolate the methyl esters Xc rather than the carboxylic acids Xb (Table IV).

Reduction of the ketones Xc with sodium borohydride gave the alcohols XI which were readily dehydrated by treatment with a trace of perchloric acid in boiling tetrahydrofuran. Hydrolysis of XIIa gave the acids XIIb (Scheme IV). The 10,11-dihydro compounds **76** and **92** were prepared by the Clemmenson reduction of **73** and **89**

Table III. Tricyclic Carboxylic Acids and Related Compounds



A

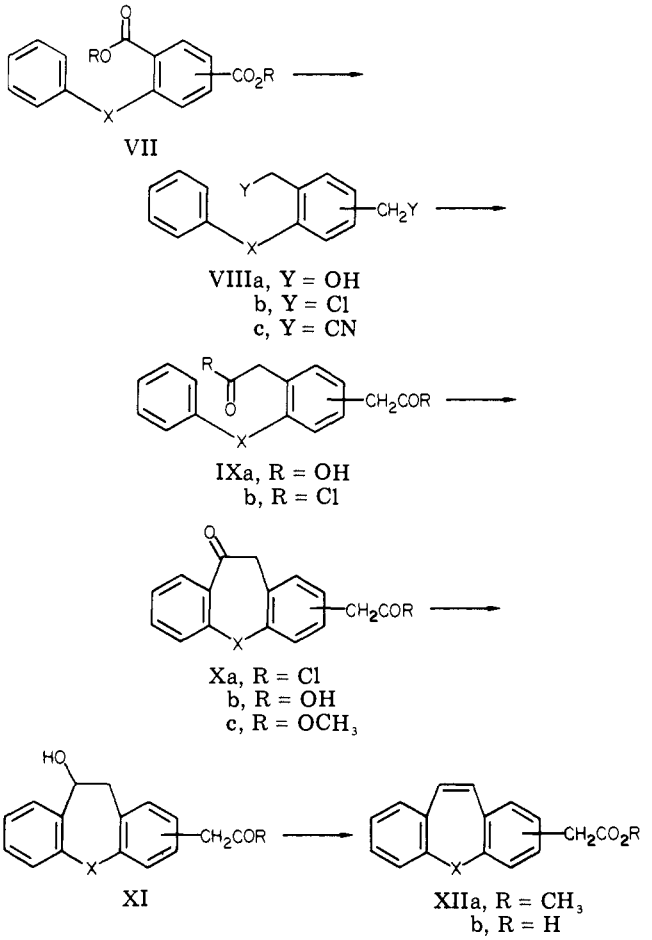


B

no.	system	substituent	mp, °C	% yield	recrystn solvent[a]	emp formula	analyses[b]
31	A	2-COCl	164	81	C_6H_6-hex	$C_{15}H_9ClO_2S$	c
32	A	2-COOH	250-252	88	EtOH	$C_{15}H_{10}O_3S$	C, H, S
33	A	2-$COCHN_2$	149-150	76	C_6H_6	$C_{16}H_{10}N_2O_2S$	H; C[d]
34	A	3-COCl	119-120	60	CH_2Cl_2-eth	$C_{15}H_9ClO_2S$	c
35	A	3-COOH	225-226	95	MeOH	$C_{15}H_{10}O_3S$	C, H
36	A	3-$COCHN_2$	153	72	C_6H_6	$C_{16}H_{10}N_2O_2S$	H, N; C[e]
37	A	3-$COCCH_3N_2$	127	73	eth	$C_{17}H_{12}N_2O_2S$	f
38	A	4-COCl	149-150	90	C_6H_6	$C_{15}H_9ClO_2S$	C, H, Cl
39	A	4-$COCHN_2$	112-113	90	CH_2Cl_2-eth	$C_{16}H_{10}N_2O_2S$	C, H, N
40	A	8-COCl	70	80	eth-hex	$C_{15}H_9ClO_2S$	c
41	A	8-COOH	275-276	80	MeOH-H_2O	$C_{15}H_{10}O_3S$	C, H
42	A	8-$COCHN_2$	142-143	70	C_6H_6-hex	$C_{16}H_{10}N_2O_2S$	C, H
43	A	8-$COCCH_3N_2$	125-126	61	eth-hex	$C_{17}H_{12}N_2O_2S$	f
44	B	7-COCl	g	60		$C_{13}H_7ClO_2S_2$	h
45	B	7-COOH	222-223	87	MeOH	$C_{13}H_8O_3S_2$	H; C[i]
46	B	7-$COOCH_3$	122-123	67	MeOH	$C_{14}H_{10}O_3S_2$	C, H
47	B	7-$COCHN_2$	149	50	eth	$C_{14}H_8N_2O_2S_2$	C, H, N
48	B	7-$COCCH_3N_2$	108	86	eth	$C_{15}H_{10}N_2O_2S_2$	C, H, N

[a] See Table I for key to abbreviations. [b] Elements shown analyzed correctly to within ±0.4% of calculated values unless stated otherwise. [c] MS M^+ 290, 288. [d] C: calcd, 65.33; found, 65.78. [e] C: calcd, 65.33; found, 65.79. [f] MS M^+ 308. [g] Amorphous solid. [h] MS M^+ 294, 296. [i] C: calcd, 56.23; found, 59.03.

Scheme IV



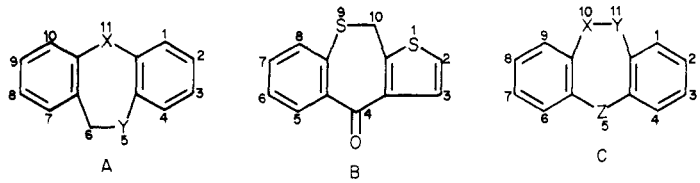
while **87** was obtained from **86** by catalytic reduction.

The sulfoxide **79** and the sulfone **82** were prepared from the acid **76** which was esterified (diazomethane) and then oxidized with the appropriate quantity of *m*-chloroperbenzoic acid. Finally, the ester groups were removed by hydrolysis to the acids. The unsaturated sulfone **80** was prepared via the alcohol XI using procedures analogous to those described above.

Structure–Activity Relationships. The antiinflammatory and analgetic activity of the compounds listed in Table V was measured using the carrageenan paw edema and the phenylquinone writhing assay, respectively (see the Experimental Section).

The compounds which were the most active as antiinflammatory agents were those in which the side chain was at a non-peri meta position with respect to the two atom unit spanning the lateral aryl moieties (e.g., **52** and **76**). Furthermore, antiinflammatory agents of exceptional potency resulted when the single atom bridge of the central seven-membered ring was a carbonyl group (e.g., **52** and **70**) or a divalent sulfur moiety (**75** and **76**). Alteration of the nature of this portion of the molecule resulted in a substantial diminution in activity as exemplified by the reduced analogues **59** and **61** of **52** and the sulfoxide **79** and sulfone **80** analogues of **76**. It is also evident that the character of the two-atom bridge has a considerable effect on the activity, especially in the diaryl[*b*,*e*]thiepinone series. For example, neither the sulfoxide **62** nor the sulfone **63** possessed appreciable antiinflammatory activity. The most surprising observation, however, was that translocation of the sulfur atom and the methylene group, of the central ring, from that found in **52** to that present in **67** caused a 40-fold decrease in activity. This suggests that the sulfide group of **52** serves more than just a passive space occupying role at the receptor level and that the sulfur atom–carboxylic acid moiety distance is related to high activity. For the dibenzo[*b*,*e*]thiepinones, this distance most closely approaches the apparent optimum when the acetic acid side chain is at C-3. A similar situation prevails for the isoelectronic dibenz[*b*,*e*]oxepinones where it has been reported[7] that the 3-acetic acids are approximately twice as potent as the 2-acetic acids. These latter

Table IV. Tricyclic Acetic Acids and Esters



A B C

no.	system	substituent	X	Y	Z	mp, °C	% yield	recrystn solvent[a]	emp formula	analyses[b]
49	A	2-CH_2COOCH_3	CO	S		100	61	eth	$C_{17}H_{14}O_3S$	C, H, S
50	A	2-CH_2COOH	CO	S		160-161[c]	90	C_6H_5Cl	$C_{16}H_{12}O_3S$	C, H, S
51	A	3-CH_2COOCH_3	CO	S		100-101	90	eth	$C_{17}H_{14}O_3S$	C, H
52	A	3-CH_2COOH	CO	S		155-156	83	C_6H_6	$C_{16}H_{12}O_3S$	C, H
53	A	(±)-3-$CHCH_3COOH$	CO	S		114.5-115.5	65	eth-hex	$C_{17}H_{14}O_3S$	C, H
54[d]	A	(±)-3-$CHCH_3COOH$	CO	S		164-165	90	C_6H_6	$C_{29}H_{37}NO_3S$	C, H, N
55[d]	A	(−)-3-$CHCH_3COOH$	CO	S		161-163		C_6H_6	$C_{29}H_{37}NO_3S$	H, N; C[e]
56[d]	A	(+)-3-$CHCH_3COOH$	CO	S		167-168		C_6H_6	$C_{29}H_{37}NO_3S$	C, H, N
57	A	3-$CHC_2H_5CO_2CH_3$	CO	S		71-73	73	eth	$C_{19}H_{18}O_3S$	C, H
58[d]	A	3-CHC_2H_5COOH	CO	S		152-153	90	C_6H_6	$C_{30}H_{39}NO_3S$	C, H
59	A	3-CH_2COOH	CHOH	S		279-280	90	acet-C_6H_6	$C_{16}H_{14}O_3S$	C, H
60	A	3-CH_2COOCH_3	CH_2	S		89-90	52	MeOH	$C_{17}H_{16}O_2S$	C, H
61	A	3-CH_2COOH	CH_2	S		218-219	87	MeOH	$C_{16}H_{14}O_2S$	C, H
62	A	3-CH_2COOH	CO	SO		185	93	EtOH	$C_{16}H_{14}O_4S$	C, H
63	A	3-CH_2COOH	CO	SO_2		215-216	88	HOAc	$C_{16}H_{14}O_5S$	C, H
64	A	4-CH_2COOCH_3	CO	S		87-88	77	MeOH	$C_{17}H_{14}O_3S$	C, H
65	A	4-CH_2COOH	CO	S		172	67	MeOH	$C_{16}H_{12}O_3S$	C, H
66	A	8-CH_2COOCH_3	CO	S		113-114	90	MeOH	$C_{17}H_{14}O_3S$	C, H
67	A	8-CH_2COOH	CO	S		166-167	95	H_2O	$C_{16}H_{12}O_3S$	C, H
68[d]	A	8-$CHCH_3COOH$	CO	S		206-207	36	MeOH	$C_{29}H_{37}NO_3S$	C, H, N
69	B	7-CH_2COOCH_3				122-123	50	MeOH	$C_{15}H_{12}O_3S_2$	C, H
70	B	7-CH_2COOH				179-180	70	MeOH	$C_{14}H_{10}O_3S_2$	C, H
71	B	7-$CHCH_3COOH$				112-113	40	eth-hex	$C_{15}H_{12}O_3S_2$	C, H
72	C	2-CH_2COOCH_3	CO	CH_2	S	82	45	C_6H_6-hex	$C_{17}H_{14}O_3S$	C, H
73	C	2-CH_2COOH	CO	CH_2	S	177-179	53	C_6H_5Cl	$C_{16}H_{12}O_3S$	C, H
74	C	2-CH_2COOCH_3	CH	CH	S	100-101	67	C_6H_6-hex	$C_{17}H_{14}O_2S$	C, H
75	C	2-CH_2COOH	CH	CH	S	144	91	eth	$C_{16}H_{12}O_2S$	C, H
76	C	2-CH_2COOH	CH_2	CH_2	S	104	80	eth	$C_{16}H_{14}O_2S$	C, H
77[d]	C	2-$CHCH_3COOH$	CH_2	CH_2	S	142-143	33	C_6H_6	$C_{29}H_{43}NO_2S$	C, H, N
78	C	2-CH_2COOCH_3	CH_2	CH_2	SO	115	89	C_6H_6-hex	$C_{17}H_{16}O_3S$	C, H
79	C	2-CH_2COOH	CH_2	CH_2	SO	169-170	78	CH_2Cl_2-hex	$C_{16}H_{14}O_3S$	C, H
80	C	2-CH_2COOH	CH	CH	SO_2	162-163	86.5	EtOAc-hex	$C_{16}H_{12}O_4S$	C, H
81	C	2-CH_2COOCH_3	CH_2	CH_2	SO_2	103-105	73	$CHCl_3$-hex	$C_{17}H_{16}O_4S$	C, H
82	C	2-CH_2COOH	CH_2	CH_2	SO_2	161-162	89	C_6H_6	$C_{16}H_{14}O_4S$	C, H
83	C	2-CH_2COOCH_3	CO	CH_2	O	oil	45		$C_{17}H_{14}O_4$	*f*
84	C	2-CH_2COOH	CO	CH_2	O	136-137	85	EtOAc-hex	$C_{16}H_{12}O_4$	H; C[g]
85	C	2-CH_2COOCH_3	CH	CH	O	76-77	70	hex	$C_{17}H_{14}O_3$	C, H
86	C	2-CH_2COOH	CH	CH	O	187-188	98	DME-hex	$C_{16}H_{12}O_3$	C, H
87	C	2-CH_2COOH	CH_2	CH_2	O	127-128	85	C_6H_6-hex	$C_{16}H_{14}O_3$	C, H
88	C	3-CH_2COOCH_3	CO	CH_2	S	107-108	60	C_6H_6	$C_{17}H_{14}O_3S$	C, H
89	C	3-CH_2COOH	CO	CH_2	S	192-193	56	CH_2Cl_2-eth	$C_{16}H_{12}O_3S$	C, H
90	C	3-CH_2COOCH_3	CH	CH	S	oil	25		$C_{17}H_{14}O_2S$	C, H
91	C	3-CH_2COOH	CH	CH	S	138-140	95	MeOH	$C_{16}H_{12}O_2S$	C, H
92	C	3-CH_2COOH	CH_2	CH_2	S	133-134	50	C_6H_6	$C_{16}H_{14}O_2S$	C, H

[a] acet = acetone; for key to other abbreviations see Table I. [b] Elements indicated analyzed to within ±0.4% of the calculated values unless stated otherwise. [c] Lit.[9a] mp 163-165 °C. [d] The data in this row refer to the dicyclohexylammonium salt. [e] C: calcd, 72.62; found, 73.05. [f] MS M⁺ 282. [g] C: calcd, 71.63; found, 71.28.

compounds are, however, still highly active, and this presumably is a reflection of the shorter nature of the C–O bond in the two-atom bridge.

The above activity differences may also be related to the conformation of the central seven-membered ring. Indeed, the presence or absence of an heteroatom in the two-atom bridge has a marked effect on the NMR chemical shifts of H-1 (H_A) and H-10 (H_B) for these compounds. Thus in the dibenzo[*b,e*]thiepinones H-1 was found at lower and H-10 at higher field than that (δ 7.85) calculated[13] for the analogous protons in a hypothetical, similarly substituted benzophenone (see Table VI). The deshielding of H-1 and the shielding of H-10 are most consistent with a twist boat conformation for the seven-membered ring. When the sulfur atom was replaced by an oxygen atom or an sp^2 carbon,[15] the chemical shift difference between the hydrogens peri to the carbonyl group progressively diminished, indicative of an increasing conformational symmetry.

The analgetic activities of the compounds listed in Table V, in general, were approximately parallel to their antiinflammatory activities. There were, however, several cases (e.g., **53** and **71**) for which the analgetic potency would not have been correctly predicted on the basis of this parallelism.

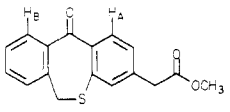
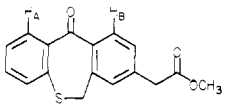
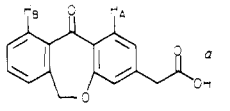
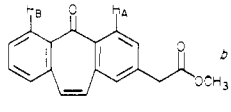
The antiinflammatory activity of compound **52** was conspicuously superior to that found for the other diarylheteropinacetic acids. The corresponding propionic acid **53** was almost three times as active as **52**, with most of the activity residing in the dextrorotatory enantiomer **56**. In contrast, the α-ethyl compound **58** was only one-half as active as the acetic acid. The heterocyclic alkanoic acids **70** and **71** were much less active (ca. one-tenth) than the

Table V. Antiinflammatory and Analgesic Activities of Diarylheteropinalkanoic Acids

no	d, l, or dl	rat paw assay, phenylbutazone = 1	mouse writhing assay, aspirin = 1
50		0.3 (96)[a]	1.5 (40)[b]
52		40 (384)	14 (70)
53	dl	115 (192)	20 (74)
55	l	≤4 (72)	NT[c]
56	d	206 (72)	NT
58[d]	dl	20 (36)	4 (24)
59	dl	<1 (18)	<0.3 (8)
61		2 (24)	1.0 (32)
62	dl	0.5 (48)	≤0.5 (10)
63		<0.2 (12)	0.2 (8)
65		<0.4 (17)	NT
67		1.0 (53)	1.0 (24)
68	dl	2.0 (18)	2.5 (24)
70		4 (36)	4 (32)
71	dl	13 (36)	20 (56)
73		0.4 (18)	1 (40)
75		2.0 (18)	<1 (10)
76		7.0 (30)	3 (40)
77	dl[d]	3 (18)	5 (30)
79	dl	≤0.2 (18)	0.8 (40)
80		0.4 (18)	0.4 (40)
82		0.4 (18)	1 (50)
84		<0.6 (12)	<0.2 (10)
86		<0.4 (17)	0.3 (24)
87		0.4 (18)	1.0 (32)
89		0.4 (18)	1 (40)
91		<0.2 (12)	<1 (10)
92		0.2 (12)	2 (50)

[a] Number of rats. [b] Number of mice. [c] NT = not tested. [d] Tested as dicyclohexylammonium salt.

Table VI. Chemical Shift of Hydrogens Peri to Ketone Carbonyl Group in Tricyclic Acetic Acids

compd	δ, ppm H_A	δ, ppm H_B
	8.18	7.55
	8.1	7.45
	8.15	7.95
	8.2	8.2

[a] For synthesis see ref 7. [b] See ref 15 for synthesis.

homocyclic counterparts **52** and **53**. These results are opposite to those observed[16] in the diaryl[*b*,*e*]oxepinone series, although a comparison may not be valid because of the different mode of fusion of the thiophene systems to the central ring (thieno[3,2-*c*][1]benzoxepin vs. thieno[2,3-*c*][1]benzothiepin in **70** and **71**).

Compounds **52** and **53** were also examined for antiinflammatory activity in the cotton pellet granuloma and adjuvant arthritis assays, both of which are of longer duration (Table VII). The acetic acid **52** was comparable in potency to indomethacin, while the propionic acid **53** was considerably more active than this standard in both assays. The single dibenzo[*b*,*f*]thiepin **76** tested had a much lower order of activity than either of the dibenzo[*b*,*e*]thiepinones. In addition, compounds **52** and **53** were evaluated for their ability to induce gastric erosion in starved rats.[17] The propionic acid was appreciably more irritating (Table VII) than its lower homologue **52**. In another study, dogs which were given a single oral dose of 10 or 30 mg/kg of **52** failed to exhibit any signs of gastrointestinal intolerance, whereas a 5 mg/kg oral dose of **53** was sufficient to evoke emesis. The low degree of gastric irritation exhibited by compound **52** was an important factor in the choice of this substance for evaluation as an antiinflammatory agent in man. It is worthy of note that **52** is reported[18] to be much less efficient than indomethacin in the inhibition of prostaglandin synthase and this may well be related to the low ulcerogenic potential thereof in the animal model.

Table VII. Long-Term Antiinflammatory Assays and Gastric Irritation Liability

compd	antiinflammatory assays: cotton pellet, indomethacin = 1	antiinflammatory assays: adjuvant arthritic, naproxen = 1	gastric irritation, ED_{50},[a] mg/kg
52	0.8 (332)[b]	10-15[c] (413)[b]	24 (14-41)[d]
53	2 (95)	70 (135)	2 (1-5)
76	0.07 (72)	0.5 (75)	NT
naproxen			13 (9-17)
indomethacin			6 (3-8)

[a] Dose required to cause irritation in 50% of the test animals (rats). [b] Number of rats. [c] Naproxen has 0.14 the potency of indomethacin in this assay. [d] 95% confidence limits.

Finally, **52** elicited antiinflammatory activity (carrageenan paw assay) in adrenalectomized rats, indicating that the antiinflammatory action was not mediated by the stimulation and or release of adrenal hormones.

Experimental Section

The animal assays referred to above were conducted as described below. "Government diluting fluid" was used as a vehicle for tests 1–4. Assay 5 was carried out with solutions of the target compounds prepared by dissolving the carboxylic acid in aqueous sodium hydroxide (1.5 equiv) and diluting with water.

(1) **Inhibition of Carrageenan-Induced Edema.** This assay was carried out essentially as described in a recent[15] publication from these laboratories (see also ref 26). Thus, 80–90-g female rats were given the test agent 1 h prior to the injection of carrageenan into one of the hind paws. The rats were sacrificed 4 h after administration of the drug, at which time both of the hind paws were excised and weighed separately. The potencies of the test agents relative to phenylbutazone were determined from dose–response plots of the percent increase in weight of the inflamed paw over the noninflamed paw. Usually, at least three doses, using six rats per dose, were employed in constructing the plots.

(2) **Inhibition of Cotton Pellet Granuloma.** This assay was effected[15] according to a modification of a procedure initially described by Meier et al.[27]

(3) **Inhibition of Adjuvant-Induced Arthritis.** This assay was carried out[15] according to the method of Pearson.[28]

(4) **Inhibition of Phenylquinone-Induced Writhing.** The assay was performed according to the procedure described in a recent[15] publication from these laboratories (see also ref 29). Thus, 18–20-g male mice were given the test substance orally 20 min prior to an intraperitoneal injection of phenylquinone. The mice were observed for the next 10 min for writhing and the potencies, relative to aspirin, were determined as in (1) using eight to ten mice per dose.

(5) **Acute Ulcerogenic or Gastric Eroding Action.** The assay was determined in the manner described by Roszkowski et al.[5]

All melting points were determined in a Mel-Temp apparatus and are uncorrected. The IR spectra were measured on a Perkin-Elmer Model 267 grating infrared spectrophotometer in chloroform solutions or as solids in potassium bromide disks. The UV spectra were recorded in methanol solution with a Perkin-Elmer UV-visible spectrophotometer. The NMR spectra were measured with a Varian T-60 NMR spectrometer or a Varian HA-100 NMR spectrometer in $CDCl_3$ or Me_2SO-d_6 solutions. The chemical shifts are expressed in parts per million (δ) from internal Me_4Si. The mass spectra were obtained with an Atlas CH-4 mass spectrometer. The spectral data for all new compounds were consistent with the assigned structures.

The following intermediates have been described in the literature: dimethyl 3-nitrophthalate,[19] dimethyl 2-nitroisophthalate,[20] dimethyl 4-nitroisophthalate,[21] dimethyl 2-nitroterephthalate,[22] 2-nitroterephthaloyl chloride,[23] and phthalide-4-carboxylic acid.[24]

Diisopropyl 2-Nitroterephthalate (4). A solution of 2-nitroterephthaloyl chloride (0.5 mol) in 2-propanol (250 mL) was boiled under reflux until the starting material was consumed (1–3 h). The solvent was removed in vacuo, the residue was suspended in water, and the product was extracted into ethyl acetate. The extract was washed with sodium carbonate solution (10%), dried ($MgSO_4$), and evaporated in vacuo to yield the oily ester (Table I).

Nucleophilic Displacement of Dialkyl Nitrobenzenedicarboxylates. Except for dimethyl 3-nitrophthalate (see below) the conditions for the displacement reactions were the same irrespective of the nature of the nucleophilic species or the nitro diester. The following procedure is typical.

A solution of the appropriate nitro diester (0.448 mol) in dry dimethylformamide (200 mL) was added to a stirred solution of the desired nucleophile [prepared from phenol, thiophenol, thenyl mercaptan, or benzyl mercaptan (0.524 mol) and sodium hydride (0.5 mol) in dimethylformamide (250 mL)] in the same solvent while maintaining the temperature at −30 °C by means of a dry ice–acetone bath. After 1 h at −30 °C, the solution was allowed to come to room temperature and after a further 2 h it was poured into water (2 L). The products were isolated by filtration or by extraction into a suitable solvent. Purification of the products was achieved by crystallization, distillation (e.g., **21**), or by column chromatography on silica gel [e.g., **1**, using hexane–ethyl acetate (6:1) as the eluting solvent]. The yields, physical constants, etc., for these compounds are found in Table I.

Dimethyl 3-benzylthiophthalate (**12**) was prepared in a manner similar to that described above except that the addition was effected at 0 °C and after 1 h at this temperature, the reaction was left at room temperature for 16 h. At the end of this time a small amount of sodium dithionite [0.5 g in water (5 mL) for a 0.0327 mol scale reaction] was added to reduce any unreacted nitro compound. The solution was poured into water, the product was extracted into benzene, and the extract was washed with water and dried over magnesium sulfate. The product was purified by column chromatography on silica gel in the manner described above for **1**.

Saponification of the Substituted Phthalic Esters. The procedure outlined below for the synthesis of 4-benzylthioisophthalic acid (**10**) was typical.

A solution of diisopropyl 4-benzylthioisophthalate (**9**) (55 g, 0.148 mol) in methanol (500 mL) and water (50 mL) containing potassium hydroxide (25 g) was boiled under reflux for 2 h. The cooled solution was concentrated in vacuo to about 100 mL and water (500 mL) was added. The solution was filtered through Celite; the filtrate was heated to 70–80 °C, acidified with 4 N hydrochloric acid, and set aside to cool. The precipitate was collected by filtration and dried at 100 °C. Crystallization of the crude (38.3 g, 90%) carboxylic acid from ethanol gave material with mp 298–300 °C dec. The physical constants of this and related compounds are found in Table I.

3-Benzylthiophthalic Anhydride (**13**). A solution of the dimethyl ester **12** (5.0 g, 0.0158 mol) in formic acid (20 mL, 99%) containing *p*-toluenesulfonic acid (0.2 g) was boiled under reflux for 12 h. The cooled solution was evaporated to dryness in vacuo and the residue was heated at reflux temperature with a solution of acetic anhydride (10 mL) in toluene (15 mL). The solution was cooled; the crystalline solid was collected by filtration, washed with benzene, and dried. The anhydride (3.5 g, 84%) had mp 160–162 °C (see Table I).

2-Phenylthiomethylterephthalic Acid (**14**). A mixture of phthalide-4-carboxylic acid (3.6 g, 0.02 mol), thiophenol (2.2 g, 0.02 mol), and potassium carbonate (2.76 g, 0.02 mol) in dimethylformamide (100 mL) was heated at reflux temperature for 5 h. The cooled solution was poured into water (500 mL) and the resultant was washed with ethyl acetate (2 × 50 mL). The aqueous phase was acidified with dilute hydrochloric acid and the solid product was extracted into ethyl acetate (2 × 100 mL). The extract was dried ($MgSO_4$) and evaporated in vacuo. The residue was crystallized from methanol to give the dicarboxylic acid (4.65 g, 80%), mp 272–273 °C (see Table I).

Synthesis of the Substituted Benzenedicarboxylic Acid Chlorides (See Table I). The synthesis of 4-benzylthioisophthaloyl chloride (**11**) is representative of the general procedure. A suspension of 4-benzylthioisophthalic acid (7.5 g, 0.026 mol) in dry dioxane (10 mL) containing thionyl chloride (10 mL, 0.08 mol) was boiled under reflux for 3 h. The cooled mixture was evaporated to dryness and the residue was slurried with ether–hexane (1:2, 20 mL). The solid was collected by filtration and after drying it had mp 99–100 °C (7.6 g, 90%).

Cyclization of the Substituted Benzenedicarboxylic Acid Chlorides. (a) Aluminum Chloride–Nitromethane Complex. The synthesis of 6,11-dihydro-11-oxodibenzo[*b*,c]thiepin-2-carbonyl chloride (**31**) is typical. A solution of 4-benzylthioisophthaloyl chloride (5.5 g, 0.017 mol) in dichloromethane (30 mL) was added to a solution of aluminum chloride (4.0 g, 0.03 mol) in dichloromethane (10 mL) containing nitromethane (4 mL, 0.072 mol). After 3 h at room temperature, the deep red solution was cooled in ice and vigorously stirred during the addition of saturated aqueous sodium chloride solution (4.5 mL). The organic phase was filtered through a pad of magnesium sulfate and the filtrate was evaporated to dryness. The crystalline acid chloride **31** was slurried with a little ether, collected by filtration, and dried. The product (4.0 g, 81%) had mp 164 °C (see Table III).

In some cases, to obtain the pure acid chloride, the crude product was converted into the methyl ester (see above) which was purified by column chromatography on silica gel or by crystallization. Saponification of the pure ester gave the carboxylic acid which was transformed into the pure acyl halide in the manner described above for **11**.

(b) 6,11-Dihydro-11-oxodibenzo[*b*,*e*]thiepin-8-carboxylic Acid (**41**). The diacid chloride **15** (2.0 g) was stirred with polyphosphoric acid (20 mL) at 110–115 °C until hydrogen chloride evolution had ceased (6 h). The cooled reaction mixture was poured into water (200 mL) and the product was extracted into ethyl acetate (2 × 50 mL). The extract was washed, dried ($MgSO_4$), and evaporated to give a residue which was crystallized from methanol–water. The dicarboxylic acid **41** (1.33 g, 80%) had mp 275–276 °C (see Table III). The acid chloride **40** was obtained from **41** in the manner described above.

Synthesis of the Diazo Ketones. (a) Diazoacetyl Compounds. The preparation of 2-diazoacetyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-one (**33**) was standard. A solution of 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-2-carbonyl chloride (**31**) (4.0 g, 0.015 mol) in dichloromethane (10 mL) was added to a solution of diazomethane (0.095 mol) in ether (200 mL) at 0 °C. The solution was allowed to reach room temperature and excess diazomethane was removed by passing a stream of nitrogen gas through the solution. The precipitated diazo ketone was collected by filtration, washed with a little ether, and dried. The product (3.0 g, 76%) had mp 149–150 °C after crystallization from benzene (see Table III).

(b) Diazopropionyl Compounds. The synthesis of 3-(2-diazo)propionyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-one (**37**) is typical of the general procedure. A solution of the acid chloride **34** (4.5 g, 0.0156 mol) in dichloromethane (25 mL) was added, over a 30-min period, to a solution of diazoethane[25] [prepared from *N*-ethyl-*N*-nitrosourea (15 g, 0.128 mol)] in ether (300 mL) at −20 °C (dry ice bath). After a further 30 min at −20 °C, the excess diazoethane was removed with a stream of nitrogen and the product **37** was collected by filtration, washed with cold ether, and dried. The product had mp 127 °C dec (3.5 g, 73%).

Wolff Rearrangement of Diazoacetyl Compounds. Synthesis of Tricyclic Acetic Acid Methyl Esters (See Table

IV). This reaction was effected using silver benzoate as the catalyst with anhydrous methanol as the reaction medium. The synthesis of methyl 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-2-acetate (**49**) was typical. Silver benzoate (0.60 g, 0.0026 mol) was added in portions (0.10 g) to a stirred, boiling solution of the diazo ketone **33** (3.0 g, 0.01 mol) in methanol (100 mL) over a 30-min period. The mixture was maintained at reflux temperature for 12 h at the end of which time it was cooled and filtered. The filtrate was evaporated in vacuo and the residual oil was subjected to column chromatography on silica gel using hexane–ethyl acetate (8:1) as the eluent. The product (1.85 g, 65%) had mp 100 °C after crystallization from ether.

Alkaline Hydrolysis of the Tricyclic Acetic Acid Methyl Esters. The preparation of 6,11-dihydro-11-oxodibenzo[*b*,*e*]-thiepin-2-acetic acid (**50**) is representative of the general procedure. A solution of the ester **49** (1.6 g, 0.0537 mol) in methanol (50 mL) and 10% aqueous potassium hydroxide (5 mL) was boiled under reflux for 1 h. The cooled solution was diluted with water (200 mL), acidified with dilute hydrochloric acid, and extracted with ethyl acetate (2 × 50 mL). The extract was washed with water, dried, and evaporated to give the acid (1.4 g, 90%), mp 160–161 °C, after crystallization from chlorobenzene.

Wolff Rearrangement of the Diazopropionyl Compounds and Synthesis of the Tricyclic Propionic Acids (See Table IV). The synthesis of *dl*-2-(6,11-dihydro-11-oxodibenzo[*b*,*e*]-thiepin-3-yl)propionic acid (**53**) is typical. The diazopropionyl compound **37** (13.5 g, 0.0438 mol) was added in portions (0.5 g) to a hot (170–180 °C) solution of benzyl alcohol (50 mL) and collidine (50 mL) over a 30-min period. The solution was cooled and evaporated in high vacuum to give a residue which was purified by column chromatography on silica gel (500 g) using hexane–ethyl acetate (7:1) as the eluent. The oily benzyl ester obtained upon evaporation of the solvent was heated at reflux temperature for 1 h in a solution of methanol (200 mL) and water (20 mL) containing potassium hydroxide (5 g). The cooled solution was evaporated in vacuo, the residue was dissolved in water (100 mL), and, after washing with chloroform (2 × 50 mL), the basic solution was made acidic with hydrochloric acid. The product was extracted into chloroform (3 × 50 mL); the extract was washed with water, dried, and evaporated in vacuo. The residue was crystallized from ether–hexane to give the carboxylic acid (8.5 g, 65%), mp 114.5–115.5 °C, which was converted into a highly crystalline dicyclohexylammonium salt, mp 164–165 °C (benzene).

11-Hydroxy-6,11-dihydrodibenzo[*b*,*e*]thiepin-3-acetic Acid (59). Sodium borohydride (0.05 g, 1.32 mmol) was added with ice cooling to a solution of the keto acid **52** (0.10 g, 0.35 mmol) in methanol (10 mL). After 2 h the reaction mixture was made acidic with acetic acid and diluted with water (100 mL). The product was extracted with ethyl acetate (2 × 30 mL); the extract was washed, dried, and evaporated. The residue was crystallized from acetone–benzene to give the hydroxy acid (0.090 g, 90%), mp 279–280 °C (see Table IV).

6,11-Dihydrodibenzo[*b*,*e*]thiepin-3-acetic Acid (61). A solution of methyl 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-acetate (**51**) (0.5 g, 1.76 mmol) in toluene (75 mL) was stirred with amalgamated zinc (15 g), acetic acid (5 mL), and concentrated hydrochloric acid (50 mL) for 1 h at room temperature. The organic phase was separated, washed with water, dried, and evaporated in vacuo. The residual oil was chromatographed on Florisil (10 g) using dichloromethane–hexane (1:20) as the eluent. Methyl 6,11-dihydrodibenzo[*b*,*e*]thiepin-3-acetate (**60**) obtained in this way (0.25 g, 50%) had mp 89–90 °C after crystallization from methanol.

A solution of the above ester (0.4 g, 1.34 mmol) in methanol (20 mL) and aqueous sodium hydroxide (1 mL, 10%) was boiled under reflux for 1 h. The cooled solution was diluted with water (100 mL) and made acidic with hydrochloric acid. The precipitated solid was collected by filtration, washed with water, and recrystallized from methanol to give the acid (0.33 g, 87%), mp 218–219 °C.

6,11-Dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-acetic Acid *S*-Oxide (62) and 6,11-Dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-acetic Acid *S*,*S*-Dioxide (63). A solution of **52** (0.15 g) in dimethoxyethane (1 mL) was mixed with a solution of *m*-chloroperbenzoic acid (0.11 g, 85%) in dichloromethane and the resultant was left at room temperature overnight. The sulfoxide **62** (0.148 g, 93%) was collected by filtration, washed with ether, and dried. After crystallization from ethanol it had mp 185 °C.

Oxidation of the above sulfoxide in acetic acid solution gave the sulfone **63** (88%) which had mp 215–216 °C after crystallization from acetic acid.

***dl*-2-(6,11-Dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)butyric Acid (58).** A suspension of sodium hydride (0.08 g, 3.33 mmol) in dry dimethylformamide (20 mL) containing methyl 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-acetate (1.0 g, 3.35 mmol) was stirred until hydrogen evolution ceased. Diethyl sulfate (0.462 g, 3.0 mmol) was added and the solution was stirred at room temperature for 1 h. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (2 × 25 mL). The extract was washed with water, dried, and evaporated in vacuo. The residual oil was subjected to column chromatography on silica gel (50 g) using hexane–ethyl acetate (9:1) as the eluent. Evaporation of the solvent gave the ester **57** (0.80 g, 73%) which had mp 71–73 °C after crystallization from ether.

The above ester was hydrolyzed in the usual manner with aqueous methanolic sodium hydroxide. The crude carboxylic acid did not crystallize spontaneously and, therefore, an ethereal solution thereof was treated with 1 equiv of dicyclohexylamine. The crystalline dicyclohexylammonium salt (90% yield) was collected by filtration, washed with ether, and dried. It had mp 152–153 °C (see Table IV).

Resolution of *dl*-2-(6,11-Dihydro-11-oxodibenzo[*b*,*e*]-thiepin-3-yl)propionic Acid. Thionyl chloride (5 mL) and dimethylformamide (3 drops) were added in succession to a solution of the racemic acid (5 g, 0.016 mol) in benzene (50 mL). After 1.5 h at room temperature, the solution was evaporated; the residue was dissolved in benzene (50 mL) and concentrated in vacuo once again. The residual oily acid chloride was dissolved in acetonitrile (250 mL) and *l*-1-phenylethylamine (10 mL) and triethylamine (6.5 mL) were added. After 2 h at room temperature the solution was diluted with water (750 mL) and extracted with ethyl acetate (400 mL). The extract was washed with water, dried, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (400 g) using benzene–ethyl acetate (10:1) as the eluting solvent. The less polar *l*-2-(6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionic acid *l*-1-phenylethylamide A (3.3 g) had mp 162–163 °C (ethyl acetate) and $[\alpha]_D$ +16.4° (0.01 g/mL, $CHCl_3$), while the more polar *dl*-amide B (2.8 g) had mp 170–171 °C [ethyl acetate–hexane (1:2)] and $[\alpha]_D$ −1.4° (0.01 g/mL, $CHCl_3$).

A solution of amide A (3.0 g) in acetic acid (62 mL) and concentrated hydrochloric acid (9.3 mL) was heated at 87 °C for 8 h. The cooled solution was diluted with water and extracted with ethyl acetate (250 mL). The extract was washed with water and then extracted with aqueous sodium carbonate solution (250 mL, 0.5 M). The organic phase on evaporation gave the starting amide (1.06 g) which was subjected to the hydrolysis conditions described above (85 °C, 14 h). The aqueous sodium carbonate extracts were made acidic with hydrochloric acid and the product was taken up in ethyl acetate. The dried extract on evaporation gave an oil (2.2 g) which was dissolved in 2-propanol (10 mL). *l*-Amphetamine (0.95 g) was added and the solution was cooled to −10 °C to give the crystalline amphetamine salt. The salt was collected by filtration and then shaken with aqueous hydrochloric acid (100 mL, 2 M) and ethyl acetate (100 mL). The organic layer was separated, washed with water, dried, and evaporated. The crystallization of the *l*-amphetamine salt and regeneration of the acid was repeated a further three times to give *d*-2-(6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionic acid (**56**) as a gum (1.65 g): $[\alpha]_D$ +37.2° (0.005 g/mL, $CHCl_3$).

The more polar amide B (2.64 g) was dissolved in acetic anhydride (111 mL) and acetic acid (21 mL) and the solution was cooled to 0 °C. Sodium nitrite (9.25 g) was added in four portions over a 1-h period. After 5 h at 0 °C and 17 h at room temperature, the mixture was stirred vigorously with water (250 mL) and ethyl acetate (100 mL) for 1.5 h. Additional water (500 mL) was added and the reaction mixture was extracted with ethyl acetate (400 mL). The extract was washed with water, dried, and evaporated to give a residue which was heated at reflux temperature in benzene (50 mL) for 1 h. The solution was cooled, washed with aqueous potassium carbonate solution (100 mL, 0.5 M), dried, and evaporated. The residue was purified by column chroma-

tography on silica gel (100 g) using benzene as the eluent. Evaporation of the eluate gave 1-phenylethyl *l*-2-(6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionate (0.75 g) as an oil with NMR δ 1.29–1.52 (m, 6 H), 3.68 (q, 1 H), 4.02 (s, 2 H), 7.00–7.60 (m, 11 H), 8.16 (m, 1 H). A solution of the above ester (0.74 g) in benzene (10 mL) and trifluoroacetic acid (10 mL) was stirred at room temperature for 2 h. The solution was diluted with water (200 mL) and the product was extracted into ethyl acetate (200 mL). The extract was washed with water, dried, and evaporated to give the *l* acid **55** (0.51 g) as a gum with $[\alpha]_D$ −37.8° (0.005 g/mL, $CHCl_3$).

Synthesis of the Diols VIIIa by Reduction of the Esters VII with Lithium Aluminum Hydride. The synthesis of 1,3-bis(hydroxymethyl)-4-phenylthiobenzene (**23**) was typical. A solution of dimethyl 4-phenylthioisophthalate (**20**) (35 g, 0.116 mol) in ether (200 mL) was slowly added to a solution of lithium aluminum hydride (7 g, 0.184 mol) in dry tetrahydrofuran (100 mL). Acetone was added to destroy the excess hydride and then saturated aqueous sodium chloride solution was introduced until the grey mixture became white in color. The inorganic salts were removed by filtration and the filtrate was evaporated to give the sulfide **23** (25 g, 88%) with mp 68–69 °C after crystallization from benzene.

Preparation of the Dichlorides VIIIb. The general procedure exemplified by the synthesis of 1,3-bis(chloromethyl)-4-phenylthiobenzene (**26**) is described. Thionyl chloride (10 mL) was added to a solution of **23** (25 g) in benzene (100 mL) and the resultant was heated at reflux temperature for 30 min. The cooled solution was evaporated in vacuo and the residual oil was distilled to give the product (26 g, 92%), bp 168 °C (0.1 mm). The other dichlorides (see Table II) were purified by crystallization or by column chromatography on alumina.

Synthesis of the Substituted Benzenediacetic Acids IXa. The preparation of 4-phenylthiobenzene-1,3-diacetic acid (**29**) is illustrative of the general procedure. The sulfide **26** (26 g, 0.092 mol) was slowly added to a stirred mixture of potassium cyanide (15 g, 0.23 mol) and dimethyl sulfoxide (200 mL). The mixture was then stirred at room temperature for 18 h and then poured into water (1 L). The product was extracted into ethyl acetate (3 × 100 mL); the extract was washed with water, dried, and evaporated in vacuo. The residual oil was subjected to column chromatography on alumina (300 g) using hexane–ethyl acetate (3:1) as the eluting solvent. The major fraction was 4-phenylthiobenzene-1,3-diacetonitrile. The crude dinitrile, phosphoric acid (200 mL, 85%), and acetic acid (200 mL) were heated at reflux temperature for 8 h. The cooled mixture was poured into water (2 L) and the product was extracted with ethyl acetate (3 × 250 mL). The extract was washed with water and then shaken with sodium bicarbonate solution. The basic extract was diluted with water (500 mL), heated to 70 °C, and slowly made acidic with hydrochloric acid. The solution was left to cool and the crystalline dicarboxylic acid (16.5 g, 60%) was collected by filtration, washed with water, and dried. After crystallization from methanol–water it had mp 176–180 °C.

Cyclization of the Substituted Benzenediacetic Acids. The cyclization of the diacid **29** via the corresponding diacid chloride illustrates the general procedure. The dicarboxylic acid **29** (5 g, 0.016 mol), oxalyl chloride (4.0 mL), and dichloromethane (20 mL) were stirred at room temperature for 48 h. The mixture was evaporated, and the crude diacid chloride, dissolved in dichloromethane (10 mL), was added to a solution of aluminum chloride (6.6 g, 0.05 mol) in dichloromethane (50 mL) containing nitromethane (7 mL). The mixture became dark green in color. After 15 min saturated aqueous sodium chloride solution (8 mL) was added to the vigorously stirred mixture and the resultant was then filtered through a pad of magnesium sulfate. Evaporation of the colorless filtrate gave an oil which was mainly the acid chloride. This material was heated at reflux temperature in a solution of dimethoxyethane (50 mL) containing water (2 mL) for 15 min. The cooled solution was diluted with water (200 mL) and cooled at 0 °C. The solid, 10,11-dihydro-10-oxodibenzo[*b*,*f*]thiepin-2-acetic acid (**73**) (2.5 g, 53%), was collected by filtration, washed with water, and dried. After crystallization from chlorobenzene it had mp 177–179 °C.

If the crude acid chloride was heated with methanol instead of aqueous dimethoxyethane, the methyl ester **74** (45%), mp 82 °C (benzene–hexane), was obtained. See Table IV for the physical constants, etc., of these and related compounds.

Synthesis of the Tricyclic Unsaturated Acetic Acids XII. The following procedure, utilized for the synthesis of dibenzo[*b*,*f*]thiepin-2-acetic acid (**75**), was typical. Sodium borohydride (0.10 g, 2.6 mmol) was added to a solution of the keto ester **72** (0.95 g, 3.2 mmol) in dimethoxyethane (10 mL) and the resultant was stirred at room temperature for 4 h. The solution was poured into water (100 mL) and extracted with ether (2 × 30 mL). The extract was washed with water, dried, and evaporated in vacuo. The residual oil was boiled under reflux in a solution of dimethoxyethane (50 mL) containing 1 drop of perchloric acid (70%) for 4 h. The cooled solution was poured into water (400 mL) and the product was extracted into ether (2 × 50 mL). The extract was washed with water, dried, and evaporated to give an oil which was chromatographed on silica gel (10 g) using hexane–ethyl acetate (7:1) as the eluting solvent. The methyl dibenzo[*b*,*f*]thiepin-2-acetate (**74**) (0.60 g, 67%) thus obtained had mp 100–101 °C after crystallization from benzene–hexane. Hydrolysis of this ester under the alkaline conditions described previously gave the carboxylic acid **75** (91%), mp 144 °C (ether).

10,11-Dihydrodibenzo[*b*,*f*]thiepin-2-acetic Acid (76). Compounds **76** and **92** were synthesized according to the method described below for **76**. A mixture of the keto acid **73** (0.5 g, 1.73 mmol), amalgamated zinc (5 g), toluene (20 mL), acetic acid (2 mL), and concentrated hydrochloric acid (10 mL) was stirred under reflux for 2 h. The cooled mixture was poured into water (50 mL); the organic phase was separated, washed with water, dried, and evaporated in vacuo. The residue on crystallization from ether gave the product **76** (0.375 g, 80%), mp 104 °C.

10,11-Dihydrodibenz[*b*,*f*]oxepin-2-acetic Acid (87). A solution of the unsaturated acid **86** (1.0 g, 3.97 mmol) in dimethoxyethane (50 mL) containing palladium on charcoal (0.10 g, 10%) was stirred in a hydrogen atmosphere at room temperature and atmospheric pressure for 24 h. The mixture was filtered, the filtrate was evaporated, and the residue on crystallization from benzene–hexane gave the product (0.85 g, 85%), mp 127–128 °C.

10,11-Dihydrodibenzo[*b*,*f*]thiepin-2-acetic Acid 5-Oxide (79). *m*-Chloroperbenzoic acid (0.350 g, 85%, 1.75 mmol) was added to a solution of the crude methyl ester (0.54 g, 1.8 mmol), derived from **76** and diazomethane, in dichloromethane (20 mL). After 5 min the mixture was washed with aqueous sodium carbonate solution; the organic phase was dried and filtered through a short column of silica gel (10 g) using methylene chloride as the eluting solvent. Crystallization of this residue, after evaporation of the solvent from benzene–hexane, gave the methyl ester **78** (0.51 g, 89%), mp 115 °C. This ester (0.51 g) was heated at reflux temperature for 3 h in methanol (20 mL) containing potassium carbonate (0.030 g, 2.2 mmol). The cooled solution was diluted with water (100 mL), made acidic with dilute hydrochloric acid, and extracted with ethyl acetate (3 × 25 mL). The extract was washed with water, dried, and evaporated in vacuo. Crystallization of the residue from dichloromethane–hexane gave the acetic acid **79** (0.38 g, 78%), mp 169–170 °C.

10,11-Dihydrodibenzo[*b*,*f*]thiepin-2-acetic Acid *S*,*S*-Dioxide (82). Methyl 10,11-dihydrodibenzo[*b*,*f*]thiepin-2-acetate *S*,*S*-dioxide (**81**), mp 103–105 °C (chloroform–hexane), was prepared (73% yield) in a manner similar to that described for the sulfoxide **78** except that 2 equiv of the peracid was used. Hydrolysis of the ester was effected by heating a solution thereof (0.40 g, 1.27 mmol), in formic acid (10 mL, 97%) containing *p*-toluenesulfonic acid (0.05 g, 0.3 mmol), at reflux temperature for 4 h. The cooled solution was diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The extract was washed with water, dried, and evaporated in vacuo. Crystallization of the residue from benzene gave the sulfone **82** (0.34 g, 89%), mp 161–162 °C.

Dibenzo[*b*,*f*]thiepin-2-acetic Acid *S*,*S*-Dioxide (80). Methyl 10,11-dihydro-10-oxodibenzo[*b*,*f*]thiepin-2-acetate (**72**) (0.74 g, 2.48 mmol) was reduced with sodium borohydride as described previously. The crude alcohol was dissolved in dichloromethane (20 mL) and *m*-chloroperbenzoic acid (1.02 g, 85%, 5.0 mmol) was added. Saturated aqueous sodium sulfite solution (1 mL) and saturated aqueous potassium carbonate (1 mL) were added to the stirred mixture. After 5 min the organic phase was

dried and evaporated in vacuo. The crude hydroxy sulfone was dissolved in formic acid (7 mL, 97%) containing *p*-toluenesulfonic acid (0.10 g, 0.58 mmol) and heated at reflux temperature for 3 h. The cooled solution was poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL); the extract was dried, decolorized with charcoal, and evaporated in vacuo. Crystallization of the residue from ethyl acetate–hexane gave the sulfone acetic acid **80** (0.64 g, 86.5%), mp 162–163 °C.

***dl*-2-(10,11-Dihydrodibenzo[*b*,*f*]thiepin-2-yl)propionic Acid (77).** A solution of methyl 10,11-dihydrodibenzo[*b*,*f*]-thiepin-2-acetate (2.2 g, 7.75 mmol) in *tert*-butyl alcohol (15 mL) containing potassium *tert*-butoxide (0.87 g, 7.77 mmol) and diethyl carbonate (1.0 g, 8.5 mmol) was boiled under reflux for 12 h. Methyl iodide (1 mL) was added to the mixture and after a further 4 h at reflux temperature the cooled mixture was poured onto ice and concentrated hydrochloric acid (2 mL). The product was extracted into benzene (2 × 25 mL); the extract was washed with water, dried, and evaporated in vacuo. The residual oil was subjected to column chromatography on silica gel (25 g) using hexane–ethyl acetate (7:1) as the eluent. The oil (1.3 g) obtained on evaporation of the eluate was dissolved in methanol (25 mL) containing aqueous potassium hydroxide (2 mL, 50%) and heated at reflux temperature for 30 min. The cooled mixture was diluted with 1 N hydrochloric acid (100 mL) and extracted with benzene (2 × 25 mL). The extract was washed with water, dried, and evaporated in vacuo. The residual oil was dissolved in benzene (5 mL) containing dicyclohexylamine (1.0 g) whereupon the dicyclohexylammonium salt of **77** (1.2 g, 33%) crystallized. It was collected by filtration, washed with ether, and dried to give a solid, mp 142–143 °C.

References and Notes

(1) Contribution No. 509 from the Syntex Institute of Organic Chemistry.
(2) (a) R. A. Scherrer and M. W. Whitehouse, Ed., "Antiinflammatory Agents. Chemistry and Pharmacology", Vol. I, Academic Press, New York, N.Y., 1974; (b) M. E. Rosenthale, *Annu. Rep. Med. Chem.*, **9**, 193–202 (1974); S. Wong, *ibid.*, **10**, 172–181 (1975).
(3) S. S. Adams, K. F. McCullough, and J. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, **178**, 115 (1969).
(4) L. Julou and J. C. Guyonnet, *J. Pharmacol.*, **2**, 259 (1971).
(5) A. Roszkowski, W. H. Rooks, A. J. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, **179**, 114 (1971).
(6) S. Wong, J. F. Gardocki, and T. P. Pruss, *J. Pharmacol. Exp. Ther.*, **185**, 127 (1973).
(7) K. Ueno, S. Kubo, H. Tagawa, T. Yoshioka, W. Tsukada, M. Taubokawa, H. Kojima, and A. Kasahara, *J. Med. Chem.*, **19**, 941 (1976).
(8) D. E. Aultz, G. C. Helsley, D. Hoffman, A. R. McFadden, H. B. Lassman, and J. C. Wilker, *J. Med. Chem.*, **20**, 66 (1977).
(9) Several patent filings on tricyclic acetic acids in this general area have also been made: e.g., (a) M. Nakanishi, T. Oe, and H. Maruyama, Japanese Patent 72 00425 (1972); *Chem. Abstr.*, **76**, 126784w (1972); (b) F. Gadient, German Offen. 2442979 (1975); *Chem. Abstr.*, **83**, 43212b (1975).
(10) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, **42**, 3419 (1977), and references cited therein.
(11) G. A. Olah, "Friedel Crafts and Related Reactions", Vol. I, G. A. Olah, Ed., Interscience, London, 1963, pp 246–249.
(12) S. Dev, *J. Indian Chem. Soc.*, **32**, 255 (1955); A. Bhati and N. Kale, *Angew. Chem., Int. Ed. Engl.*, **6**, 1086 (1967).
(13) G. W. Smith, *J. Mol. Spectrosc.*, **12**, 146 (1964).
(14) These compounds were recently disclosed in the patent literature: K. Ueno and R. Dohmori, Japanese Kokai 77 83591 (1977); *Chem. Abstr.*, **88**, 22872e (1978).
(15) J. P. Dunn, D. M. Green, P. H. Nelson, W. H. Rooks, A. Tomolonis, and K. G. Untch, *J. Med. Chem.*, **20**, 1557 (1977).
(16) D. E. Aultz, A. R. McFadden, and H. B. Lassman, *J. Med. Chem.*, **20**, 456 (1977).
(17) This test was conducted using a single dose of an aqueous solution of the sodium salts of **52** and **53**.
(18) D. V. Krishna Murthy and M. Kruseman-Aretz, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 622 (1978) (abstract no. 2363).
(19) R. Wegschneider and A. Lipschitz, *Monatsh. Chem.*, **21**, 787 (1900).
(20) A. Wohl, *Chem. Ber.*, **43**, 3474 (1910).
(21) R. Meyer and H. Wesche, *Chem. Ber.*, **50**, 444 (1917).
(22) H. Kaufmann and L. Weissel, *Justus Liebigs Ann. Chem.*, **393**, 10 (1912).
(23) M. A. Soderman and T. B. Johnson, *J. Am. Chem. Soc.*, **47**, 1393 (1925).
(24) L. S. Forney, *J. Org. Chem.*, **35**, 1695 (1970).
(25) J. A. Marshall and J. L. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).
(26) See also C. A. Winter, E. A. Riley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(27) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).
(28) C. W. Pearson, *Proc. Soc. Exp. Biol. Med.*, **91**, 95 (1956).
(29) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1958).

2-Pyrrolidinylideneureas, a New Class of Central Nervous System Agents†

C. R. Rasmussen,* Joseph F. Gardocki, James N. Plampin, Barbara L. Twardzik, Brian E. Reynolds, Albert J. Molinari, Norman Schwartz, Walter W. Bennetts, Beth E. Price, and Janis Marakowski

Departments of Chemical Research and Pharmacology, McNeil Laboratories, Fort Washington, Pennsylvania 19034.

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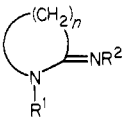
A series of *N*-aryl-*N'*-(1-methyl-2-pyrrolidinylidene)ureas was prepared and screened for pharmacological activity. Congeners possessing either phenyl or phenyl substituted with 4-nitro, 3-bromo, 3-chloro, 3-fluoro, and 3-methyl groups were found to demonstrate anxiolytic activity. 2,6-Disubstitution of the phenyl ring with methyl, chloro, and bromo imparted potent muscle-relaxant properties which appear to be centrally mediated. A significant separation of the anxiolytic and muscle-relaxant properties from other CNS activities, e.g., anticonvulsant, sedative, and hypnotic, was achieved.

Semicyclic amidines (lactamimides) 1 show a variety of pharmacologic activities, among which are hypoglycemic,[1a,b] antithrombotic,[1a] antianginal,[1c] and antiarrhythmic.[1c,d]



1

It became of interest to explore chemical modifications designed to lower the basicity of these substances and to submit the resulting compounds for broad pharmacological

† This paper is dedicated to the memory of our dear friend and consultant, the late Dr. Edward E. Smissman. Ed's long and fruitful association with these laboratories remains a cherished experience for us all.

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