(25) R. Adams, C. K. Cain, and B. R. Baker, *J. Am. Chem. Soc.*, **62**, 2201 (1940).
(26) S. Kimaye, *Ber.*, **67**, 12 (1934).
(27) A. R. L. Dohme, E. H. Cox, and E. Miller, *J. Am. Chem. Soc.*, **48**, 1688 (1926).
(28) W. Baker, *J. Chem. Soc.*, 956 (1939).
(29) W. Baker, N. C. Brown, and J. A. Scott, *J. Chem. Soc.*, 1922 (1939).
(30) K. Takahashi and S. Miyashita, *Chem. Pharm. Bull.*, **11**, 209 (1963).
(31) A. I. Vogel, "Practical Organic Chemistry", 3rd ed, Longman, London, 1956, p 702.
(32) K. W. Rosenmund, R. Buchwald, and Th. Deligiannis, *Arch. Pharm. (Weinheim, Ger.)*, **271**, 342 (1933).
(33) R. E. Omer and C. S. Hamilton, *J. Am. Chem. Soc.*, **59**, 642 (1937).
(34) Y. Tahara, *Ber.*, **25**, 1292 (1892).
(35) St. V. Kostanecki and L. Lloyd, *Ber.*, **34**, 2942 (1901).
(36) H. Remmer, J. Schenkman, R. W. Estabrook, R. W. Sasame, J. Gillette, S. Narasimhulu, D. Y. Cooper, and O. Rosenthal, *Mol. Pharmacol.*, **2**, 187 (1966).
(37) A. Bobik, G. M. Holder, A. J. Ryan, and L. I. Wiebe, *Xenobiotica*, **5**, 65 (1975).

Oxime Ether Derivatives, a New Class of Nonsteroidal Antiinflammatory Compounds

Jan van Dijk* and Jan M. A. Zwagemakers

Philips-Duphar B.V., Research Laboratories, Weesp, The Netherlands. *Received January 19, 1977*

A series of new 2-hydroxyethyl and carboxyalkyl ethers of aromatic oximes was found to possess pronounced antiinflammatory activity in the carrageenan-induced edema test in the rat. The activity was limited mainly to derivatives of *p*-haloacetophenone oxime and of *p*-halobenzaldehyde oxime. Nevertheless, the hydroxyethyl and carboxyalkyl groups may be converted into many derivatives with maintenance of activity. Some structure–activity relationships are in contrast to those of the well-known antiinflammatory arylacetic acids. The activity is limited to the *E* stereoisomers. The hydrochloride of 2-(dimethylamino)ethyl (*E*)-[[(*p*-chloro-α-methylbenzylidene)-amino]oxy]acetate (**36**, INN name Cloximate) was chosen for clinical evaluation. The first results agree with the pharmacological prospects.

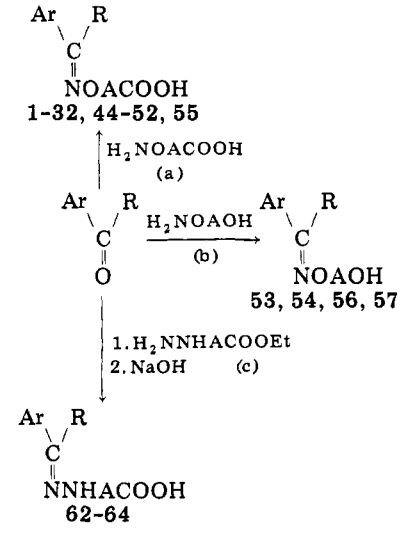
In the course of pharmacological investigations of different types of oxime ethers,[1] we found *p*-chloroacetophenone oxime ether of acetic acid (**7**) to possess a pronounced antiinflammatory activity (AIA) and favorable toxicity. A great number of analogues were synthesized and investigated with respect to this activity. This paper describes the syntheses of the compounds and structure–activity relations (SAR) are discussed.

Chemistry. As early as 1896 the first oxime acetic acid and its ethyl ester were synthesized from benzaldehyde oxime and chloroacetic acid.[2] At the same time a synthesis of aminooxyacetic acid was described,[3] which compound was used some 40 years later for isolation procedures, etc., of ketones.[4,5] Limited groups of oxime ethers of alkanoic acids have since then been prepared by Richardson[6] and recently by Buzas et al.[7]

As indicated in Schemes I and II we used ketones (and aldehydes) as well as the oximes for the preparation of our oxime ethers. The condensation of a ketone with a hydroxylamino ether (Scheme I) was the most convenient way of making oxime ethers of a large series of variably substituted aromatic ketones and aldehydes. For the preparation of oxime ethers composed of variable acids linked with a few preferable oximes, the methods of Scheme II were chosen, which were variations of known conversions.

An interesting phenomenon was the fact that with phenyl ketones always the *E* oximes or *E* oxime ethers were obtained in large excess, whereas analogous thienyl derivatives gave both stereoisomers, *E* and *Z*, in considerable amounts. The reason might be sought in steric effects, i.e., the influence of the absence of one "ortho" substituent in the α-thienyl derivatives. The amount of *Z* isomer found in **2** and **48** (respectively 9 and 6% of the theoretical yield), which seems in contradiction with this explanation, might be a coincidence (N.B. **23** contained no *Z* isomer). The amount formed seems rather small and cannot be conclusive.

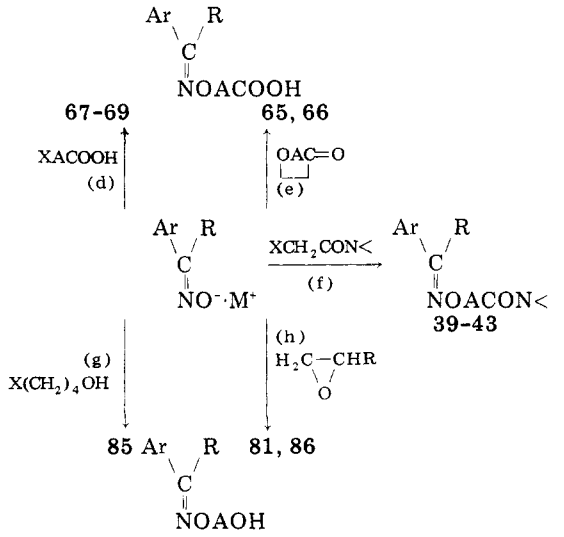
Scheme I. Conversions of Ketones and Aldehydes[a]



[a] A = alkylene; Ar = (substituted) aryl or heteroaryl; R = mainly H or Me; numbers, see Table I; letters in parentheses, see Experimental Section under methods.

Different types of the oxime ethers were easily obtainable from others, without isomerization or instability of the oxime ether function being observed (Scheme III). For instance, anhydrous (alcoholic) acid leads from acids to esters quantitatively (Scheme III, method j). Acid chlorides are formed with $SOCl_2$ (k), and these are converted into esters with additional functional groups, e.g., into basic esters (m). Only with anhydrous HCl in ether an *E* isomer is isomerized to the *Z* isomer (n). In an aqueous acidic medium the oxime ether is slowly hydrolyzed to the hydroxylamino ether and the ketone (p). In alkaline conditions the oxime ether is stable as is shown by the formation of the oxime ethers from the oximate ion (Scheme II) and in the formation of oxime ether amides

Scheme II. Conversions of Oximes[a]



[a] X = Cl or Br; M^+ = mainly Na^+; for A, Ar, R, numbers, and letters, see Scheme I.

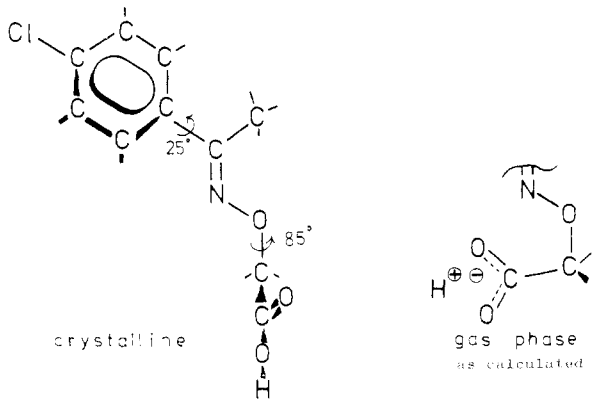


Figure 1. Steric structure of (*E*)-[[(*p*-chloro-α-methylbenzylidene)amino]oxy]acetic acid (**7**).

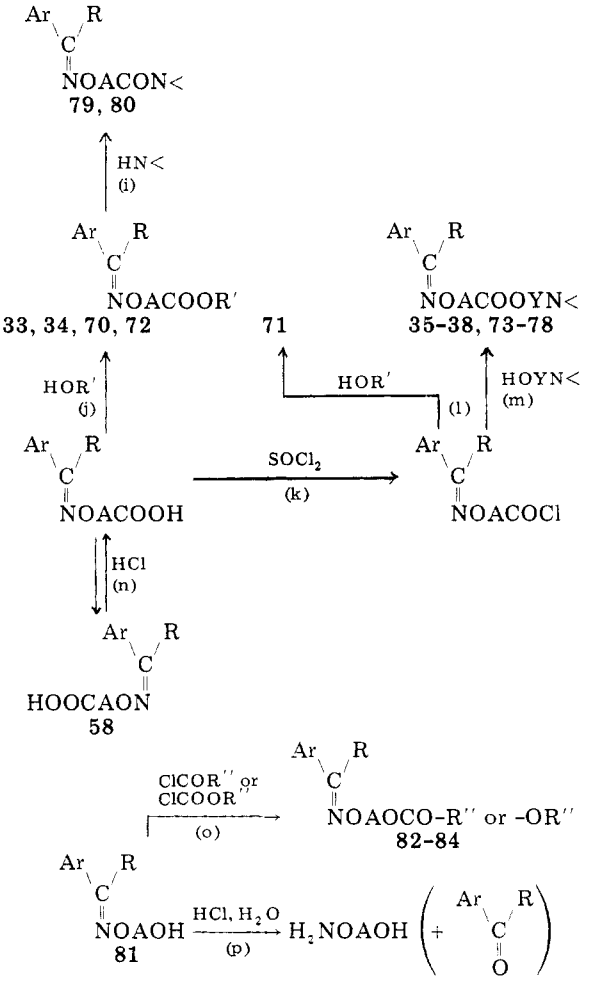
from corresponding esters (i).

Table I shows in respect of each compound the method(s) of preparation used, the yield, the melting or boiling point, and the analyses carried out.

The configuration of the oxime ether function in the different kinds of derivatives was deduced from NMR measurements, in particular with the help of lanthanide-induced shifts.[8] An x-ray diffraction analysis of a *p*-chloroacetophenone oxime ether by Braun and Hornstra[9] confirmed the configuration. The steric structure of this molecule is shown in Figure 1. The conformation of this compound is such that (in the crystalline state) the oxime ether function lies in a plane making an angle of 25° with the phenyl ring. The carboxyl function is almost perpendicular (85°) to the oxime ether grouping. Calculations by Tipker,[10] based on CNDO/2 molecular orbital calculations,[11] indicated a similar conformation in the gas phase, except that then the carboxyl function was in the oxime ether plane and directed to the N atom.

Antiinflammatory Activity. The values collected in Table I are those of the carrageenan-induced edema test in the rat (Experimental Section). Of compounds showing more than 30% reduction of the edema at 50 mg/kg orally, the dose that causes a 50% reduction (ED_{50}) has been determined. Those showing a 20–30% reduction are classified as active (+) but not further evaluated. Less than 20% reduction is indicated as (–).

Scheme III. Conversions of Oxime Ethers[a]



[a] HOR' and HOYN< are neutral and basic OH compounds; R'' = alkyl; for A, Ar, R, numbers, and letters, see Scheme I.

Structure–Activity Relationships. Compounds **1–27** (Table I) show the influence of variations in aromatic substitution on the AIA. A conspicuous feature is that the *p*-chlorophenyl and *p*-bromophenyl derivatives (**7** and **8**) possess the highest activity, followed by *m*,*p*-Cl_2, *p*-F, *p*-CF_3, and *o*,*p*-Cl_2 (**24**, **6**, **13**, and **23**), whereas the other compounds have little or no activity. This shows that the AIA in this series is very dependent on the aromatic substitution pattern; substitution with *p*-Cl or *p*-Br is most favorable. A second conclusion is that the introduction of highly lipophilic substituents, which are optimal in the well-known arylacetic acid series, e.g., ibufenac, brufen, and (3-chloro-4-cyclohexylphenyl)acetic acid,[12] has no effect in the oxime ether series (**10**, **11**, and **26**). Rather surprisingly, the SAR found in the oxime ethers are quite different from that of the arylacetic acids.

The structural specificity of the aromatic substitution pattern is confirmed by some benzaldoxime derivatives, some acetamides, and some esters (**28–43**).

7, **29**, **44**, and **45** show the influence of variation of R (Figure 2) in the 4-chlorophenyl oxime ethers and **46–52** of the aromatic ring, both for the acetic acids. The highest activity was observed with the methyl ketoxime ethers, followed by the benzaldoxime ethers. Other variations of R in the *p*-chlorophenyl derivatives (**44** and **45**) gave inactive compounds. The same phenomenon was observed for corresponding amides, esters, etc. In view of such a structural dependence of the AIA, it is not surprising that oxime ethers of quite different ketones should possess little

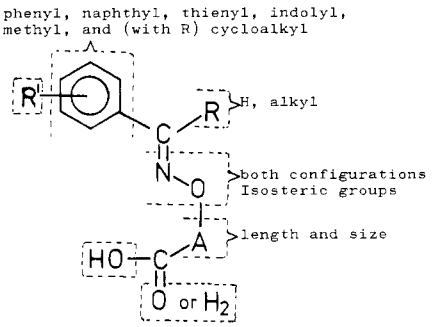


Figure 2. Summary of structural variations.

or no activity. Only some thienyl derivatives (e.g., **49**) were found to be active, but then the structural resemblance of these compounds to active phenyl derivatives is evident.

The configuration of the oxime ether function is essential, as can be concluded from the activities of the *E* isomers (**49**, **53**, and **56**) compared with related *Z* isomers (**54**, **55**, **57**, and **58**).

Summing up the findings regarding the AIA in the above series, we arrive at the conclusion that only the *E* oxime ethers of *p*-chloro- and *p*-bromoacetophenone and 5′-chloroacetothienone exhibit optimum AIA in these series and that the AIA is quite structure specific for this part of the molecule.

Replacement of the oxime ether function in the *p*-chlorophenyl compounds by more or less isosteric functions gave less valuable compounds, illustrating the importance of this function for the AIA. Activity (low) in the cinnamic acids and homologues is practically limited to **59**. The hydrazone acetic acids (**62** and **63**) are active, and the same SAR as found with the oxime ethers seem to be present (compare **63** with **64**). Also, esters and amides of these hydrazones (not mentioned in the table) possess good activity. However, in this series the toxicity forms an obstacle to further investigation.

The acetic acid part of the structure can be varied in several ways, with retention of the AIA. **7** and **65–69** show that the acetic acid derivatives are optimum but the different homologues show the same order of activity. The activity of the α,α-dimethyl derivative **69** was unexpected. In known acetic acid series this variation is inactive, whereon the assumption was based that an α-H atom was essential in these series.[13]

The carboxyl function itself can be varied without notable loss of activity. Variations are illustrated in **33**, **36**, and **74–86**. As a summary of the structure requirements necessary for AIA in this class of compounds, it can be said that the structural specificity of the 4-chlorophenyl and 4-bromophenyl group is indicative of the necessity of this part of the molecule, including the oxime ether function. The *E* configuration of the oxime ether link, prefered for AIA, indicates the necessity of a special steric arrangement of the link between the aromatic part and carboxyl variant.

Pharmacological Profile. In most compounds the toxicity values (LD_{50}[48] as well as ED_{50} in neurotoxicity) were much higher than 320 mg/kg ip and higher than 1000 mg/kg orally. Pronounced effects on the circulation and on the central and autonomic nervous systems were absent. Besides in the carageenan-induced edema test, a limited group of the most active compounds was tested in other animal tests for AIA. In all these tests good activity was found. Compound **36**,[14] for example, shows good inhibitory activities in other local exudative tests and in the proliferative and in the functional aspects of experimental inflammation, as well as in the bradykinin-evoked bronchoconstriction test. Compound **36** distinguishes itself favorably from standard antiphlogistics by showing a marked activity against traumatic edema and in the Arthus antigen–antibody test. Moreover, just like most of the active compounds, **36** has good peripheral analgetic and antipyretic activity. Compared with the established drugs, many of the selected group excelled in their effects on the gastrointestinal tract. Especially **36** showed almost no harmful effects on the gastrointestinal mucosa (tested in acute and chronic experiments in rat and dog) and no influence upon the emptying rate of the stomach. The inhibition (by **36**) of the biosynthesis of PG E2 by bovine seminal vesicle microsomes[15] was found to be of the same magnitude as by phenylbutazone. Details of the pharmacological profilation of a selected group, especially of **36**, will be published in the future.

Based on the complete profile, **36**[14] was chosen for clinical evaluation. The results of the first trials are in agreement with the pharmacological prospects.

Experimental Section

Pharmacology. The AIA was measured as inhibition of carrageenan-induced edema in the hind paw of the rat (180–220 g) according to the procedure of Winter et al.[16] Primarily all the test compounds were orally administered in a dose of 50 mg/kg to groups of four animals 1 h before injecting the phlogistic agent using a 1% tragacanth solution as vehicle. Edema formation was measured 3 h after intraplantar injection of 0.05 mL of a 1% solution of carrageenan.

Where 30% inhibition or more was found, the compound was further tested in a series of doses in order to obtain an ED_{50} value. ED_{50} values (mg/kg) found for some established drugs were 34 (phenylbutazone), 98 (ibufenac), and 25 (ibuprofen). The ED_{50} values were calculated by means of a graphical method. Confidence limits were calculated for some compounds by means of a method of Finney.[17] They were found to depend of the slope of the dose–inhibition curves. Most of the more active compounds had a steep slope. In this case the lower and upper bound of the 95% confidence limits were 0.8 respectively, 1.3 times the ED_{50} values. In cases of a more flat slope, values up to 0.6 and 1.7 were found.

The LD_{50}[48] was determined on mice and calculated according to the method of Horn.[18] For neurotoxicity studies a modification of the method of Irwin[19] was used. In the testing of amines the hydrochloride is used, except in the case of **78** (free base used).

Chemistry. For each new compound the method used, yield, melting point, recrystallization solvent(s), and analyses carried out are summarized in Table I. Each method (Schemes I–III) is illustrated by a representative example. Deviations of the procedure for some compounds are mentioned in an introduction to the description of each method. Column chromatography (CC) and thin-layer chromatography TLC) were performed with Merck silica gel; the solvents used are indicated. In TLC analysis for control of the progress of the reaction C_6H_6–EtOAc (3:1) was frequently used. Drying of solutions was performed with Na_2SO_4. If the reaction temperature is not mentioned, room temperature was used (ca. 20–25 °C). All mentioned oxime ethers have the *E* configuration, unless otherwise indicated.

All new compounds were analyzed by NMR (spectra taken on a Varian HA 100). In some cases additional measurements (IR, mass, and UV spectra) were made. All spectra were consistent with the assigned structure. The purity was further checked by combinations of TLC, titrimetric methods (COOH, NH_2, $-NMe_2$, Cl^-, for all relevant compounds), melting range, boiling range (where considered useful), and elemental analysis. The elemental analyses indicated were within ±0.4% of the theoretical values. The other checks also gave no evidence of deviations in the purity. Melting points (determined in an apparatus developed by Dr. Tottoli) are uncorrected. *Warning*: care should be taken in the preparation of dry sodium oximates; they may decompose abruptly when coming into contact with air (see methods f and g).

Method a. In most cases NaOAc was used for binding of the HCl (method a1). Then the sodium salt of the reaction product sometimes crystallized from the reaction mixture (e.g., **49**). In

Table I. Antiinflammatory Activity and Chemical Data

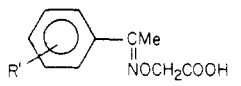
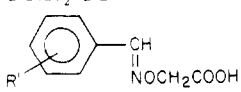
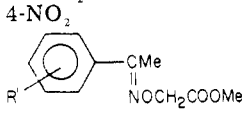
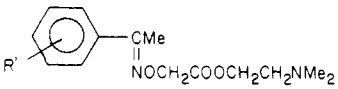
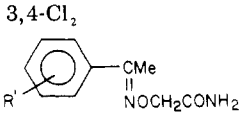
No.	Structure	AIA,[a] ED_{50}, + or −	Method (lit. ref)	% yield	Mp or bp (mm), °C	Crystn solvent[b]	Formula	Analyses
								
	R′ =							
1	H	−	a3 (6)	83	97-98	B-P	$C_{10}H_{11}NO_3$	
2	2-Cl (12% *Z* isomer)	−	a2	74	46-53	P	$C_{10}H_{10}ClNO_3$	H, N; C[c]
3	2-OH	−	a1	81	153-155	B-P	$C_{10}H_{11}NO_4$	
4	2-COOH	−	a2	68	120-122	Et-P	$C_{11}H_{11}NO_5$	C, H, N
5	3-Cl	+	a1	57	93-94.5	B-P	$C_{10}H_{10}ClNO_3$	
6	4-F	85	a1	94	104-105.5	B-P	$C_{10}H_{10}FNO_3$	
7	4-Cl	28	a1	78	118-119	Et-P	$C_{10}H_{10}ClNO_3$	C, H, N; IR; UV; MS
8	4-Br	27	a1	87	133-134	B-P	$C_{10}H_{10}BrNO_3$	
9	4-Me	+	a1	86	114-116	B-P	$C_{11}H_{13}NO_3$	
10	4-*t*-Bu	−	a1	71	119-124	B-P	$C_{14}H_{19}NO_3$	
11	4-(Cyclohexylmethyl)	−	a1	77	107-108	B-P	$C_{17}H_{23}NO_3$	
12	4-Cyclopropyl	−	a1	62	116-118	B-P	$C_{13}H_{15}NO_3$	C, H, N
13	4-CF_3	120	a1	93	94-95	Et-P	$C_{11}H_{10}F_3NO_3$	
14	4-C≡N	−	a1	94	138-141	B	$C_{11}H_{10}N_2O_3$	
15	4-OH	−	a1	71	146-149	B-Et	$C_{10}H_{11}NO_4$	
16	4-OMe	−	a1	87	102-103	B-P	$C_{11}H_{13}NO_4$	
17	4-SMe	−	a1	67	140-141.5	B	$C_{11}H_{13}NO_3S$	
18	4-SO_2Me	+	a1	91	144-146	EtA	$C_{11}H_{13}NO_5S$	
19	4-NH_2	+	a3	67	152-153	M-Et-P	$C_{10}H_{12}N_2O_3$	H, O; C, N[d]
20	4-NHAc	−	a1	79	232-233.5	M	$C_{12}H_{14}N_2O_4$	
21	4-NMe_2	−	a1	58	171-173	EtA-P, E-W	$C_{12}H_{16}N_2O_3$	
22	4-NO_2	−	a1	77	141-144	B-P	$C_{10}H_{10}N_2O_5$	
23	2,4-Cl_2	120	a2	87	87-88	Et-P	$C_{10}H_9Cl_2NO_3$	
24	3,4-Cl_2	65	a1	85	129-131	B-P	$C_{10}H_9Cl_2NO_3$	
25	3-Me-4-Cl	+	a1	82	98-101	B-P	$C_{11}H_{12}ClNO_3$	C, H, N
26	3-Cl-4-cyclohexyl	−	a2	79	104-105	Et-P	$C_{16}H_{20}ClNO_3$	
27	3-NH_2-4-F	+	a3	93	124-126.5	W	$C_{10}H_{11}FN_2O_3$	C, H, N
								
	R′ =							
28	2-Cl	−	a1 (23)	79	106-107	Et-P	$C_9H_8ClNO_3$	
29	4-Cl	45	a1	89	121-123	B-P	$C_9H_8ClNO_3$	
30	4-Br	46	a1	70	118-119	Et-P	$C_9H_8BrNO_3$	
31	4-NMe_2	−	a3	64	128-129.5	B-EtA	$C_{11}H_{14}N_2O_3$	
32	4-NO_2	−	a1 (6)	84	142-144	Et-P	$C_9H_8N_2O_5$	
								
	R′ =							
33	4-Cl	24	j	87	38.8-40.2	P	$C_{11}H_{12}ClNO_3$	C, H, N; IR; UV; MS
34	4-Br	14	j	99	49-50.5	P	$C_{11}H_{12}BrNO_3$	C, H, N
								
	R′ =							
35	4-F	+	klm	49	147-149	E	$C_{14}H_{19}FN_2O_3 \cdot HCl$	C, H, N
36	4-Cl	34	klm	63	160-162	E	$C_{14}H_{19}ClN_2O_3 \cdot HCl$	C, H, N, O, Cl; IR; UV; MS
37	4-Br	47	klm	57	180-182	E	$C_{14}H_{19}BrN_2O_3 \cdot HCl$	C, H, N
38	3,4-Cl_2	80	klm	77	167-168	E	$C_{14}H_{18}Cl_2N_2O_3 \cdot HCl$	C, N; H[e]
								
	R′ =							
39	H	−	fg	43	112-114	Et-P	$C_{10}H_{12}N_2O_2$	C, H, N
40	4-F	+	fg	67	106-108	B	$C_{10}H_{11}FN_2O_2$	C, H, N
41	4-Cl	24	fg	70	102-103	I	$C_{10}H_{11}ClN_2O_2$	C, H, N; IR; UV; MS
42	4-Br	62	fg	69	104-106	B	$C_{10}H_{11}BrN_2O_2$	
43	3,4-Cl_2	55	fg	65	111-111.5	C-Et-P	$C_{10}H_{10}Cl_2N_2O_2$	C, H, N

Table I (*Continued*)

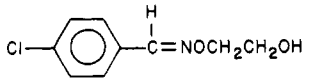
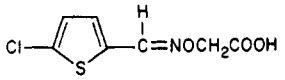
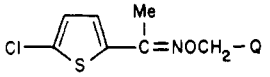
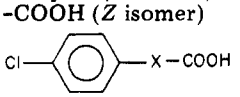
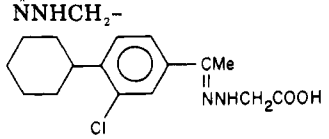
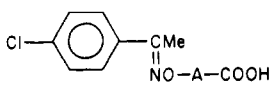
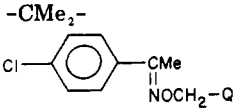
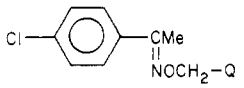
No.	Structure	AIA,[a] ED_{50}, + or −	Method (lit. ref)	% yield	Mp or bp (mm), °C	Crystn solvent[b]	Formula	Analyses
	$Y-\underset{\|\|}{C}-R$ $NOCH_2COOH$							
	Y = R =							
44	4-Chlorophenyl Et	−	a1	61	87.5-88.5	B-P	$C_{11}H_{12}ClNO_3$	
45	4-Chlorophenyl *n*-Pentyl	−	a1	87	81-82	B-P	$C_{14}H_{18}ClNO_3$	
46	Me Me	+	(20)					
47	α-Naphthyl H	−	a1 (6)	79	129-130	Et-P	$C_{13}H_{11}NO_3$	
48	α-Naphthyl Me (20% *Z* isomer)	+	a1	31	100-130	B-P	$C_{14}H_{13}NO_3$	
49	5-Chlorothienyl Me	34	a1	50[f]	133-134	B	$C_8H_8ClNO_3S$	
50	β-Indolyl Me	−	a1	67	152-154	Et-P	$C_{12}H_{12}N_2O_3$	C, H, N
	$Y-\underset{\|\|}{C}-R$ =							
51	Cyclohexylidene	−	a1 (24)	67	92.5-94	B-P	$C_8H_{13}NO_3$	
52	5-Chloroindenylidene-1	−	a1	85	144-146	EtA	$C_{11}H_{10}ClNO_3$	
								
53	*E* isomer	~90	b[g]	83	62-64	B-P	$C_9H_{10}ClNO_2$	C, H, N
54	*Z* isomer	−	b[g]	3	Liquid		$C_9H_{10}ClNO_2$	
								
55	*Z* isomer	−	a1	64	103-105	B-P	$C_7H_6ClNO_3S$	
								
	Q =							
56	$-CH_2OH$ (*E* isomer)	~60	a1[g]	34	66-67.5	P	$C_8H_{10}ClNO_2S$	C, H, N
57	$-CH_2OH$ (*Z* isomer)	−	a1[g]	53	61-62	P	$C_8H_{10}ClNO_2S$	C, H, N
58	−COOH (*Z* isomer)	−	m	53	114-116	B	$C_8H_8ClNO_3S$	
								
	-X- =							
59	$-\underset{\|\|}{C}Me$ (*Z*:*E* = 1:3) $HCCH_2-$	70	*h*	51	63-67		$C_{11}H_{11}ClO_2$	
60	$-\underset{\|\|}{C}Me$ $HCCH_2CH_2-$	−	*h*	47			$C_{12}H_{13}ClO_2$	C, H, O
61	−C≡C−	−	(25)					
62	$-\underset{\|\|}{C}H$ $NNHCH_2-$	25	c	79	133-145	B	$C_9H_9ClN_2O_2$	C, H, N
63	$-\underset{\|\|}{C}Me$ $NNHCH_2-$	22	c	39	120-123	A-P	$C_{10}H_{11}ClN_2O_2$	C, H; N[i]
64		−	c	64	124-127[j]	B	$C_{16}H_{21}ClN_2O_2$	
								
	-A- =							
65	$-(CH_2)_2-$	80	e	19	80-83	P	$C_{11}H_{12}ClNO_3$	
66	$-(CH_2)_3-$	58	e	33	106-108	30% AcOH	$C_{12}H_{14}ClNO_3$	
67	$-(CH_2)_5-$	92	d	62	65-68	L	$C_{14}H_{18}ClNO_3$	
68	−CHMe−	55	d	47	88-89	B-P	$C_{11}H_{12}ClNO_3$	
69	$-CMe_2-$	42	d	34	110-112	L	$C_{12}H_{14}ClNO_3$	C, H, N
								
	Q =							
70	−COOEt	32	j	94	28-29	P	$C_{12}H_{14}ClNO_3$	C, H, N
71	−COO-*n*-Pr	14	klm	94	$n^{20}D$ 1.5272		$C_{13}H_{16}ClNO_3$	C, H, N
72	−COO-*i*-Pr	50	j	68	130-132 (0.7)		$C_{13}H_{16}ClNO_3$	C, H, N

Table I (*Continued*)

No.	Structure	AIA,[a] ED_{50}, + or −	Method (lit. ref)	% yield	Mp or bp (mm), °C	Crystn solvent[b]	Formula	Analyses
	 Q =							
73	-$COOCH_2CH_2NHMe$	26	klm[k]	25	181-182	E-Et	$C_{13}H_{17}ClN_2O_3 \cdot HCl$	C, H, O
74	-$COOCH_2CH_2NH$-cyclohexyl	26	klm	73	173-174	E-W	$C_{18}H_{25}ClN_2O_3 \cdot HCl$	C, H, N
75	-$COOCH_2CH_2$-morpholyl-4	44	klm	74	159-162	E	$C_{16}H_{21}ClN_2O_4 \cdot HCl$	C, H, N
76	-$COOCH_2CH_2$-c-$N(CH_2CH_2)_2$N-Me	54	klm	71	205-208	E	$C_{17}H_{24}ClN_3O_3 \cdot 2HCl$	H, N; C[l]
77	-$COOCH_2CMe_2NMe_2$	27	klm	37	169-171	I	$C_{16}H_{23}ClN_2O_3 \cdot HCl$	C, H, N
78	-$COO(CH_2)_6NMe_2$	66	klm[m]	49	Liquid		$C_{18}H_{27}ClN_2O_3$	C, H, N
79	-CONHMe	70	i	87	115-116	B-P	$C_{11}H_{13}ClN_2O_2$	C, H, N
80	-$CONMe_2$	120	i	59	64.5-66	B-P	$C_{12}H_{15}ClN_2O_2$	
81	-CH_2OH	29	h	50	41.5-42.5	B-P[n]	$C_{10}H_{12}ClNO_2$	C, H, N
82	-CH_2OAc	43	o	73	132-134 (0.7)		$C_{12}H_{14}ClNO_3$	C, H, N
83	-$CH_2OCOCMe_3$	38	o	74	144-146 (0.8)		$C_{15}H_{20}ClNO_3$	C, H, N
84	-$CH_2OCOOMe$	33	o	74	55-56	P	$C_{12}H_{14}ClNO_4$	C, H, N
85	-$(CH_2)_3OH$	−	fg[m]	12	Liquid		$C_{12}H_{16}ClNO_2$	
86	-CHMeOH	−	h	32	130-132 (1.0)		$C_{11}H_{14}ClNO_2$	C, H, N, O, Cl

[a] Antiinflammatory activity in the carrageenan-induced rat paw edema test.[15] ED_{50} = dose (mg/kg, orally) that causes a 50% reduction of the edema. Compounds showing 20-30% reduction at 50 mg/kg orally are classified as +; those showing less than 20% reduction are indicated as −. ED_{50}'s found for reference compounds are 34 (phenylbutazone), 98 (ibufenac), and 25 (ibuprofen). Lower and upper bounds of the 95% confidence limits, calculated for some compounds, are in most cases 0.8 respectively, 1.3 times the ED_{50} values (see Experimental Section). [b] Solvents: A (acetone), B (benzene), C (chloroform), E (ethanol), Et (ether), EtA (ethyl acetate), I (2-propanol), L (ligroine), M (methanol), $MeCl_2$, P (petroleum ether), W (water). [c] C: calcd, 52.76; found, 52.17. [d] C: calcd, 57.68; found, 54.62. N: calcd, 13.46; found, 12,86. [e] H: calcd, 5.18; found, 5.66. [f] ~22% *Z* isomer was formed. [g] Stereoisomers separated by CC. [h] Prepared in analogy to that described in ref 26. [i] N: calcd, 12.36; found, 11.89. [j] After 1 week of exposure to light the melting point was 99-100 °C. [k] Product crystallized from the reaction mixture. [l] C: calcd, 47.84; found, 45.99. [m] Purified by CC. [n] Compound absorbs C_6H_6.

some instances (e.g., some ortho-substituted phenyl ketones) pyridine was used instead of NaOAc (method a2) (**2**). Also 0.5 or 1 equiv of NaOH instead of NaOAc was sometimes used (method a3).

Method a1. 2-[[(5-Chloro-α-methylthenylidene)amino]oxy]acetic Acid (49). A solution of 12.8 g (0.080 mol) of 5-chloro-2-acetylthiophene, 8.8 g (0.080 mol) of 2-(aminooxy)acetic acid hemihydrochloride,[20] and 19.6 g (0.240 mol) of NaOAc in 200 mL of 80% EtOH was refluxed for 5 h. After the mixture had stood overnight at room temperature, the sodium salt of **49** crystallized. This was collected (7.2 g). On concentrating the mother liquor, a second crop was obtained (3.0 g). The products (10.2 g, 50%) were mixed with 100 mL of 0.5 N hydrochloric acid and the mixture was extracted with Et_2O. The ethereal solution was washed with H_2O, dried, and then concentrated. The concentrate (8.0 g, 43%) was crystallized from 35 mL of C_6H_6, leaving 5.2 g (28%) of *E* isomer **49**. The filtrate of the sodium salts, after acidification, extraction, etc., gave a mixture of *E* and *Z* isomers, which were difficult to separate by crystallization.

Method a2. 2-[[(2-Chloro-α-methylbenzylidene)amino]oxy]acetic Acid (2). A solution of 5.0 g (0.032 mol) of 2′-chloroacetophenone and 3.6 g (0.032 mol) of 2-(aminooxy)acetic acid hemihydrochloride[20] in a mixture of 15 mL of pyridine and 40 mL of EtOH was refluxed for 1 h. Then the mixture was concentrated in vacuo, mixed with aqueous NaOH (0.040 mol), and extracted with Et_2O. The aqueous solution was then acidified (40 mL of 2 N HCl) and extracted again with Et_2O. This latter extract was dried. After removal of the solvent, the residue (5.4 g, 74%) was recrystallized: yield, 3.7 g of a mixture of *E* and *Z* isomers of **2**.

Method b and Separation of *E* and *Z* Isomers. *E* and *Z* Isomer of the *O*-(2-Hydroxyethyl) Oxime of 2-Acetyl-5-chlorothiophene (56 and 57). 2-Acetyl-5-chlorothiophene (3.2 g, 0.020 mol), 2.3 g (0.020 mol) of 2-(aminooxy)ethanol hydrochloride (method p, see below), and 4.9 g (0.060 mol) of NaOAc were dissolved in 100 mL of 80% EtOH and the solution was refluxed for 10 h. The mixture was concentrated in vacuo and the concentrate mixed with 100 mL of H_2O and 50 mL of Et_2O. Then the layers were separated and the aqueous layer was extracted with Et_2O. The combined ethereal solutions were washed with H_2O, dried, and concentrated. The concentrate (4.0 g) was chromatographed (CH_2Cl_2), giving 1.5 g (34%) of *E* stereoisomer of the product. Continuing the elution with CH_2Cl_2–Me_2CO (1:1) gave 2.3 g (53%) of the *Z* isomer. Both products were recrystallized.

***E* and *Z* Isomer of the *O*-(2-Hydroxyethyl) Oxime of 4-Chlorobenzaldehyde (53 and 54).** In the same way as before, 4-chlorobenzaldehyde was condensed with 2-(aminooxy)ethanol. In this case the product (4 g) crystallized after removal of the solvent. Recrystallization from 100 mL of petroleum ether, bp 40–60 °C, containing 5% C_6H_6 gave 3 g (83%) of the *E* isomer. Chromatography [CH_2Cl_2–Me_2CO (9:1)] of the mother liquor gave 0.1 g (3%) of the *Z* isomer.

Method c. 2-[2-(4-Chlorobenzylidene)hydrazino]acetic Acid (62). A solution of 9.83 g (0.070 mol) of 4-chlorobenzaldehyde, 11.9 g (0.077 mol) of the ethyl ester of 2-hydrazinoacetic acid,[21] and 17.20 g (0.21 mol) of NaOAc in 350 mL of 80% EtOH was refluxed for 2.25 h. The solvent was removed in vacuo and the residue was shaken with 200 mL of H_2O and 100 mL of Et_2O. The layers were separated and the aqueous one was washed once more with Et_2O. The combined ethereal solution was washed with H_2O, dried, and concentrated. To the residue a solution of 10 g of NaOH in 250 mL of EtOH was added and the mixture refluxed for 1 h. Then the EtOH was removed in vacuo and the residue was mixed with 200 mL of H_2O and 100 mL of Et_2O, the layers were separated, and the aqueous layer was washed with Et_2O. After acidification (pH 4) of the aqueous layer with 2 N HCl, it was extracted with Et_2O. This ethereal extract was washed with H_2O, dried, and concentrated at a temperature below 50 °C.[22] The residue was recrystallized: yield 7.8 g (79%).

Method d. α-Bromopropionic acid was allowed to react with the sodium oximate at room temperature and α-bromoisobutyric acid at reflux temperature for 2 h, and 6-bromohexanoic acid was allowed to react with the oxime in the presence of NaOH in 70% EtOH (instead of NaOEt) by refluxing for 10 h.

2-[[(4-Chloro-α-methylbenzylidene)amino]oxy]propionic

Acid (68). To a solution of 1.85 g (0.080 mol) of Na in 150 mL of EtOH, 6.8 g (0.040 mol) of 4′-chloroacetophenone oxime was added. Then 8.6 g (0.056 mol) of 2-bromopropionic acid was added and the mixture stirred for 1 h. After concentration of the mixture in vacuo, the concentrate was mixed with H_2O and extracted with Et_2O. The aqueous solution was acidified and extracted with Et_2O. This Et_2O extract was washed with H_2O, dried, concentrated, and recrystallized: yield 4.5 g (47%).

Method e. In contrast to γ-butyrolactone (in the example noted below) β-propiolactone was allowed to react with a sodium oximate in benzene at +5 °C (2 h) and 2 h at room temperature.

4-[[(4-Chloro-α-methylbenzylidene)amino]oxy]butyric Acid (66). To a solution of 11.9 g (0.070 mol) of 4′-chloroacetophenone oxime in 28 mL of *N*-methyl-2-pyrrolidone was added 1.62 g (0.070 mol) of pieces of Na and the mixture stirred at 60 °C. After 6 h of stirring, the mixture was cooled to room temperature and 6.0 g (0.070 mol) of γ-butyrolactone was added. Then the reaction mixture was refluxed for 4 h, somewhat concentrated in vacuo, and (still warm) poured into 1 L of water. After removal of some undissolved material by filtration, the filtrate was acidified with AcOH. The precipitated acid was separated by suction and dissolved in acetone, and the solution was treated with "Norite". The solvent was removed and the residue recrystallized: yield 5.9 g (33%).

Methods f and g. For each experiment the oximate was freshly prepared. *In two preparations an explosion occurred when air was let into the evacuated flask containing the dry oximate. It is advisable to displace the air by N_2.* The halo compound was used in excess [1.5 times with $Br(CH_2)_4OH$] or in equimolar amount ($ClCH_2CONH_2$). **85** was purified by CC (CH_2Cl_2), the others by crystallization.

2-[[(4-Fluoro-α-methylbenzylidene)amino]oxy]acetamide (40). To a solution of 0.91 g (0.039 mol) of Na in 50 mL of EtOH, 6.0 g (0.039 mol) of 4′-fluoroacetophenone oxime was added. Then the solvent was removed in vacuo, the evacuated flask filled with N_2, and the residue dissolved in 75 mL of DMF. To this solution 3.7 g (0.039 mol) of 2-chloroacetamide was added and the mixture stirred for 18 h. The solvent was removed in vacuo below 60 °C and the residue shaken with 75 mL of $CHCl_3$ and 75 mL of H_2O. The layers were separated and the aqueous layer was extracted twice with 75-mL portions of $CHCl_3$. The extract was washed with H_2O, dried, and concentrated in vacuo. The concentrate (8.6 g) was crystallized from 60 mL of C_6H_6 giving 5.5 g (67%) of **40**.

Method h. With ethylene oxide an excess of oxide was used (example) and with propylene oxide equimolar amounts of oxide and oxime were used.

***O*-(2-Hydroxyethyl) Oxime of 4′-Chloroacetophenone (81).** Lithium (4.9 g, 0.7 mol) was dissolved in 400 mL of MeOH. This solution was mixed with 1.2 L of EtOH and then 322 g (1.90 mol) of 4′-chloroacetophenone oxime was dissolved in it. With stirring at 55–60 °C, 140 g (3.20 mol) of ethylene oxide was introduced in the course of 1.5 h. After stirring for another 1 h at 55–60 °C, 50 mL of AcOH was added and the mixture concentrated in vacuo. The concentrate was mixed with 1 L of H_2O and 1 L of Et_2O, the layers were separated, and the water layer was extracted with 500 mL of Et_2O. The combined ethereal solutions were washed twice with 300-mL portions of H_2O, dried, and concentrated. The concentrate was fractionated at 0.7 mm and the fraction with bp 120–160 °C (0.7 mm) (264 g) was purified by CC [C_6H_6–EtOAc (3:1)]: yield 203 g (50%). Recrystallization from 3 L of petroleum ether, bp 40–60 °C, containing 4% C_6H_6 gave 166 g.

Method i. This reaction was carried out with (e.g., EtOH) or without a solvent and both at room temperature and a reflux temperature, and progress was followed by TLC.

***N*-Methyl-2-[[(4-chloro-α-methylbenzylidene)amino]-oxy]acetamide (79).** A mixture of 5.0 g (0.021 mol) of the methyl ester of 2-[[(4-chloro-α-methylbenzylidene)amino]oxy]acetic acid (**33**) and 40 mL of a 35% aqueous $MeNH_2$ solution was stirred for 2 h. Then the mixture was extracted with Et_2O containing some $CHCl_3$. The extract was washed with H_2O and dried. After removal of the solvent, the product was recrystallized: yield 4.3 g (87%).

Method j. The esterifying alcohol was used as the solvent, except in the case of higher boiling alcohols, for which C_6H_6 was used, and sometimes the water formed was removed during the reaction. Purification was carried out by vacuum distillation and/or CC and/or crystallization.

Methyl Ester of 2-[[(4-Chloro-α-methylbenzylidene)-amino]oxy]acetic Acid (33). A solution of 100 g (0.414 mol) of 2-[[(4-chloro-α-methylbenzylidene)amino]oxy]acetic acid in 500 mL of MeOH was mixed with 6 mL of 96% H_2SO_4 and then refluxed for 8 h. The solution was concentrated in vacuo and the concentrate mixed with 500 mL of Et_2O and 100 mL of H_2O. The layers were separated and the ethereal solution was washed with 100 mL of saturated $NaHCO_3$ solution, three times with 100 mL of 2 N NaOH, and twice with 100 mL of H_2O. After drying, the washed solution was concentrated and the concentrate mixed with 500 mL of petroleum ether, bp 40–60 °C, seeded, and stored at about 5 °C. The crystallized ester was separated and by concentrating the mother liquor a second crop was obtained: yield 93 g (87%).

Methods k, l, and m. This procedure was used for basic as well as neutral esters. In some cases, especially neutral esters, pyridine was used for binding of the HCl. If the esterifying HO– compound was poorly soluble in benzene, other inert solvents (e.g., DMF) were used instead. For the preparation of basic esters with a secondary NH function, equimolar amounts of the hydrochloride of the amino alcohol and the acid chloride were allowed to react in DMF solution. In that case the ester was purified in the basic form, as were the tertiary amino compounds, but immediately after the washing converted to the hydrochloride.

Hydrochloride of 2-(Dimethylamino)ethyl (*E*)-[[(4-Chloro-α-methylbenzylidene)amino]oxy]acetate (36). To a suspension of 45.5 g (0.200 mol) of 2-[[(4-chloro-α-methylbenzylidene)amino]oxy]acetic acid (**7**) in 260 mL of C_6H_6 was added 21.6 mL (0.3 mol) of $SOCl_2$ and the mixture was refluxed for 1.25 h. Then the reaction mixture was concentrated in vacuo to about 150 mL. After the addition of 100 mL of C_6H_6, the solution was concentrated again to 150 mL. The concentrate, containing the acid chloride of the starting acid, was cooled in an ice bath and then mixed with a solution of 40 g (0.44 mol) of 2-(dimethylamino)ethanol in 400 mL of C_6H_6. After standing overnight the precipitated material was removed by suction filtration and washed with Et_2O. The filtrate was washed with 50 mL of H_2O, three times with 30-mL portions of 10% $NaHCO_3$ solution and three times with 50-mL portions of H_2O. Then the benzene–ether solution was dried and concentrated. The concentrate (53.2 g, 89%) was mixed with 100 mL of EtOH and then acidified with an HCl solution in EtOH to pH 3–4. After standing overnight at +5 °C, the crystallized material was collected by suction filtration and dried at room temperature: yield 42.0 g (63%).

Method n. *Z* Isomer of 2-[[(5-Chloro-α-methylthenylidene)amino]oxy]acetic Acid (58). HCl gas was bubbled for 1 h through a solution of 2.0 g (0.0086 mol) of the *E* isomer **49** in 100 mL of Et_2O. After the solution had stood overnight, HCl was introduced again for 1 h. After standing 1 h, the crystallized product (1.24 g, 53%) was separated by suction and mixed with 15 mL of water, and this suspension was extracted with Et_2O. The extract was washed with H_2O, dried, and concentrated. Crystallization of the concentrate from C_6H_6 gave 0.73 g (37%) of the *Z* isomer.

Method o. *O*-(2-Pivaloyloxyethyl) Oxime of 4′-Chloroacetophenone (83). To a solution of 4.3 g (0.020 mol) of **81** in 50 mL of pyridine, a solution of 3.6 g (0.030 mol) of pivaloyl chloride in 50 mL of C_6H_6 was gradually added at 0 °C with stirring and cooling. After overnight stirring the mixture was concentrated in vacuo and the residue mixed with 100 mL of H_2O and 40 mL of Et_2O. After separation, the aqueous phase was extracted again with Et_2O. The ethereal solution was washed with H_2O, $NaHCO_3$ solution, and H_2O again. Then it was dried and concentrated (5 g), and the concentrate distilled at 0.8 mm: yield 4.4 g (74%).

Method p. 2-(Aminooxy)ethanol Hydrochloride. A solution of 12 g (0.056 mol) of **81** in 550 mL of EtOH and 550 mL of 5 N HCl was heated to 60 °C for a short time. After cooling it was continuously extracted in the course of 20 h with petroleum ether (bp 40–60 °C). The extracted acid solution was concentrated in vacuo; the concentrate was dissolved in 50 mL of H_2O and extracted with three 20-mL portions of Et_2O. Then the water was removed from the aqueous solution by concentrating in vacuo, adding C_6H_6, and azeotropic (vacuum) distillation: residue 5.0

g (0.044 mol, 79%) of the product; pure in TLC.

Acknowledgment. We gratefully acknowledge the collaboration in our laboratories with Messrs. W. de Koning, H. A. W. Lüschen, and K. Groendijk in the syntheses, Mr. R. Mooyman and Mr. G. Breman concerning the NMR analyses, and Mr. A. Vedder with respect to the pharmacological experiments. The elemental microanalyses were carried out in the laboratory of Drs. F. Pascher and E. Pascher, Bonn, West Germany, and by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of W. J. Buis.

References and Notes

(1) J. van Dijk, H. B. A. Welle, V. Claassen, Th. A. C. Boschman, and J. E. Davies, *Chim. Ther.*, **5**, 366 (1970).
(2) A. Hantzsch and W. Wild, *Justus Liebigs Ann. Chem.*, **289**, 285 (1896).
(3) A. Werner and E. Sonnenfeld, *Ber. Dtsch. Chem. Ges.*, **27**, 3350 (1894).
(4) M. Anchel and R. Schoenheimer, *J. Biol. Chem.*, **114**, 539 (1936).
(5) D. O. Holland and F. A. Robinson, *J. Chem. Soc.*, 182 (1948).
(6) A. Richardson, Jr., *J. Med. Chem.*, **7**, 824 (1964).
(7) A. Buzas, A. Dehnel, C. Egnell, C. Herrison, E. Bourillet, P. Linee, and J. C. Simon, *Chim. Ther.*, **7**, 135–142 (1972).
(8) G. Breman (Philips-Duphar Research Laboratories), unpublished results.
(9) P. B. Braun and J. Hornstra (Philips Research Laboratories, Eindhoven), unpublished results.
(10) J. Tipker (Philips-Duphar Research Laboratories), unpublished results.
(11) J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.*, **43**, S129 (1965).
(12) T. Y. Shen, *Chim. Ther.*, **2**, 459 (1967).
(13) P. F. Juby, W. R. Goodwin, T. W. Hudyma, and R. A. Partyka, *J. Med. Chem.*, **15**, 1302 (1972).
(14) Tested as the hydrochloride; code number DU 22599; international nonproprietary name, Cloximate.
(15) G. van den Berg, T. Bultsma, and W. Th. Nauta, *Biochem. Pharmacol.*, **24**, 1115 (1975).
(16) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
(17) D. J. Finney, "Statistical Methods in Biological Assay", Charles Griffin and Co., Ltd., London, 1952, p 27.
(18) H. J. Horn, *Biometrics*, **12**, 311 (1956).
(19) S. Irwin, *Psychopharmacologia*, **13**, 222 (1968).
(20) H. S. Anker and H. T. Clarke, *Org. Synth.*, **27**, 15 (1947).
(21) A. Carmi, G. Polak, and H. Yellin, *J. Org. Chem.*, **25**, 44–46 (1960); A. Darapski and M. Prabhakar, *Ber. Dtsch. Chem. Ges.*, **45**, 1660 (1912).
(22) During one crystallization, complete decomposition occurred.
(23) M. S. Newman, W. Fones, and M. Renoll, *J. Am. Chem. Soc.*, **69**, 718 (1947).
(24) J. Kamlet, U.S. Patent 3 115 518; *Chem. Abstr.*, **60**, 9166d (1964).
(25) C. J. Wilson and H. H. Wenzke, *J. Am. Chem. Soc.*, **56**, 2025 (1934).
(26) H. S. Corey, Jr., J. R. D. Mc Cormick, and W. E. Swensen, *J. Am. Chem. Soc.*, **86**, 1884 (1964).

Notes

Electronic Factors in the Structure–Activity Relationship of Some 1,4-Benzodiazepin-2-ones

T. Blair and G. A. Webb*

Department of Chemical Physics, University of Surrey, Guildford, Surrey, England. *Received January 17, 1977*

Some significant correlations are observed between the CNS activities of a series of 59 benzodiazepines and some calculated electronic indices. The parameters concerned are the net charge on the carbonyl oxygen atom of the lactam ring and the total molecular dipole moment, correlations with the latter index being superior. The utility of the observed relationships is discussed.

It has been widely proposed[1-5] that geometrical factors play a major part in determining the chemical reactivity, and resultant pharmacological activity, of compounds containing lactam rings. The degree of nonplanarity of the amide group is thought to determine the lability of the lactam ring. However, if the geometry of the lactam ring remains essentially constant in a series of compounds then it is probable that electronic factors play an important role. This has been observed in a series of nine *N*-phenyl β-lactams with various phenyl substituents.[6] A good correlation is reported between rate constants for base hydrolysis of the amide linkage and Hammett substituent parameters.[6]

The 1,4-benzodiazepin-2-ones are a series of lactams including the clinically employed drugs diazepam, nitrazepam, oxazepam, and fluroazepam.[7] Although several empirical rules have been observed for the molecular design of these lactams with high central nervous system (CNS) activity,[8] so far no mechanistic rationale has been provided to account for these rules.

We report the results of some CNDO/2 molecular orbital calculations on 59 substituted 1,3-dihydro-2*H*-1,4-benzadiazepin-2-ones with a view to finding the electronic quantities most relevant to drug activity. The calculations are based upon atomic coordinates obtained from the crystal structure of diazepam (1-methyl-5-phenyl-7-chloro-1,3-dihydro-2*H*-benzodiazepin-2-one).[9] It is assumed that the placement and alteration of substituents does not affect the skeletal structure of the molecule. In the present context this is perhaps most tenuous for the replacement of the 1-methyl group by hydrogen (Chart I), since slight changes of lactam ring geometry are probably very critical to reactivity.[1-5]

Results and Discussion

CNDO/2 calculations were performed on a series of 25 substituted 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones with a variety of substituents in the 7 and 2′ positions (Chart