of XXVI in 200 ml of Et_2O and 300 ml of 5% aq NaOH with shaking at room temp, and the shaking was continued for a further 1 hr. The organic layer was sepd, washed (10% aq NaOH and H_2O), dried (K_2CO_3), and evapd to leave 2.6 g (88.1%) of XXV as a colorless oil: ir ν_{max}^{liquid} cm^{-1}, 1755 and 1645 (C=O).

3-Hydroxy-*N*-benzyl-9-azamorphinan (XX).—A suspension of 0.5 g of XXIII and 1.0 g of LAH in 100 ml of dry dioxane was refluxed for 6 hr and then the excess of LAH was decompd with H_2O. The organic layer was collected by decantation, dried ($MgSO_4$), and evapd to leave a solid, after trituration with hexane, which was recrystd from PhH–hexane to give 0.25 g (67.6%) of XX as colorless needles, mp 124–125°. XX·HCl was recrystd from EtOH to afford colorless needles: mp 245° dec; ir ν_{max}^{KBr} cm^{-1}, 3200 (OH); nmr δ (in CF_3COOH), 4.68 (2 H, s, $NCH_2C_6H_5$). *Anal.* ($_{22}H_{27}ClN_2O$), C, H, N.

3-Hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (XXI).—A suspension of 1.3 g of XXIV and 1 g of LAH in 80 ml of dry THF was refluxed for 7 hr, and the excess of LAH was decompd with H_2O. The organic layer was collected by decantation, dried ($MgSO_4$), and evapd to leave a yellow oil, which was solidified on trituration with Et_2O and recrystd from EtOH–Et_2O to afford 0.8 g (78.4%) of XXI as colorless prisms: mp 172–174°; ir ν_{max}^{KBr} cm^{-1}, 2750–2200 (N^+H); nmr δ (in $CDCl_3$) 4.07 (2 H, s, $ArCH_2N$), 8.26 (1 H, broad s, OH). *Anal.* ($C_{19}H_{26}ON_2$) C, H, N.

3-Hydroxy-*N*-phenethyl-9-azamorphinan (XXII).—A suspension of 2.6 g of XXV and 3.0 g of LAH in 200 ml of dry dioxane was refluxed for 6 hr and the excess LAH was decompd with H_2O. The organic layer was separated by decantation, dried ($MgSO_4$), and evapd to leave a colorless oil, which was solidified by trituration with Et_2O and then recrystd from EtOH to give 1.03 g (50.0%) of XXII as colorless prisms, mp 178–180°. This sample was identical with a standard sample in all aspects.

Acknowledgment.—We thank President A. Yanagisawa and Director O. Takagi of the Grelan Pharmaceutical Co. Ltd. for their encouragement. We also thank Miss A. Kawakami and Miss C. Yoshida for microanalyses, Mr. S. Hayashida and Mr. O. Koyama for technical assistance. We are also grateful to Dr. K. Fukumoto, Pharmaceutical Institute, Tohoku University for his helpful suggestions.

Potential Antiinflammatory Agents. Aralkoxyhydrouracils and Aralkoxyhydantoins[1]

L. SIMET, D. B. REISNER, B. J. LUDWIG, F. DÜRSCH, AND F. M. BERGER

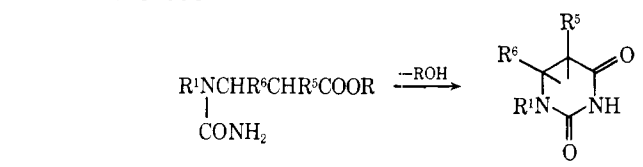
Wallace Laboratories, Division of Carter-Wallace, Inc., Cranbury, New Jersey 08512

Received June 16, 1970

A number of 1-aralkoxyhydrouracils and 1-aralkoxyhydantoins were prepared and evaluated as antiinflammatory agents. The hydrouracils were synthesized by a novel route from *N*-aralkoxyurethans and α,β-unsaturated carboxamides or from *N*-aralkoxyureas and α,β-unsaturated carboxylic esters. The hydantoins were prepared from *N*-aralkoxyureas by alkylation with bromo- or chloroacetic acid, followed by cyclization of the resultant α-ureido acids. The three most active 1-aralkoxyhydrouracils showed activities intermediate between those of aspirin and phenylbutazone against kaolin-induced inflammation of the rat foot. No consistent relationship could be found between the activities of the compounds described herein and the activities of their 1-aralkyl analogs.

Our long-standing interest in hydroxylamine derivatives,[2] bolstered by the finding that certain 1-aralkylhydrouracils possess antiinflammatory activity,[3] led us to investigate the synthesis and biological activity of a series of 1-aralkoxyhydrouracils (Table I) and 1-aralkoxyhydantoins (Table II). We first attempted to synthesize the 1-aralkoxyhydrouracils by the classical reaction sequence shown in Scheme I.[4]

SCHEME I



When R^1 is alkyl, the β-amino ester starting material may be prepared by addition of an amine to an α,β-unsaturated ester, by aminomethylation of an appropriately substituted malonic ester followed by decarboxylation, or by reduction of an enamine of a β-keto ester. However, when R^1 is aralkoxy, we found that only benzyloxyamine and a few ring-substituted benzyloxyamines could be added to ethyl acrylate and these amines failed to add to methyl methacrylate. The aminomethylation reaction and enamine reduction also failed to yield the esters needed for cyclization to C-5 and C-6 substituted 1-aralkoxyhydrouracils.

Since the classical sequence (Scheme I) proved to have limited utility in the aralkoxy series, we employed a synthetic route which utilized aralkoxyurethans or aralkoxyureas instead of aralkoxyamines (see Scheme II). This route provided the C-5 and C-6 substituted 1-aralkoxyhydrouracils as well as the C-5 and C-6 unsubstituted members in good yield.

The reaction of I with II depicted in Scheme II and the reaction of aralkoxyamines with acrylic esters both involve a Michael-type addition of a nucleophilic agent to an activated unsaturated system, yet the latter reaction is much more limited in scope than the former. Since the addition is a reversible reaction, we believe this difference is due to the tendency for the adduct III to undergo cyclization driving the addition step toward completion. The amino ester formed by addition of an aralkoxyamine to an acrylic ester cannot cyclize. It is unlikely that the observed difference in scope is a consequence of differences in the strengths of the nucleophilic agents involved.

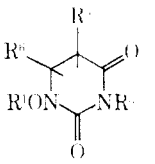
[1] A portion of this material was presented at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 7–11, 1969.

(2) B. J. Ludwig, F. Dürsch, M. Auerbach, K. Tomeczek, and F. M. Berger, *J. Med. Chem.*, **10**, 556 (1967).

(3) F. M. Berger, F. Dürsch, and B. J. Ludwig, U. S. Patent 3,325,360 (1967); *Chem. Abstr.*, **68**, 49642 (1968).

(4) See D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, pp 434–435, for a discussion.

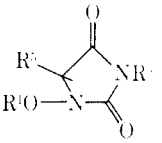
TABLE I
1-ARALKOXYHYDROURACILS



No.	R^1	R^3	R^5	R^6	Method	Mp or bp (mm), °C	Recrystn solvent or $n^{25}D$	Formula	Analyses	ED_{50}[a]
1	$C_6H_5CH_2$	H	H	H	A,B,C	138–139	EtOH	$C_{11}H_{12}N_2O_3$	C,H,N	135
2	$C_6H_5CH_2$	Me	H	H	D	85–86	MeOH	$C_{12}H_{14}N_2O_3$	C,H,N	>120
3	$C_6H_5CH_2$	H	Me	H	A	136–137.5	MeOH	$C_{12}H_{14}N_2O_3$	C,H,N	55
4	$C_6H_5CH_2$	H	H	Me	A	94.5–96.5	MeOH	$C_{12}H_{14}N_2O_3$	C,H,N	>120
5	$C_6H_5CH_2$	HO_2CCH_2	H	H	*b*	210.5–213	EtOH	$C_{13}H_{14}N_2O_5$	C,H,N	>150
6	$C_6H_5CH_2$	Allyl	H	H	D	147.5 (0.1)	1.5452	$C_{14}H_{16}N_2O_3$	C,H,N	>80
7	$C_6H_5CH_2$	H	H	C_6H_5	B	145.5–147.5	MeOH–H_2O	$C_{17}H_{16}N_2O_3$	C,H,N	
8	$C_6H_5CH_2$	$C_6H_5CH_2$	H	H	D	85–87	MeOH	$C_{18}H_{18}N_2O_3$	C,H,N	>150
9	3-$MeC_6H_4CH_2$	H	H	H	C	111–112	EtOH	$C_{12}H_{14}N_2O_3$	C,H,N	>200
10	2-$EtC_6H_4CH_2$	H	H	H	A	129–131	EtOAc	$C_{13}H_{16}N_2O_3$	C,H,N	>150
11	4-(*i*-Pr)$C_6H_4CH_2$	H	H	H	A	149.5–151.5	EtOH	$C_{14}H_{18}N_2O_3$	C,H,N	>150
12	3-$CF_3C_6H_4CH_2$	H	H	H	A	100.5–101.5	EtOH	$C_{12}H_{11}F_3N_2O_3$	C,H,F,N	>150
13	3-$MeOC_6H_4CH_2$	H	H	H	A	112.5–113.5	EtOH	$C_{12}H_{14}N_2O_4$	C,H,N	>120
14	4-$ClC_6H_4CH_2$	H	H	H	C	152.5–153.5	MeOH	$C_{11}H_{11}ClN_2O_3$	C,H,Cl,N	96
15	4-$ClC_6H_4CH_2$	H	Me	H	A	170–171	MeOH	$C_{12}H_{13}ClN_2O_3$	C,H,Cl,N	80
16	3,4-$Me_2C_6H_3CH_2$	H	H	H	A	147.5–149.5	EtOH	$C_{13}H_{16}N_2O_3$	C,H,N	>150
17	3,4-$Me_2C_6H_3CH_2$	Me	H	H	D	106.5–108.5	EtOH	$C_{14}H_{18}N_2O_3$	C,H,N	>150
18	3,4-$Me_2C_6H_3CH_2$	Allyl	H	H	D	43–51	Et_2O–hexane	$C_{16}N_{20}N_2O_3$	C,H,N	>150
19	3,4-$Me_2C_6H_3CH_2$	Pr	H	H	D	62.5–64.5	EtOH–ligroin	$C_{16}H_{22}N_2O_3$	C,H,N	>150
20	3,4-$Cl_2C_6H_3CH_2$	H	H	H	C	158.5–159.5	MeOH	$C_{11}H_{10}Cl_2N_2O_3$	C,H,Cl,N	145
21	3,4-$CH_2O_2C_6H_3CH_2$	H	H	H	A	176–179	MeOH	$C_{12}H_{12}N_2O_5$	C,H,N	>150
22	C_6H_5CHMe	H	H	H	A	123.5–125.5	EtOAc	$C_{12}H_{14}N_2O_3$	C,H,N	>100
23	3,4-$Cl_2C_6H_3CHMe$	H	H	H	A	160–161	MeOH	$C_{12}H_{12}Cl_2N_2O_3$	C,H,Cl,N	65
24	4-FC_6H_4CHEt	H	H	H	A	121.5–123	MeOH	$C_{13}H_{15}FN_2O_3$	C,H,F,N	48
25	4-FC_6H_4CHEt	H	Me	H	A	89–95[c]	*i*-PrOH–Et_2O	$C_{14}H_{17}FN_2O_3$	C,H,F,N	>45
26	1-Indanyl	H	H	H	A	147.5–148.5	MeOH	$C_{13}H_{14}N_2O_3$	C,H,N	>150
27	$C_6H_5(CH_2)_2$	H	H	H	A	81–82	EtOAc–Et_2O	$C_{12}H_{14}N_2O_3$	C,H,N	>100
28	$C_6H_5(CH_2)_3$	H	H	H	A	127–129	MeOH	$C_{13}H_{16}N_2O_3$	C,H,N	120
29	(2-C_5H_4N)CH_2[d,e]	H	H	H	A	182.5–184.5	EtOH	$C_{10}H_{12}ClN_3O_3$	C,H,Cl,N	>150
30	(2-C_4H_3S)CH_2[f]	H	H	H	A	126–128	EtOH	$C_9H_{10}N_2O_3S$	C,H,N,S	>120
31	2,4-$Cl_2C_6H_3O(CH_2)_2$	H	H	H	A	132–134	MeOH	$C_{12}H_{12}Cl_2N_2O_4$	C,H,Cl,N	>150
32	Me	H	H	C_6H_5	B	152–153.5	EtOH	$C_{11}H_{12}N_2O_3$	C,H,N	
33	H	H	H	H	E	214–215	MeOH	$C_4H_6N_2O_3$	C,H,N	150
34	H	$C_6H_5CH_2$	H	H	E	119–121	*i*-PrOH–Et_2O	$C_{11}H_{12}N_2O_3$	C,H,N	>150

[a] Dose, mg/kg, producing 50% inhibition of kaolin-induced inflammation in rats; see text for details of method. [b] See Experimental Section. [c] Diasteriomeric mixture. [d] 2-Pyridylmethyl. [e] HCl salt. [f] 2-Thenyl.

TABLE II
1-ARALKOXYHYDANTOINS

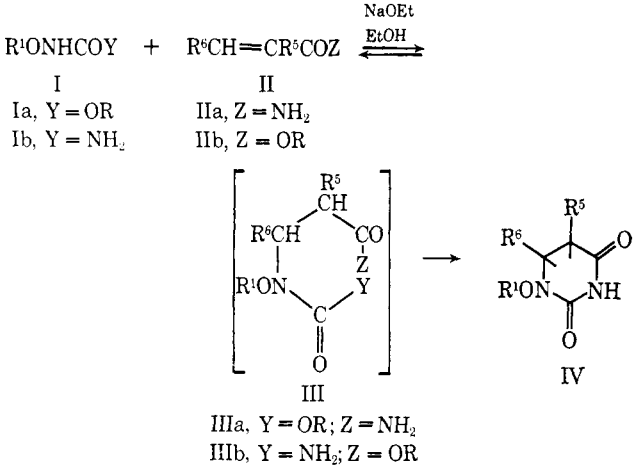


No.	R^1	R^3	R^5	Method	Mp, °C	Recrystn solvent	Formula	Analyses	ED_{50}[a]
35	$C_6H_5CH_2$	H	H	F	165–166	MeOH	$C_{10}H_{10}N_2O_3$	C,H,N	93
36	$C_6H_5CH_2$	H	Me	F	107–109.5	MeOH–H_2O	$C_{11}H_{12}N_2O_3$	C,H,N	>150
37	*m*-$MeC_6H_4CH_2$	H	H	F	119–120.5	MeOH–H_2O	$C_{11}H_{12}N_2O_3$	C,H,N	>150
38	*p*-$ClC_6H_4CH_2$	H	H	F	159–160.5	MeOH	$C_{10}H_9ClN_2O_3$	C,H,Cl,N	>150
39	*p*-$ClC_6H_4CH_2$	Me	H	D	125–126.5	$CHCl_3$–hexane	$C_{11}H_{11}ClN_2O_3$	C,H,Cl,N	>150
40	$C_6H_5(CH_2)_3$	H	H	F	74.5–76.5	MeOH–H_2O	$C_{12}H_{14}N_2O_3$	C,H,N	>50
41	2,4-$Cl_2C_6H_3O(CH_2)_2$	H	H	F	145.5–148	MeOH	$C_{11}H_{10}Cl_2N_2O_4$	C,H,Cl,N	125
42	H	H	H	E	145–147.5	EtOH	$C_3H_4N_2O_3$	C,H,N	>150
43	3-Benzyloxyhydantoin			*b*	119–121	EtOH	$C_{10}H_{10}N_2O_3$	C,H,N	140

[a] See footnote *a* in Table I. [b] See Experimental Section.

Although we have used the reactions of Ia with IIa and Ib with IIb interchangeably, we have noted a difference in the steric requirements for the respective reactants. Benzyloxyurethans, including those with bulky substituents such as *o*-ethylbenzyloxy- and α-ethylbenzyloxyurethan, react readily with acrylamide. Benzyloxyurethan itself, however, fails to react with cinnamamide even at elevated temperatures. Benzyl-

SCHEME II



IIIa, Y = OR; Z = NH_2
IIIb, Y = NH_2; Z = OR

oxyurea, on the other hand, reacts smoothly with methyl cinnamate. It appears that when R^1 in Ia is α-aralkyl, the presence of an R^6 aromatic substituent in IIa inhibits the reaction. The reaction of Ib with IIb is not subject to this limitation.

We have not found published reports of condensations of urethans with α,β-unsaturated amides analogous to the reaction of Ia with IIa for the preparation of 1-alkyl- or 1-aralkylhydrouracils. Urea has been condensed with α,β-unsaturated acids[5] and esters[6] in reactions analogous to that of Ib with IIb to give hydrouracils having no substituents at N^1 and N^3.

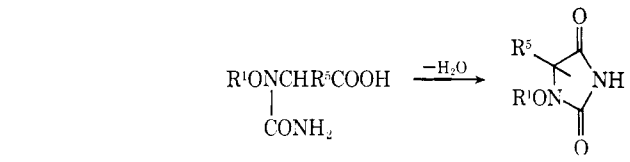
The reaction of Ib with IIb yields a single product of unambiguous structure even though Ib is an unsymmetrical urea. The aralkoxy substituent renders the N^1-H much more acidic than the N^3-H. Under the alkaline conditions of the reaction, the anion is formed preferentially at N^1, and this N becomes attached to the β-C atom of the carboxylic ester.

Two of the 1-aralkoxyhydrouracils, **1** and **16**, were treated with several alkyl halides under alkaline conditions to obtain the corresponding 3-alkyl dreivatives. 1-Benzyloxyhydrouracil (**1**) and its 3-benzyl derivative 8 were debenzylated by catalytic hydrogenation to obtain the corresponding 1-hydroxyhydrouracils **33** and **34**.

We attempted the synthesis of 1-aralkoxyhydantoins by an alkylation–cyclization sequence analogous to that of I with II using benzyloxyurethan and α-haloamides or benzyloxyurea and α-halo esters. We were unable to isolate either the desired hydantoin or its open-chain precursor. Consequently, the 1-aralkoxyhydantoins in Table II were prepared by a 2-step route consisting of alkylation of an aralkoxyurea with an α-halo acid in aq NaOH, followed by cyclization of the intermediate ureido acid by heating with $SOCl_2$ or PCl_3 in anhyd dioxane (Scheme III). We found aq mineral acid to be unsatisfactory for the cyclization of these aralkoxyureido acids.

3-Benzyloxyhydantoin (**43**) was prepared for comparison with the isomeric 1-benzyloxyhydantoin (**35**). It was obtained by the reaction of benzyloxyamine with ethyl isocyanatoacetate followed by cyclization of

SCHEME III



the resulting ω-benzyloxyhydantoic ester with anhyd HCl in abs EtOH.

The aralkoxy compounds described here were isolated as white to light tan solids. Their uv and ir spectra have the same characteristics as those of the corresponding aralkyl compounds, and the pmr spectra show only one significant difference. The aralkoxy α-H resonates at about a 0.4 ppm lower field than the corresponding aralkyl α-H.

Antiinflammatory Activity.—The 1-aralkoxyhydantoins and 1-aralkoxyhydrouracils prepared in this study were evaluated for their antiinflammatory activity in rats according to a modification of the method of Hillebrecht.[7] In this method the inflammation is produced by injection of 0.05 ml of a 10% aq kaolin suspension sc in the upper planar surface of the rat foot. The compounds are administered ip 60 min before and 60 min after the kaolin injection. Five hours after the kaolin injection, the volume of the kaolin-injected foot is compared with the volume of the vehicle-injected foot for each rat. The compounds are administered in various doses, and 6 rats are used for each dose.

To compute the antiinflammatory value of the test compound, the volume of the control foot is subtracted from the volume of the inflamed foot. The volume differences of the rats in each dose group are averaged and the ED_{50} value, obtained by plotting the per cent of inhibition of inflammation against the log of the dose, is the dose which will inhibit inflammation by 50%.

The antiinflammatory activities of the compounds are included in Tables I and II. Neither series of compounds possessed outstanding antiinflammatory activity, and the hydantoin derivatives were especially inactive according to this assay procedure. The most active members of the hydrouracil series, **3**, **23**, and **24**, possessed an activity intermediate between that of aspirin (ED_{50} = 76) and phenylbutazone (ED_{50} = 41).

A comparison of the antiinflammatory activities presented here with those of the corresponding 1-aralkylhydrouracils[3] reveals that no consistent activity relationship exists within these two series of compounds. The ED_{50} value for 3,4-dichloro-α-phenethylhydrouracil, the most active compound reported by Berger, *et al.*,[3] was 35 mg/kg compared with 65 mg/kg for the corresponding hydroxylamino analog **23**. However, **3** possessed somewhat greater activity than its aralkyl counterpart. Substitution in the heterocyclic nucleus had little effect on the antiinflammatory activity.

The LD_{50} (ip) values in the rat for these aralkoxy hydrouracils and hydantoins ranged from about 500 to about 2000 mg/kg.

(5) E. Fischer and G. Roeder, *Ber.*, **34**, 3751 (1901).
(6) E. Philippi and E. Spenner, *Monatsh. Chem.*, **36**, 97 (1915).
(7) J. Hillebrecht, *Arzneimittel-Forsch.*, **9**, 625 (1959).

TABLE III
INTERMEDIATE HYDROXYLAMINE DERIVATIVES
$R^1ONR^2R^3$

No.	R^1	R^2	R^3	Mp or bp (mm), °C	Recrystn solvent or n_D (°C)	Formula	Analyses
44	3,4-$CH_2O_2C_6H_3CH_2$ Et |	H	COOEt	57–59	*i*-Pr_2O	$C_{11}H_{13}NO_5$	C,H,N
45	4-FC_6H_4CH	H	COOEt	116 (0.5)	1.4900 (25)	$C_{12}H_{16}FNO_3$	H,F,N,C[a]
46	1-Indanyl	H	COOEt	*b*	1.5335 (25.5)	$C_{12}H_{15}NO_3$	C,H,N
47	(2-C_5H_4N)CH_2[c]	H	COOEt	76–77.5	EtOH	$C_9H_{12}N_2O_3$	C,H,N
48	(2-C_4H_3S)CH_2[d]	H	COOEt	103.5 (0.08)	1.5232 (25.5)	$C_8H_{11}NO_3S$	C,H,N,S
49	4-$ClC_6H_4CH_2$	H	$CONH_2$	162–163.5	EtOH	$C_8H_9ClN_2O_2$	C,H,Cl,N
50	$C_6H_5(CH_2)_3$	H	$CONH_2$	89.5–91	C_6H_6	$C_{10}H_{14}N_2O_2$	C,H,N
51	$C_6H_5CH_2$	H	CH_2CH_2COOMe	88–90 (0.2)	1.5063 (23.5)	$C_{11}H_{13}NO_3$	C,H,N
52	3-$MeC_6H_4CH_2$	H	CH_2CH_2COOMe	103 (0.05)	1.5046 (25.5)	$C_{12}H_{17}NO_3$	C,H,N
53	4-$ClC_6H_4CH_2$	H	CH_2CH_2COOMe	112–116.5 (0.1)	1.5206 (25.2)	$C_{11}H_{14}ClNO_3$	C,H,Cl,N
54	3,4-$Cl_2C_6H_3CH_2$	H	CH_2CH_2COOMe	134–136 (0.07)	1.5315 (25.5)	$C_{11}H_{13}Cl_2NO_3$	[e]
55	$C_6H_5CH_2$	$CONH_2$	CH_2COOH	148–149 dec	$CHCl_3$	$C_{10}H_{12}N_2O_4$	C,H,N
56	3-$MeC_6H_4CH_2$	$CONH_2$	CH_2COOH	153 dec	EtOH–H_2O	$C_{11}H_{14}N_2O_4$	C,H,N
57	4-$ClC_6H_4CH_2$	$CONH_2$	CH_2COOH	148–149.5 dec	[f]	$C_{10}H_{11}ClN_2O_4$	[e]
58	$C_6H_5CH_2$	$CONH_2$	CH_2CH_2COOMe	98–100	EtOH	$C_{12}H_{16}N_2O_4$	C,H,N
59	3-$MeC_6H_4CH_2$	$CONH_2$	CH_2CH_2COOMe	89–91	EtOH	$C_{13}H_{18}N_2O_4$	C,H,N
60	4-$ClC_6H_4CH_2$	$CONH_2$	CH_2CH_2COOMe	80.5–83	Et_2O	$C_{12}H_{15}ClN_2O_4$	C,H,Cl,N
61	3,4-$Cl_2C_6H_3CH_2$	$CONH_2$	CH_2CH_2COOMe	67–68.5	Et_2O	$C_{12}H_{14}Cl_2N_2O_4$	C,H,Cl,N

[a] C: calcd, 59.74; found, 60.24. [b] Molecularly distilled under 3.8-μ pressure at a bath temperature of 107°. [c] 2-Pyridylmethyl. [d] 2-Thenyl. [e] Not analyzed. [f] Purified by dissolution in NaOH and reprecipitation with HCl.

Experimental Section[8]

The α-halo acids and the α,β-unsaturated esters and amides used in the procedures given below are commercially available. Most of the aralkoxyurethans and aralkoxyureas have been described previously.[2,9,10] The aralkoxyurethans not previously described (Table III) were prepared by alkylation of *N*-hydroxyurethan[2] with known aralkyl halides. New aralkoxyureas (Table III) were prepared by alkaline hydrolysis of the corresponding aralkoxyurethans, acidification of the reaction mixture, and addition of KNCO to the acid soln.

Preparation of 1-Aralkoxyhydrouracils. Method A.—A soln of 0.1 mole of NaOEt in 100–200 ml of anhyd EtOH was treated with 0.1 mole of *N*-aralkoxyurethan and stirred for 0.5 hr. The α,β-unsaturated amide (0.1 mole) was added and the soln was refluxed for 20–30 hr. The reaction mixture was acidified by addition of glacial AcOH and concentrated under reduced pressure. The crude product, generally in 50–80% yield, was washed with H_2O, dried, and purified by crystallization.

Method B.—The procedure is the same as for method A except that an *N*-aralkoxyurea was used in place of the *N*-aralkoxyurethan and an α,β-unsaturated carboxylic ester was used in place of the amide. Yields were comparable with those obtained with method A.

Method C.—A solution of 0.2 mole of an aralkoxyamine[2] and 0.2 mole of methyl acrylate in 100 ml of MeOH was refluxed for 5–10 hr. The MeOH was removed *in vacuo* and the residual β-aralkoxyaminopropionate was purified by distn (Table III).

The β-aralkoxyaminopropionate was treated with 1 equiv of HCl or H_2SO_4 (0.3–1.0 *N*), and to the resulting soln or suspension of its salt, 1 equiv of KNCO was added slowly. After being stirred for 1–2 hr, the resulting suspension was filtered and the β-ureidopropionate was washed with H_2O, dried, and purified by recrystallization (Table III).

A soln of 0.05 mole of the β-ureidopropionate in 200 ml of MeOH was added to a soln of 0.05 mole of NaOMe in 100 ml of MeOH and the mixture was refluxed for 1–5 hr. The MeOH was removed *in vacuo* and the residue was dissd or dispersed in cold H_2O. HCl was added to pH 6 and the product was separated by filtration, washed with H_2O, and recrystd. Overall yields based on aralkoxyamine were below 25%. In the case of **14**, the last step of this procedure yielded the β-ureidopropionic acid instead of the hydrouracil. The acid was cyclized by heating it on a steam bath with 5.5 times its weight of Ac_2O for 4 hr, shaking the reaction mixture with H_2O overnight, and separating the hydrouracil by filtration.

Alkylation of 1-Aralkoxyhydrouracils and 1-Aralkoxyhydantoins. Method D.—To a soln of 0.1 mole of NaOMe in 200 ml of MeOH was added 0.1 mole of the hydrouracil or hydantoin. The soln was stirred for 1.5 hr, then concd under reduced pressure. The residue was dissd or suspended in 200 ml of DMF and 0.1 mole of the alkyl halide was added, the temp of the reaction mixture being kept below 35° by regulating the rate of addn and by cooling. The reaction mixture was stirred for 1.5 hr after the addn, then heated at 50–70° for 4–8 hr. The DMF was removed *in vacuo* and the residue was treated with Et_2O and H_2O. The Et_2O layer was washed with dil NaOH and H_2O, then dried, and after removal of the Et_2O, the crude product was purified by crystn or distn. Yields before purification were 60–70%.

Debenzylation of 1-Benzyloxyhydrouracils and 1-Benzyloxyhydantoins. Method E.—A soln of 0.1 mole of the hydrouracil or hydantoin in 150 ml of EtOH or EtOH–H_2O, with 2.0 g of 5% Pd–C catalyst, was shaken at room temperature with H_2 at 3 atm. The reduction stopped when 1 equiv of H_2 was absorbed. The catalyst was removed, the solvent was evaporated, and the residue was recrystallized, yielding about 80% of purified product.

Preparation of 1-Aralkoxyhydantoins. Method F.—A soln of 0.1 mole of the aralkoxyurea in 105.5 g of 15% (w/w) aq KOH was chilled and 0.15 mole of the α-halo acid was added in portions with stirring and cooling. The resulting soln was stirred with cooling for 0.5 hr and then allowed to stand for 2–3 days. The pH of the soln was adjusted to 4–5 with AcOH, and the soln was filtered. The filtrate was acidified further to pH 1–2 and was refrigerated overnight during which time the α-ureido acid slowly pptd. The ureido acid, after filtn and washing with H_2O, was purified by recrystn (Table III).

The ureido acid was dissd or suspended in dioxane (5 ml g of acid) and PCl_3 (0.3 ml/g of acid) was added. The mixture was heated rapidly to reflux, refluxed for 15 min, then cooled, and poured onto ice, pptg the crude hydantoin. After filtering, washing with H_2O, and drying, the crude product (35% yield) was purified by recrystn.

The starting ureas for the preparation of **37** and **41**, and the intermediate α-ureido acids for **36**, **40**, and **41** were used without purification or characterization.

1-Benzyloxy-3-carboxymethylhydrouracil (5).—A suspension of the Na salt of **1** in DMF was prepared as described in method D and a suspension of 1 equiv of Na chloroacetate in DMF was added all at once. The reaction mixture was heated at 70–75° for

(8) Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Analyses were performed by the Galbraith Laboratories, Knoxville, Tenn. 37921.

(9) B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 1381 (1962).

(10) L. W. Jones and R. T. Major, *J. Amer. Chem. Soc.*, **49**, 1527(1927).

13 hr, after which the DMF was removed *in vacuo*. The residue was washed with abs Et_2O, dissolved in H_2O, and the soln was acidified with HCl. The product was removed by filtration, washed with H_2O, and dried. Purification was effected by recrystn.

3-Benzyloxyhydantoin (43).—A soln of 36.9 g of benzyloxyamine and 38.7 g of ethyl isocyanatoacetate in 300 ml of abs Et_2O was refluxed for 1.25 hr. The Et_2O was removed *in vacuo*, 250 ml of 3.9 *M* HCl in abs EtOH was added to the residue, and the soln was refluxed for 2 hr. About 100 ml of EtOH was evaporated under reduced pressure and the remainder of the soln was refrigerated, yielding 14.6 g of product which was sepd by filtration and purified by recrystn.

Acknowledgment.—The authors wish to acknowledge the valuable assistance of Miss Kazimiera Tomeczek and Melvin Auerbach for their contributions in the preparation of some of the compounds described in this publication.

Aminobenzoic Acid Diuretics. 1. 4-Halogeno-5-sulfamylmetanilic Acid Derivatives

Peter W. Feit, Herta Bruun, and Christian Kaergard Nielsen

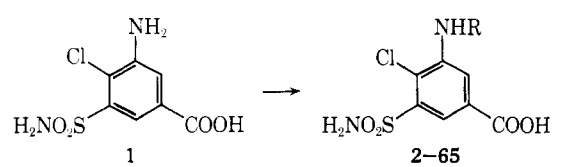
Leo Pharmaceutical Products, 2750 Ballerup, Denmark

Received June 22, 1970

Sixty-seven N-substituted 4-halogeno-5-sulfamylmetanilic acids were prepared from the corresponding metanilic acids by different alkylation processes. The compounds were screened in dogs for their diuretic and saluretic properties and compared with 3 selected N-substituted 4-chloro-5-sulfamylanthranilic acids including furosemide, a well-established, high-ceiling diuretic. Several compounds of the new metanilic acid derivatives were found to possess activity to be comparable with that of the anthranilic acid series. However, there are differences in the influence of the N-substituent on the activity. The dose–response curves after iv and oral administration for *N*-*n*-butyl-4-chloro-5-sulfamylmetanilic acid (**45**) are presented.

Among the sulfonamide diuretics certain 4-halogeno-5-sulfamylanthranilic acid derivatives showed an outstanding characteristic of structure and diuretic effect.[1] The most interesting compound of this series is 4-chloro-*N*-(2-furylmethyl)-5-sulfamylanthranilic acid (furosemide), a well-established, nonthiazid type, high-ceiling diuretic.[2] To the best of our knowledge the corresponding metanilic acid derivatives have never been investigated. Consequently, in line with our interest in the structure–activity relationship of diuretics, we decided to determine what effect the moving of the substituted amino group from the 2 to the 3 position would have on the saluretic and diuretic effect.

Chemistry.—The N-alkylated 4-chloro-5-sulfamylmetanilic acids[3] (**2**–**65**) listed in Tables I and II were prepared by alkylation of 4-chloro-5-sulfamylmetanilic acid (**1**) using different alkylation processes. Details are given in the Experimental Section. Dialkylation and attack at the sulfonamide nitrogen could be avoided. The required metanilic acid **1** was available from 4-chloro-5-chlorosulfonylbenzoic acid by nitration followed by amidation to 4-chloro-3-nitro-5-sulfamylbenzoic acid and reduction of the NO_2 group. The bromo analogs (**66**, **67**, **68**) were prepared in a similar way and are listed in Table III.



1 **2–65**

Diuretic Effect and Structure–Activity Relationships.—Although the metanilic acid derivatives described in this paper are related in structure to the corresponding anthranilic acid derivatives, it does not follow that these compounds should possess similar activities. The derivatives were screened in dogs for their saluretic and diuretic properties following 10 mg/kg iv (solution in NaOH). For details see the Experimental Section. The urinary volume and electrolyte excretion from the 3-hr test period for those compounds resulting in a Na^+ excretion ≥ 1.5 mequiv per kg per 3 hr are summarized in Table IV. The onset of diuresis was within 1 hr after injection and became almost negligible after 3 hr.

Compared with 3 selected anthranilic acid derivatives including furosemide the results (Table IV) indicate that in the metanilic acid series compounds could be found showing the same order of activity. The principal difference between these 2 series seems to be that *N*-2-methylfuryl substitution afforded outstanding activity[1] in the anthranilic acid series while in the metanilic acid series several N-substituted compounds approximated the corresponding *N*-2-methylfuryl compound in its activity. Generally, however, minor changes of the N-substituent had great influence on the activity. Compounds **45** and **66** carrying the *n*-Bu side chain were the most potent derivatives in the new series. Compound **45** was subjected, therefore, to further investigation. The dose–response curves after iv and oral dosage are given in Figures 1 and 2, respectively. After oral administration the onset of diuresis was still within the first hour. A prolonged effect at higher dosage levels made it necessary to extend the test period to 5 hr. It is interesting to note, that **45** is relatively inactive in the rat assay. Given orally only doses exceeding 80 mg/kg showed statistically significant diuretic action.

(1) K. Sturm, W. Siedel, R. Weyer, and H. Rushig, *Chem. Ber.*, **99**, 328 (1966).

(2) See R. Muschaweck and K. Sturm, "Arzneimittel," G. Ehrhart and H. Rushig, Ed., Vol. 1, Verlag Chemie, Weinheim, Germany, 1968, chapter 16, pp 700–703.

(3) P. W. Feit and H. Bruun, South African Patent 68/3145 (1968); *Chem. Abstr.*, **21**, 3141 (1969).