The Synthesis and Activity of Some 3-Substituted 1,2,3,4-Pseudooxatriazol-5-ones and Their Precursors and Related Compounds

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The synthesis of a variety of semicarbazides, aminoguanidines, thiosemicarbazides, hydrazines, and glycines, as well as many of their *N*-nitroso derivatives, are reported here. Some of the *N*-nitroso derivatives have been cyclized to the corresponding mesoionic compounds.

The synthesis and testing of some 3-substituted 1,2,3,4-pseudooxatriazol-5-ones and their precursors were undertaken as part of a study on potential antihypertensive agents. Some hypotensive activity had been found in a few 3-(lower alkyl)-substituted pseudooxatriazolones,[1] justifying further evaluation of this class of compounds. Most of the intermediates for the preparation of the target compounds were also tested for activity, and it was found that the 1-nitrososemicarbazides had considerably more activity than did the pseudooxatriazolones.

In past work on pseudooxatriazolones the 1-nitrososemicarbazides were usually cyclized without isolation.[1,2]

The pseudooxatriazolones were prepared by cyclization of the appropriate 1-nitrososemicarbazides. The procedure used by Boyer, *et al.*,[2] (adding a large excess of $NaNO_2$ to a cold aqueous acidic solution of the semicarbazide, followed, after a short time, by heating to about 60°) gave by-products which sometimes made purification of the pseudooxatriazolones difficult.

To avoid this problem no appreciable excess of HNO_2 was allowed during nitrosation, and when nitrosation was complete the nitroso compound was isolated when possible. If isolation was impractical any excess HNO_2 was destroyed with sulfamic acid or urea. The nitroso compound was then heated in dilute HCl to cause cyclization. In several instances the aqueous acid procedure was found to give no mesoionic compound, so a less severe route was devised: either the dry isolated 1-nitrososemicarbazide was refluxed with a slight excess of AcOH in a halocarbon, such as *n*-bromobutane, or a cold $CHCl_3$ slurry of the nitroso compound was treated with trifluoroacetic acid.

The semicarbazides, a number of which have not been previously reported, were made either by catalytic hydrogenation of the corresponding semicarbazone or by the action of HCNO on the hydrazine. The hydrazines were prepared by several different methods. Some of them were made from the amine by the sydnone method[3] shown in Scheme I.

In one case, that of *N*-(2,3,3-trimethyl-2-norcamphanyl)sydnone, the usual Ac_2O cyclization conditions were too severe for the *N*-nitrosoglycine, and complete decomposition occurred; a good yield of the sydnone was obtained by cyclizing with *N,N'*-dicyclohexylcarbodiimide. The sydnone, however, was very acid sensitive and none of the desired hydrazine could be obtained on acid hydrolysis. An attempt was thus made to circumvent the use of strongly acidic conditions by the sequence shown in Scheme II.

Since 1-(α-fenchyl)semicarbazide had already been unambiguously prepared, the sequence was first tried out on α-fenchylamine. Unfortunately the hydride reduction step could not be made to work satisfactorally, so this procedure was abandoned. 2,3,3-Trimethyl-2-norcamphanylhydrazine was finally prepared in very poor yield *via* the diaziridine by a slight modification of the Schmitz[4] procedure which is outlined in Scheme III.

Nitroso compounds with terpenoid residues were found to have the highest activity and the least toxicity, but, unfortunately, stability at ambient temperatures varied from poor to very poor. The presence of a basic group in the 1 position caused a great reduction in the already poor stability of the 1-nitrososemicarbazides; these derivatives rapidly cyclized to the corresponding pseudooxatriazolones.

Consequently it was decided to synthesize some S and N analogs to see if stability could be enhanced without loss of activity. Several (*N*-nitrosoalkylamino)guanidines were prepared by aqueous nitrosation of the corresponding (alkylamino)guanidines. The latter were made by: (a) the action of cyanamide or a substituted cyanamide on a mixture of the hydrazine and its hydrochloride,[5] (b) the action of an amine on the *S*-methylisothiosemicarbazide, or (c) the action of an *S*-methylpseudothiourea on the free hydrazine (see Scheme IV).

3-Substituted 1-(alkylamino)guanidines were best prepared by the last method. When an aminoguanidine hydriodide was formed conversion into the hydrochloride was necessary prior to nitrosation. Nitrosation of the hydriodide caused decomposition of the product. Since most of the alkylaminoguanidines were unstable as the free base the hydriodides were converted into the hydrochlorides using ion exchange resins. While this work was in progress the first report of this class of compounds was published by Finnegan and Henry,[6] though their compounds were apparently not tested for pharmacological activity.

It was found that the (*N*-nitrosoalkylamino)guanidines containing terpene residues had high activity,

(1) (a) L. B. Kier, personal communication; (b) L. B. Kier, A. Al-Shammari, D. Campbell, P. N. Patil, and A. Tye, *Nature*, **210**, 742 (1966).

(2) (a) J. H. Boyer, and J. A. Hernandez, *J. Amer. Chem. Soc.*, **78**, 5124 (1956); (b) J. H. Boyer, and F. C. Canter, *ibid.*, **77**, 1280 (1955).

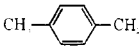
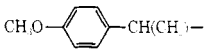
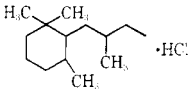
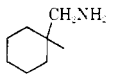
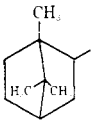
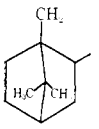
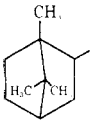
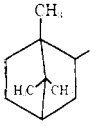
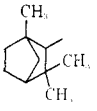
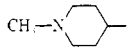
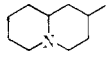
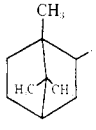
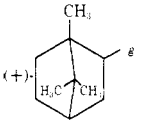
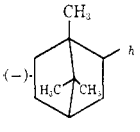
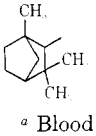
(3) B. V. Shetty, *J. Org. Chem.*, **26**, 3002 (1961).

(4) (a) E. Schmitz, and R. Ohme, *Ber.*, **95**, 680 (1962); (b) E. Schmitz, and D. Habisch, *ibid.*, **94**, 2166 (1961).

(5) A variation of the procedure developed by J. H. Paden and A. F. MacLean and reported in U.S. Patent 2,425,341 (1944).

(6) W. G. Finnegan and R. A. Henry, *J. Org. Chem.*, **30**, 567 (1965).

Table I: New Semicarbazides and Analogs, R—NHNH—C(=X)NR′R″

R	X	NR′R″	Method of prepn	Recrystn solvent	Yield, %	Mp, °C	Formula	Analyses	Act.[a]
$C_6H_5(CH_2)_2$	O	NH_2	B	*i*-PrOH	40	138–140	$C_9H_{13}N_3O$	C, H, N	–
	O	NH_2	B	*i*-PrOH	70	168–169	$C_9H_{13}N_3O$	C, H, N	–
	O	NH_2	B	*i*-PrOH	77	135–136	$C_{10}H_{15}N_3O_2$	C, H, N	–
	O	NH_2	A	EtOH–EtAc (1:2.5)	66	166–168[b]	$C_{14}H_{29}N_3O$	C, H, N, Cl	–
	O	NH_2	A	*i*-PrOH	67	178–179	$C_8H_{15}N_3O$	C, H, N	–
	O	NH_2	C	*i*-PrOH	54	237–238	$C_{11}H_{19}N_3O$	C, H, N	–
	O	NH_2	A	MeOH	59	216–220[b]	$C_8H_{20}Cl_2N_4O$	C, H, N, Cl	
	NH	$NHCH_3$	G		39	175–178[b]	$C_{12}H_{25}ClN_4$	C, H, N	+
	NH	$N(CH_3)_2$	F or G		37	219–221[c]	$C_{13}H_{27}IN_4$	C, H, N, I	+[d]
		NCH_2CH_2NH	G		46	160–161[c]	$C_{13}H_{25}IN_4$	C, H, N, I	–
	S	NH_2	C	*i*-PrOH	12	209.5–210	$C_{11}H_{21}N_3S$	C, H, N, S	–
	S	NH_2	C	MeOH	29	211–212	$C_{11}H_{21}N_3S$	C, H, N, S	–
	O	NH_2	A		60	169.5–172	$C_7H_{16}N_5O$	C, H, N	–
	O	NH_2	A		48	193.5–194.5 dec.	$C_{10}H_{20}N_5O$	H, N, C[e]	–
	O	NH_2	A	*n*-BuOH	89	184–187[f]	$C_8H_{18}Cl_2N_4O$	C, H, N, Cl	–
	NH	NH_2	E	*n*-BuOH	33	253–256[b]	$C_{11}H_{23}ClN_4$	C, H, N, Cl	+
	NH	NH_2	E	*n*-BuOH	30	256–261	$C_{11}H_{23}ClN_4$	C, H, N, Cl	+
	NH	NH_2	E	*n*-BuOH	35	258–262	$C_{11}H_{23}ClN_4$	C, H, N, Cl	+
	NH	NH_2	E	*i*-PrOH	38	221–226[b]	$C_{11}H_{23}ClN_4$	C, H, N, Cl	+

[a] Blood pressure lowering for a 5 mg/kg iv dose: – ≡ negligible, + ≡ ≤15%, ++ ≡ 15–30%, +++ ≡ ≥30%, ++++ ≡ ≥30% for a dose of 0.5 mg/kg. [b] Hydrochloride. [c] hydriodide. [d] Toxic (ED_{50} near LD_{50}). [e] Calcd; 56.57, found: 57.00. [f] Dihy-

TABLE II

NITROSOSEMICARBAZIDES AND ANALOGS, $RNNHC(=X)NR'R''$

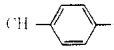
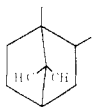
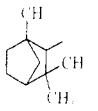
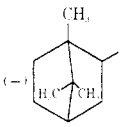
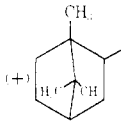
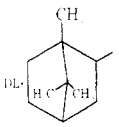
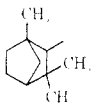
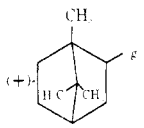
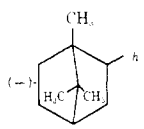
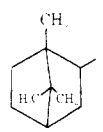
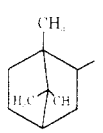
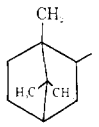
R	X	NR′R″	Recrystn solvent	Yield, %[a]	Mp, °C[b]	Formula	Analyses	Act[c]
$C_2H_5CH_2CH(CH_3)-$	O	NH_2	*i*-PrOH[b]	88	122–123	$C_6H_{14}N_4O_2$	C, H, N	+++[d]
$(CH_3)_2CHCH_2CH(CH_3)-$	O	NH_2	C_6H_6[b]	35[d]	108–109	$C_7H_{16}N_4O_2$	C, H, N	-
	O	NH_2	*i*-PrOH[b]	83	131–131.5	$C_9H_{12}N_4O_2$	H, N, C[e]	+[e]
	O	NH_2		52	101–102	$C_9H_{12}N_4O_2$	C, H, N	+++[e]
	O	NH_2	*i*-PrOH[b]	85	128–129	$C_{11}H_{20}N_4O_2$	C, H, N	++++
	O	NH_2		75	128–129	$C_{11}H_{20}N_4O_2$	C, H, N	++
	O	NH_2		91	129–130	$C_{11}H_{20}N_4O_2$	C, H, N	++++
	O	NH_2		95	128.5–129.5	$C_{11}H_{20}N_4O_2$	C, H, N	+++
	O	NH_2		78	128–129	$C_{11}H_{20}N_4O_2$	C, H, N	+++
	O	NH_2		85	99–101	$C_8H_{14}N_4O_2$	C, H, N[f]	++[e]
	O	NH_2		96	166	$C_{13}H_{18}N_4O_2$	C, H, N	-
	NH	NH_2		79	149–151	$C_{11}H_{21}N_5O$	C, H, N	+++
	NH	NH_2		96	153.5–155	$C_{11}H_{21}N_5O$	C, H, N	+++
	NH	NH_2		63	153–155	$C_{11}H_{21}N_5O$	C, H, N	+++
	NH	NH_2		74	151–154	$C_{11}H_{21}N_5O$	C, H, N	+++
	NH	$NHCH_3$		70	127–129	$C_{12}H_{23}N_5O$	C, H, N	++++
	NH	$N(CH_3)_2$		57	124–127	$C_{13}H_{25}N_5O$	C, H, N	++[e]

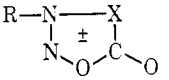
Table II (*Continued*)

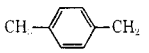
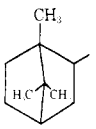
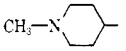
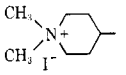
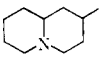
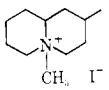
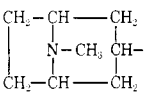
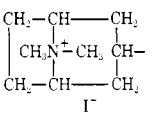
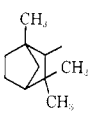
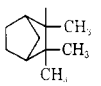
R	X	NR′R″	Recrystn solvent	Yield, %	Mp, °C[k]	Formula	Analyses	Act[a]
		NCH_2CH_2–NH	THF–hexane	20	163–165	$C_{13}H_{23}N_3O$	C, H, N	
	O	NH_2		99	128–129	$C_7H_8N_4O_2$	C, H, N[i]	
	O	NH_2		57	114–115	$C_8H_{13}N_3O_2$	C, H, N	

[a] See footnote *a*, Table I. [b] Recrystallization lowered the melting point by a few degrees. [c] See Table I, footnote *d*. [d] Based on 4-methyl-2-pentanone. [e] Calcd: 51.91; found: 51.24. [f] Calcd: 28.27; found: 27.78. [g] $[\alpha]^{365}$ (+) 97.0°. [h] $[\alpha]^{436}$ (−) 95.6°. [i] Calcd: 31.10; found:[j] 32.63, 30.33. [j] Material very unstable. Decomposed before third analysis attempted. [k] Rapid rough melting point determined, then melting point bath preheated to within 5–8° of melting point before immersing melting point capillary. All the *N*-nitroso compounds decompose at their melting point.

Table III

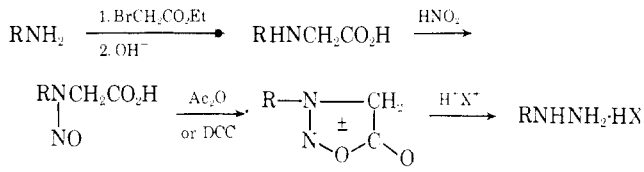
Mesoionic Compound



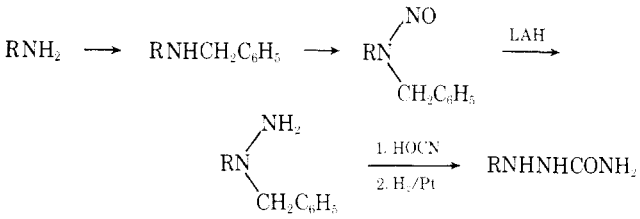
R	X	Method of prepn	Recrystn solvent	Yield, %	Mp or bp (mm), °C	Formula	Analyses	Act[a]
$H_3CCH(CH_3)CH_2CH(CH_3)$–[b]	N	H		51	86–88 (0.03)	$C_7H_{13}N_3O_2$	C, H, N	+
$CH_3(CH_2)_3CH(C_2H_5)CH_2$–	N	H		60	114–116 (0.03)	$C_9H_{17}N_3O_2$	C, H, N	+
$-(CH_2)_6-$ (bis compound)	N	H	*i*-PrOH	10	52.5–53.5	$C_8H_{12}N_6O_4$	C, H, N	++
$C_6H_5CH_2CH(CH_3)$–	N	H		70	128–134 (0.05)	$C_{10}H_{11}N_3O_2$	C, H, N	++
$C_6H_5CH(CH_3)$–	N	K or L		49	Oil[c]	$C_9H_9N_3O_2$	H, N, C[d]	
$C_6H_5(CH_2)_2$	N	H	*i*-PrOH	66	63.5–65.5	$C_9H_9N_3O_2$	H, N, C[e]	−
	N	K or L	*i*-PrOH	33	133–133.5	$C_9H_9N_3O_2$	C, H, N	+
	N	K or L	Hexane	37 (F) 44 (G)	87–89	$C_{11}H_{17}N_3O_2$	N, H, C[f]	
	N	H	*i*-PrOH	60	122–123.5	$C_7H_{12}N_4O_2$	C, H, N	++
	N	P	EtOH	76	218–220 dec	$C_8H_{15}IN_4O_2$	C, H, N	−
	N	H	*i*-PrOH	40	59–50	$C_{10}H_{16}N_4O_2$	C, H, N	±[g]
	N	P	EtOH–H_2O (1:1)	57	208–210 dec	$C_{11}H_{19}IN_4O_2$	C, H, N	−
	N	H	*i*-PrOH	35	69–70	$C_9H_{14}N_4O_2$	C, H, N[h]	±
	N	P	EtOH–H_2O (1:1)	70	240 dec	$C_{10}H_{17}IN_4O_2$	C, H, N	−
	CH	M	Cyclohexane	82	102–104	$C_{12}H_{18}N_2O_2$	C, H, N	−
	CH	N	THF	67	153–155	$C_{12}H_{18}N_2O_2$	C, H, N	−

[a] See footnote *a*, Table I. [b] Mentioned in ref 1b but no data given. [c] Too unstable to distil. [d] Calcd: 56.54; found: 56.17. [e] Calcd: 56.54; found: 56.11. [f] Calcd: 59.17; found: 59.69. [g] Calcd: 26.65; found: 27.51. [h] See footnote *d*, Table I.

SCHEME I



SCHEME II



being of the same order of magnitude as the corresponding 1-nitrososemicarbazides. The stability, while not being exceptional, was considerably better than for the corresponding 1-nitrososemicarbazides in most instances.[7] An added advantage, as far as pharmacological testing was concerned, was the ready solubility in weakly acidic solutions.

Attempts were also made to prepare nitrosated 3-thiosemicarbazides analogous to some of the more active compounds, but in all cases the product was too unstable for isolation.

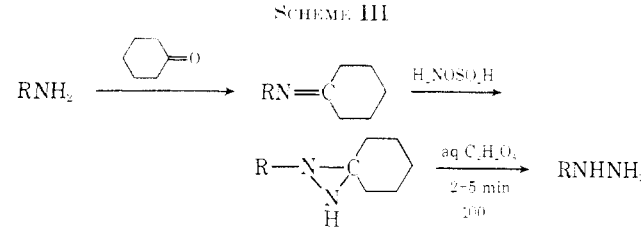
Pharmacology.—Most of the compounds were tested on mice and dogs. Some were also tested on cats and hypertensive rats. The compounds were administered intravenously in dose ranges from 1 to 20 mg/kg. In dogs oral doses of 1 to 25 mg/kg in Clearjel suspension were administered in some cases. The vehicles had a negligible effect on the responses measured. Blood pressure in anesthetized dogs was monitored continuously with a pressure transducer in either the femoral or carotid artery.

In the cases of (*N*-nitrosobornylamino)guanidine and 1-bornyl-1-nitrososemicarbazide, the most extensively tested compounds, the ratio of LD_{50} to $HNSD_{50}$ was about 10:1. The symptoms characteristic of the low doses are the same as those produced by guanethidine,[8] suggesting a common mechanism of action.

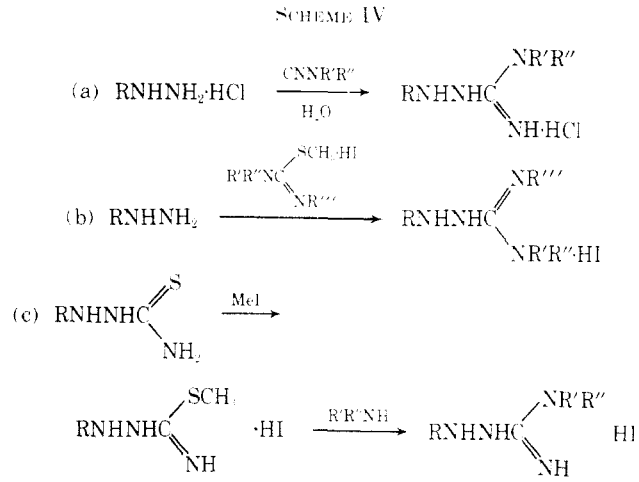
The blood pressure records demonstrated that there was a rapid onset of action by both p.o. and i.v. administration, the drop in blood pressure beginning within minutes, and reaching its maximum by 0.5 hr. Systolic, diastolic, and pulse pressure all decreased. A graded response curve was obtained over the dose range from 1–10 mg/kg orally, reaching a maximum of about 35% decrease with 10 mg/kg. Higher doses (up to 25 mg/kg) did not cause a further decrease in blood pressure.

Intravenously the (*N*-nitrosobornylamino)guanidine gave a graded response curve from 1 to 10 mg/kg (maximum dose administered was 10 mg/kg) reaching a maximum decrease of about 65% with 10 mg/kg.

SCHEME III



SCHEME IV



1-Bornyl-1-nitrososemicarbazide gave a 63–65% drop in blood pressure with from 1 to 10 mg/kg, and an 80% drop with 20 mg/kg.

Heart rate seemed little affected and the changes were not associated systematically with changes in blood pressure or doses of the compound.

The oral LD_{50} of both compounds was greater than 500 mg/kg.

Most of the nonterpenoid *N*-nitroso compounds tested had fair to good activity, but were quite toxic. Most of the aminoguanidines and mesoionic compounds showed some activity, but generally did not compare favorably with the uncyclized nitroso compounds. The majority of the other intermediates had little or no hypotensive activity.

The approximate activities of all the compounds are shown in Tables I–IV.

Experimental Section

Semicarbazides and Thiosemicarbazides. Method A.—The semicarbazone (which did not need to be completely dry) was slurried or dissolved in about 700 ml of 5% HCl in MeOH/mol, and was hydrogenated at 4.2 kg/cm² starting pressure using 2.5 g of PtO_2/mol. When reduction was complete the catalyst was filtered off and the solvent removed under reduced pressure. H_2O was added and the crude product precipitated with NaOH or KOH filtered, washed neutral where possible, and dried.

Method B.—Essentially the same as Method A, except that glacial AcOH was used as the solvent.

Method C.—The semicarbazide was prepared from the corresponding hydrazine·HCl (used as a 10% aqueous solution) by reaction with a 50% excess of KCNO[9] (dissolved in the minimum quantity of H_2O) at room temperature for 12–24 hr. The product was filtered off, washed with H_2O, and recrystallized.

To prepare the thiosemicarbazide, a solution of the hydrazine·HCl at 90–100° was treated with a 50% excess of KSCN and heated for 2 hr. A second equal quantity of KSCN was then added followed by an equivalent amount of concentrated HCl,

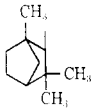
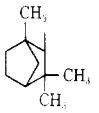
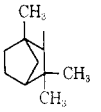
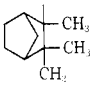
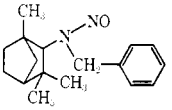
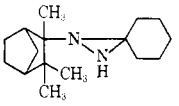
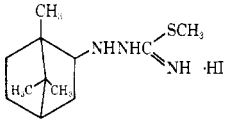
(7) At ambient temperature the 1-nitrososemicarbazides usually were completely decomposed within a year, while the (*N*-nitrosoalkylamino)-guanidines investigated appeared to be unchanged after a year.

(8) R. Fielden and A. L. Green, *Brit. J. Pharmacol.*, **24**, 408 (1965).

(9) K. A. Taipale, *Ber.*, **63B**, 243 (1930).

TABLE IV

PRECURSORS TO SOME OF THE COMPOUNDS IN TABLE I

R	R′	Recrystn solvent	Yield, %	Mp, °C	Formula	Analyses	Act[a]
				i. Glycine derivatives, $R-N(R')-CH_2COOH$			
	H	*i*-PrOH–Et_2O	49	222–224[b]	$C_{12}H_{22}ClNO_2$	C, H, N, Cl	–
	NO	Et_2O, *ca.* −60°	57	151–152	$C_{12}H_{20}N_2O_3$	C, H, N	–
	NO		85	157.5–158	$C_{12}H_{20}N_2O_3$	C, H, N	–
				ii. Hydrazines, $RNHNH_2 \cdot HCl$			
			97	254–256	$C_{10}H_{19}ClN_2$	C, H, N, Cl	–
		*n*-PrOH	47	296–298	$C_{10}H_{21}ClN_2$	C, H, N, Cl	–
		*i*-PrOH	57	291.5–292	$C_{10}H_{21}ClN_2$	C, H, N, Cl	–
				iii. Miscellaneous compounds			
		Hexane	54	92–92.5	$C_{17}H_{24}N_2O$	C, H, N	±
			13	Unstable oil	$C_{16}H_{28}N_2$	C, H, N	
			99	156–158	$C_{12}H_{24}IN_3S$	C, H, N, I, S	+[d]

[a] See footnote *a*, Table I. [b] Hydrochloride. [c] H. U. Daeniker, *Helv. Chim. Acta*, **50**, 2008 (1967). [d] See footnote *d*, Table I.

and heating was continued for 2 more hr. The reaction mixture was then cooled, basified, filtered, washed with H_2O, and dried. The crude product was slurried with Et_2O to remove a red by-product and recrystallized from a suitable solvent.

***S*-Methyl Derivatives. Method D.**—These were prepared by treating the thiourea derivative with an excess of MeI in absolute EtOH for several hours. The solvent was then either removed until crystallization occurred, then cooled, filtered, and washed, or all solvent was removed on the Rotovap and then under high vacuum. In either case pure product was usually obtained in virtually quantitative yield.

Aminoguanidines. Method E.—An approximately 10% aqueous solution of the corresponding hydrazine·HCl was brought to a pH ≥6 with aqueous NaOH (use of a pH meter is recommended since the reaction will not proceed satisfactorily below a pH of 6, and the pH will not rise much above 6 until most of the hydrazine has been freed, giving a poor yield of aminoguanidine·HCl). A pH of about 6.3 is usually satisfactory. The solution was then rapidly heated to 60° and 1 mol of H_2NCN (as a *ca.* 25% aqueous solution) was added per mole of hydrazine. Heating was continued rapidly to 95° and another 2 mol of H_2NCN solution was added over about 45 min. After an additional 15 min at 95° the solution was allowed to cool to room temperature, then cooled to 0° in an ice bath. The product was filtered off, washed thoroughly with Et_2O, and recrystallized.

Method F.—The *S*-methylisothiosemicarbazide·HI (0.01 mol) in 8 ml of EtOH was treated with 0.012 mol of the amine in 2.5 ml EtOH and the mixture was stirred for 4–7 days. The solvent was then removed on a Rotovap and the crude product slurried first in Et_2O, then in H_2O. The crude product could then be recrystallized from an appropriate solvent.

Method G.—The hydrazine·HCl (0.15 mol) was added to 8.4 g (12.9 ml of 45%, 0.15 mol) of KOH in 90 ml absolute EtOH in a low actinic flask, rinsing in with 50 ml of EtOH. To the resulting slurry was added 0.155 mol of the pseudothiourea·HI and the reaction was allowed to proceed at room temperature for 2 to 7 days. At the end of this time the NaCl was filtered off and washed with EtOH. Most of the solvent was removed from the filtrate on a Rotovap and the crude product was then shaken with 300 ml of Et_2O until a smooth slurry was formed. After filtering and washing with Et_2O the solid was stirred with 100 ml of H_2O, filtered, washed with H_2O, and dried *in vacuo* over P_2O_5. The product was usually analytically pure at this point.

Nitrosation of Semicarbazides and Analogs.—The compound (0.25 mol) was slurried in 500 ml of H_2O and 75 ml of concentrated HCl and cooled to <0°. A solution of 18 g of $NaNO_2$ in 250 ml of

H_2O was then added at such a rate that very little excess HNO_2 was present at any time. After the nitrite ceased being taken up the slurry was stirred at ~0° with a slight excess of HNO_2 for 15–30 min, then filtered and washed neutral with H_2O if it was a *N*-nitrososemicarbazide. If an aminoguanidine had been nitrosated the solution was made alkaline with dilute NaOH before filtering and washing neutral. The product was usually analytically pure at this point and recrystallization often did more harm than good.

Mesoionic Compounds. I. 1,2,3,4-Oxatriazol-5-ones. Method H.—The pure nitroso compound was added to 10 parts of H_2O and 2 parts of concentrated HCl, or, alternately, the semicarbazide was nitrosated as described previously, but instead of isolating the nitrosated product the excess HNO_2 was destroyed at about 0° with $(H_2N)_2CO$ or H_2NSO_3H. The resulting slurry or solution was heated for 30 min at 60–100°. The mixture was cooled and the product filtered off or extracted with $CHCl_3$ except in the case of mesoionic compounds containing a basic group. In those cases the compounds were isolated by saturating the reaction mixture with K_2CO_3 and either filtering off the product or extracting it into Et_2O. The extracts were washed with H_2O, dried, and evaporated. The product was distilled or recrystallized.

Method K.—The dry nitrososemicarbazide was refluxed with 10 parts of an inert solvent, such as *n*-bromobutane, and 2 equiv of AcOH for about 1 hr (30 min after the nitrososemicarbazide goes into solution). The solution was then cooled and the product filtered off or the solvent was removed on a Rotovap. The crude product was distilled or recrystallized.

Method L.—The dry nitroso compound was slurried in 10–15 parts of $CHCl_3$, and 2 equiv of CF_3CO_2H in $CHCl_3$ was added over about 20 min. After stirring for 2 hr the solution was extracted with H_2O, dilute NaOH and again with H_2O. Removal of solvent left the crude product which could be recrystallized or distilled.

II. Sydnones. Method M.[10]—The *N*-nitrosoglycine was heated at 100° with four parts of Ac_2O for 3 hr. Most of the Ac_2O was then removed under reduced pressure and the residue dissolved in $CHCl_3$ and washed with dilute NaOH and H_2O. Drying ($MgSO_4$) and removal of the solvent gave the crude product which was recrystallized.

Method N.—The nitrosoglycine was dissolved in five parts of THF and 1.1 equiv of DCI in five parts of THF was added. After allowing to stand for 24 hr the excess DCI was destroyed with AcOH. The dicyclohexylurea was filtered off, the THF removed under reduced pressure, and the crude product recrystallized.

Preparation of Methiodides. Method P.—The basically substituted mesoionic compound was dissolved in 5–10 parts of Me_2CO and 1.1 equiv of MeI was added to the solution. After 2 hr the methiodide was filtered off, washed with Me_2CO, and recrystallized from an appropriate solvent.

Miscellaneous Procedures. *N*-(α-Fenchyl)glycine·HCl.—A solution of α-fenchylamine (766 g, 5 mol) and 418 g (2.5 mol) of $BrCH_2CO_2Et$ in 2000 ml of C_6H_6 was refluxed for 4 hr, then cooled and extracted with H_2O (α-fenchylamine·HBr is quite soluble in C_6H_6). After drying ($MgSO_4$) the solvent was removed on a rotary evaporator and the crude ester was refluxed with 175 ml of 50% NaOH in 140 ml of H_2O for 1 hr. The solution was cooled to room temperature and extracted with Et_2O. Concentrated HCl (1000 ml) was added at ≤35°, the solution was concentrated to about 1800 ml under vacuum and filtered, and the precipitate washed thoroughly with Et_2O giving 226 g of product, mp 214–217°. Further concentration of the filtrate to about 1400 ml gave 279 g more product, mp 200–205°. The product could be further purified by dissolving in *i*-PrOH (9 ml/g), filtering off any salt present, and precipitating the product with five volumes of Et_2O. The recovery was 85–90%, mp 222–224°.

***N*-(α-Fenchyl)-*N*-nitrosoglycine.**—To *N*-(α-fenchyl)glycine·HCl (500 g, 2 mol) in 12000 ml of H_2O and 200 ml of concentrated HCl was added a solution of 185 g of $NaNO_2$ in 500 ml of H_2O. After 128 hr at 25° the product was filtered off and washed with H_2O, yielding 296 g of product, mp 145–146°. Recrystallization of 13.6 g from 300 ml of Et_2O at −60° gave 10 g of the title compound, mp 151–152°.

***N*-Nitroso-*N*-(2,3,3-trimethyl-2-norcamphanyl)glycine.** i. ***N*-(2,3,3-Trimethyl-2-norcamphanyl)glycine·HCl.**—2,3,3-Trimethyl-2-norcamphanylamine[11] (313 g, 2 mol) and 168 g (1 mol) of $BrCH_2CO_2Et$ in 1000 ml of C_6H_6 were refluxed for 20 hr. Et_3N (140 ml, 1 mol) was added and refluxing continued for 6 hr. $BrCH_2CO_2Et$ (54 ml, 0.5 mol) was then added and refluxing continued for 18 hr. This procedure was repeated twice, using 0.5 and then 0.25 the amounts of Et_3N and $BrCH_2CO_2Et$. The solution was cooled and the C_6H_6 was decanted from the solid, which was treated with 500 ml of H_2O and extracted with C_6H_6. The combined C_6H_6 solutions were extracted with H_2O, dilute NH_3, and again with H_2O. After drying ($MgSO_4$) the yield of crude ester resulting from removal of the solvent was 273 g. This yield was about 20% higher, based on the 2,3,3-trimethyl-2-norcamphanylamine, than if the Et_3N–$BrCH_2CO_2Et$ additions were left out.

The crude ester was hydrolyzed by refluxing with 550 ml of H_2O and 57 g of NaOH for 30 min and allowing to cool. The solution was extracted with Et_2O and acidified at <35° with 300 ml of concentrated HCl. The solution was cooled to 0° overnight and filtered, and the precipitate washed thoroughly with Et_2O. The weight of product was 184 g, mp 162–164°. The product could be purified further by dissolving in *i*-PrOH (5 ml/g), filtering off any salt present, and precipitating with 5 volumes of anhydrous Et_2O (recovery 75%, mp 164–166°). The product was found to lose HCl spontaneously and gave a low Cl analysis.

ii. *N*-Nitroso-*N*-(2,3,3-trimethyl-2-norcamphanyl)glycine. *N*-(2,3,3-Trimethyl-2-norcamphanyl)glycine·HCl (153 g, 0.62 mol) was dissolved in 5000 ml of H_2O and 160 ml of concentrated HCl. To this was added 90 g of $NaNO_2$ in 500 ml of H_2O. After standing 10 days at 25° the product was filtered off, washed with H_2O, and dried; weight 107 g, mp 153–154°. Recrystallization from *i*-PrOH gave a product, mp 157.5–158°.

1-Adamantylhydrazine·HCl.—A mixture of 5.3 g (0.024 mol) of 1-bromoadamantane and 30 ml of anhydrous H_2NNH_2 was refluxed with stirring on a magnetic stirrer–hot plate for 3 hr under a slow stream of N_2. A little sublimate that accumulated in the condenser was periodically pushed back into the reaction mixture with a glass rod. After 1 hr most of the bromoadamantane had gone into solution. After 2.5 hr, tlc showed no bromoadamantane left in the reaction mixture. The solution was poured while hot (solidifies on cooling) into 125 ml of cold 45% KOH solution, extracted into Et_2O, and washed three times with 45% KOH solution to remove free H_2NNH_2. After drying ($MgSO_4$) for a short time the solution was filtered, and the product precipitated with dry HCl, filtered, and washed with Et_2O. The crude product weighed 4.6 g, mp 250–253°. Recrystallization from 140 ml of *i*-PrOH and 230 ml of Et_2O gave 3.9 g of the title compound, mp 254–256°.

α-Fenchylhydrazine·HCl. *N*-(α-Fenchyl)syndone (212 g, 0.95 mol) was heated on a steam bath with 500 ml of concentrated HCl for 30 min with frequent swirling. A smooth slurry formed at first, then after about 20 min two liquid layers formed, the upper one solidifying after about 5 min. The slurry was cooled to 25°, filtered, and washed thoroughly with Et_2O. The yield was 96 g, mp 293.5–294.5°. Recrystallization of 2.4 g from 25 ml of *n*-PrOH gave 1.9 g of material, mp 296–298°.

α-Fenchylhydrazine·HCl *via* the Diaziridine. i. 1-(α-Fenchyl)-1,2-diazaspiro[2.5]octane.—α-Fenchylamine (15.3 g, 0.1 mol) and 10.3 g (0.105 mol) of cyclohexanone were refluxed in 100 ml of C_6H_6 with a Dean–Stark trap for 2 hr, 1.6 ml of H_2O being collected during this time. The solvent was removed; 3.5 g (0.015 mol) of the crude Schiff base and 2.6 g (0.155 mol) of α-fenchylamine were dissolved in 10 ml of MeOH, cooled to 0°, and treated with 1.9 g of 90% hydroxylamine-*O*-sulfonic acid, added portionwise over 10 min. After stirring for 1.5 hr at 0° it was allowed to warm up to room temperature, diluted with 50 ml of H_2O, and extracted with Et_2O. The Et_2O solution was washed with H_2O and K_2CO_3 solution and dried (K_2CO_3). Removal of the solvent left 1.4 g of crude product which could not be distilled. The ir spectrum was appropriate for the desired compound (the absence of N=C was indicated by lack of absorption in 1650–1600 cm^{-1} region; a singlet at 3200 cm^{-1} indicated NH but no NH_2; the presence of both types of Me groups was indicated by a doublet at 1380 cm^{-1} and another band at 1360 cm^{-1}). The material showed a single spot R_f 0.78 on a silica tlc using 10% MeOH in $CHCl_3$ as developer.

ii. α-Fenchylhydrazine·HCl.—When the above material was refluxed for 30 min with 10 ml of 10% $(COOH)_2$ solution, a 46%

(10) J. C. Earl and A. W. Mackey, *J. Chem. Soc.*, 899 (1935).

(11) K. Pfister III, and G. A. Stein, U. S. Patent 2,831,027 (1955).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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