chromatograms of the reaction mixture, when subjected to bioautography on agar plates inoculated with *C. xerosis* showed a zone of inhibition with an R_f value corresponding to that of fusidic acid. The solvent was removed *in vacuo* and the residue was dissolved in benzene (5 ml.) and seeded with fusidic acid–benzene solvate. After standing overnight, a crystalline solid was collected. The crude product (120 mg.) was recrystallized from benzene to yield 95 mg. of fusidic acid–benzene solvate identical in every respect with an authentic sample.

Hydrogenation of 6a to 8a.—A solution of **6a** (520 mg.) in acetic acid (5 ml.) was hydrogenated under 1 atm. of hydrogen in the presence of PtO_2 (50 mg.). In 3 hr. the theoretical amount of hydrogen was absorbed, and the consumption ceased. The catalyst was removed, and the filtrate was precipitated with water to yield a semicrystalline solid which was collected and dissolved in ether (20 ml.). The ethereal solution was washed with water, dried, and evaporated. The residue crystallized from ether to afford 440 mg. of colorless crystals, m.p. 180–183°. Recrystallization from acetonitrile gave pure **8a**, m.p. 184.5–185°, $[\alpha]^{23}D$ −39°. No selective absorption occurred in the ultraviolet spectrum above 200 mμ.

Anal. Calcd. for $C_{31}H_{52}O_6$: C, 71.50; H, 10.07. Found: C, 71.44; H, 10.09.

Hydrolysis of 8a to 8n.—A solution of **8a** (350 mg.) in a mixture of ethanol (10 ml.) and 2 *N* NaOH (10 ml.) was refluxed for 5 hr. After cooling and acidification, most of the ethanol was removed under reduced pressure. Working up through ether gave a product which crystallized from methanol–water to yield 300 mg. of **8n**, m.p. 189–192°. Recrystallization from the same solvents gave 270 mg., mp. 184–186°, $[\alpha]^{23}D$ −66°.

Anal. Calcd. for $C_{29}H_{50}O_5 \cdot 0.5H_2O$: C, 71.41; H, 10.54. Found: C, 71.51; H, 10.44.

Acetylation of 8a.—Compound **8a** (200 mg.) was dissolved in a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.). After standing for 3 hr., water was added to precipitate an oil which was extracted with ether. The extract was repeatedly washed with water, dried, and evaporated to a foam which failed to crystallize: $[\alpha]^{26}D$ −38°.

Anal. Calcd. for $C_{33}H_{54}O_7$: C, 70.43; H, 9.67. Found: C, 70.13; H, 9.76.

Acetylation of 8n.—Compound **8n** (100 mg.) was acetylated as described for **8a**. The infrared spectrum (KBr) of the product was identical with that of the compound obtained on acetylation of **8a**.

Acetylation of 9a to 9b.—16-Deacetylfusidic acid lactone (200 mg.) was dissolved in a mixture of acetic anhydride (2 ml.) and pyridine (2 ml.). After standing for 16 hr. the product was precipitated with water. The crude product was recrystallized from ether–hexane to yield crystals with m.p. 191–192°, $[\alpha]^{20}D$ +40°.

Anal. Calcd. for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found: C, 74.51; H, 9.18.

Acetylation of 11a to 11c.—Compound **11a** (1.0 g.) was dissolved in 5 ml. of a mixture of acetic acid (40 ml.), acetic anhydride (20 ml.), and *p*-toluenesulfonic acid (10 g.). After standing for 20 min., water was added to precipitate an amorphous solid which crystallized from methanol–water to yield 900 mg. of **11c**, m.p. 202–203°. Recrystallization from methanol raised the melting point to 203–204°, $[\alpha]^{26}D$ −24°.

Anal. Calcd. for $C_{35}H_{52}O_6$: C, 72.75; H, 9.62. Found: C, 72.97; H, 9.51.

Sodium Borohydride Reduction of 9a to 13a.—To a solution of compound **9a** (200 mg.) in methanol (10 ml.) 5% aqueous $NaBH_4$ (1 ml.) was added. After standing for 30 min., the solution was acidified with acetic acid and precipitated with water to yield 150 mg. of crude **13a**, m.p. 168–171°. Two recrystallizations from ether–hexane raised the melting point to 174–176° (sintering at 136–138°); $[\alpha]^{20}D$ −42°; λ_{max} 203 mμ (ε 5200); ν^{KBr} 1580 (w), 1655 (w), and 1750 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 75.84; H, 10.26.

Acknowledgment.—The authors wish to thank Dr. A. Melera, Varian A. G., Zürich, for determination and interpretation of the n.m.r. spectra, and to Dr. P. Mörch for the infrared and ultraviolet spectra.

Biologically Active Guanidines and Related Compounds. II. Some Antiinflammatory Aminoguanidines[1]

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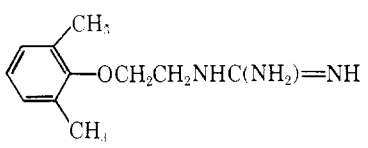
A series of N-amino-N-substituted guanidines have been synthesized and evaluated for antiinflammatory activity.

In a previous publication,[1] we discussed a series of phenoxyalkylguanidines and related compounds which exerted a potent blocking action on the sympathetic nervous system. Of particular interest was 2-(2,6-xylyloxy)ethylguanidine (I), which may be considered as combining the structural features of choline 2,6-



I

xylyl ether bromide[2] and guanethidine [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate.[3] Further investigations have shown that compounds in this series are also active in certain assays for antiinflammatory activity, and in an extension of this work structurally related aminoguanidines have been synthesized, some of which have proved to be active in a range of tests for antiinflammatory activity.

Chemistry.—1-Amino-3-substituted guanidines (III) were prepared by the reaction of 2-methyl-2-thioisosemicarbazide with phenoxyalkylamines[4] (see Scheme I). However, as it is laborious and often difficult to separate the products (III) from tetrazine derivatives[5] and other products[6] formed by the alkaline decompo-

(1) Part I of this series: D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, **6**, 705 (1963).

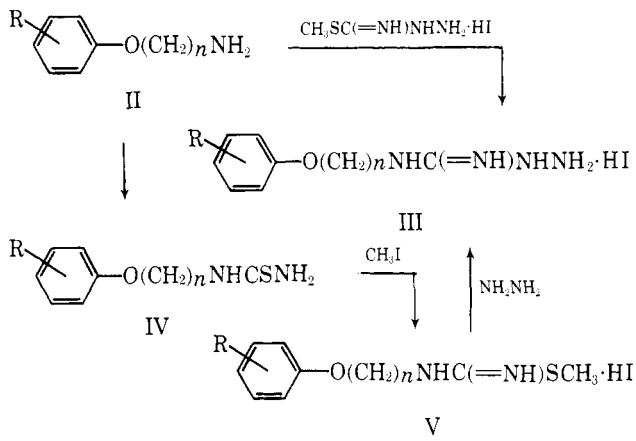
(2) P. Hey and G. L. Willey, *Brit. J. Pharmacol.*, **9**, 471 (1954); "TM10."

(3) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959).

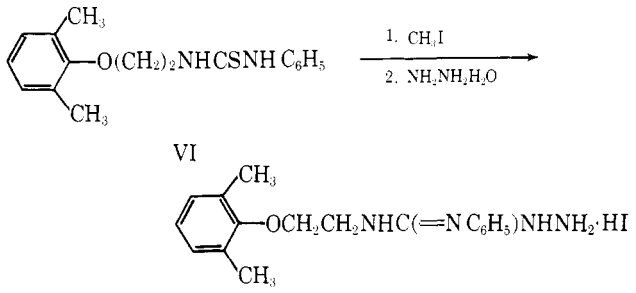
(4) G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).

(5) (a) F. L. Scott and J. Reilly, *Chem. Ind.* (London), 907 (1952); (b) F. L. Scott, *ibid.*, 158 (1954); (c) C. Lin, E. Lieber, and J. P. Horwitz, *J. Am. Chem. Soc.*, **76**, 427 (1954).

SCHEME I

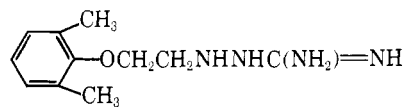


sition of 2-methyl-2-thioisosemicarbazide, the alternative route *via* the thiourea IV was investigated. The thioureas were prepared readily from the phenoxyalkylamine and benzoyl isothiocyanate[7] followed by alkaline hydrolysis of the intermediate benzoylthiourea. Methylation, yielding the 2-methyl-2-thiopseudourea derivative V and subsequent hydrazinolysis afforded the pure aminoguanidines III. Similarly, reaction of II (R = 2,6-$(CH_3)_2$; $n = 2$) with phenyl isothiocyanate gave the 1-phenylthiuronium derivative VI which was readily converted to the arylaminoguanidine VII.

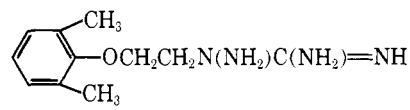


VII

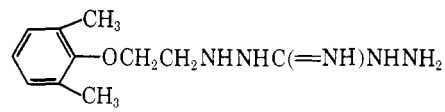
Reaction of 2-(2,6-xylyloxy)ethylhydrazine with 2-methyl-2-thiopseudourea sulfate yielded the aminoguanidine VIII. Our structural assignment was made



VIII



IX

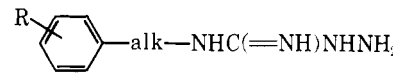


X

on the basis of the failure of VIII to yield a benzal derivative but independently, Augstein and coworkers[8] have confirmed that compounds of type VIII (rather than the isomeric structure IX) are formed by the reaction of 2-(2,6-disubstituted phenoxy)ethylhydrazine with 2-methyl-2-thiopseudourea sulfate. Similarly, reaction of this hydrazine with 2-methyl-2-thioisosemicarbazide yielded the diaminoguanidine X.[9]

The phenoxyalkylaminoguanidine derivatives are listed together with physical data and antiinflammatory activity in Table I.

1-Amino-3-substituted guanidines (XI) were also prepared from phenylalkylamines. Similar methods were employed and the compounds synthesized are



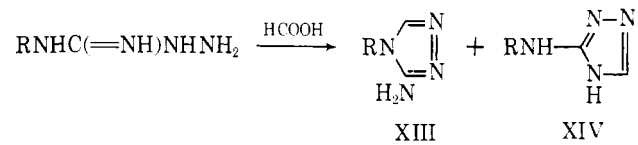
XI

$R_1R_2N(CH_2)_2NHC(=NH)NHNH_2$

XII

listed in Table II. Miscellaneous aminoguanidines synthesized including the dialkylaminoalkyl derivatives XII are listed in Table III.

Cyclization of the 1-amino-3-substituted guanidines by formylation with formic acid followed by treatment with aqueous alkali gave mixtures of the isomeric triazoles XIII [R = 2,6-$(CH_3)_2C_6H_3O(CH_2)_2$ and $C_6H_5CH_2$] and XIV[10,11] (R = $C_6H_5CH_2$).



XIII XIV

Biological Activity.—Antiinflammatory activity was measured by a rat paw edema test using yeast as irritant.[12] In this assay, 2-(2,6-xylyloxy)ethylguanidine (I, Table I, **1**) was shown to have a pronounced activity and a dose of 100 mg./kg. *p.o.* caused 50% inhibition of edema formation. As phenylbutazone and most other clinically effective antiinflammatory drugs only show significant activity in this test at doses approaching the LD_{50}, **1** was used as a standard for assaying the relative potency of other compounds in the series. The results are listed in Table I. 2-Phenoxyethylguanidine[13] (**2**) had a marked potency in this assay and the aminoguanidine **3** derived from **1** was also highly active. Structural modifications of this latter compound including lengthening of the side chain beyond 3 carbon atoms (**5** and **6**), methylation of the guanidine group on the substituted nitrogen (**9**), the introduction of a phenyl group on the unsubstituted

(6) A. F. McKay, D. L. Garmaise, H. A. Baker, L. R. Hawkins, V. Falta, R. Gaudry, and G. Y. Paris, *J. Med. Chem.*, **6**, 587 (1963).

(7) R. L. Frank and P. V. Smith, "Organic Synthesis," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 735.

(8) J. Augstein, S. M. Green, A. R. Katritsky, and A. M. Monro, *J. Med. Chem.*, **8**, 395 (1965).

(9) We find that 2-(2,6-xylyloxy)ethylhydrazine reacts with potassium cyanate and benzoyl isothiocyanate almost exclusively at the secondary amino function. This point will be discussed in a future publication.

(10) K. Shirakawa, *J. Pharm. Soc. Japan.*, **80**, 1550 (1950).

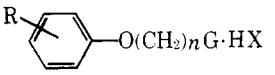
(11) Y. Makisumi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 67 (1963).

(12) (a) J. Selitto and H. O. Randall, *Federation Proc.*, **13**, 403 (1954); (b) H. Selye, *Brit. Med. J.*, **2**, 1129 (1949).

(13) Statements in recent publications [(a) J. Augstein and S. M. Green, *Nature*, **20**, 628 (1964); (b) J. Augstein, S. M. Green, A. M. Monro, G. W. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965)] that 2-phenoxyethylguanidine was investigated by Kuroda in 1934 are incorrect. The compound examined by A. Kuroda [*Folia Pharmacol. Japon.*, **18**, 106 (1934); **19**, 18, (1934)] was in fact 1-hydroxyphenethylguanidine, and the mistake presumably arose by the incorrect translation from the original German in *Chem. Abstr.*, **29**, 1504 (1935).

TABLE I

PHENOXYALKYLGUANIDINE DERIVATIVES

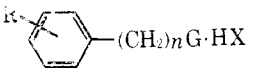


No.	R	n	G	HX	Antiinflammatory activity: Rat paw test[a]	Antiinflammatory activity: Ultraviolet erythema test[b]	LD_{50} (mice), mg./kg. p.o.
1[c]	2,6-$(CH_3)_2$	2	$NHC(NH_2)=NH$	$0.5H_2SO_4$	1.0	0	>500
2[c]	H	2	$NHC(NH_2)=NH$	$0.5H_2SO_4$	2.0	0	750
3	2,6-$(CH_3)_2$	2	$NHC(NHNH_2)=NH$	HI	2.0	0.14	500
4	H	2	$NHC(NHNH_2)=NH$	HI	0.9	0.04	>500
5	2,6-$(CH_3)_2$	3	$NHC(NHNH_2)=NH$	HI	1.3	0	...
6	2,6-$(CH_3)_2$	4	$NHC(NHNH_2)=NH$	HI	0	0	...
7	4-Br	2	$NHC(NHNH_2)=NH$	HI	0	0	...
8	2,6-(i-$C_3H_7)_2$	2	$NHC(NHNH_2)=NH$	HI	...	0	...
9	2,6-$(CH_3)_2$	2	$N(CH_3)C(NHNH_2)=NH$	HI	0	0	...
10	2,6-$(CH_3)_2$	2	$NHC(NHNH_2)=NC_6H_5$	HI	0	0	...
11	2,6-$(CH_3)_2$	2	$NHC(NHN=CHC_6H_5)=NH$	$0.5H_2SO_4$	0	0	...
12	2,6-$(CH_3)_2$	2	$NHNHC(NH_2)=NH$	$0.5H_2SO_4$	1.1	0	>500
13	2,6-$(CH_3)_2$	2	$NHNHC(NHNH_2)=NH$	HI	1.7	0	>500
14	2,6-$(CH_3)_2$	2		...	0	0	2000

[a] Potency relative to 1 using yeast as irritant. Initial assay at 40% mouse LD_{50}, *p.o.* [b] Potency relative to phenylbutazone (rated as 1.0). Initial assay at 30% mouse LD_{50}, *p.o.* [c] For analytical data see ref. 1. [d] Recrystallized from isopropyl alcohol–ether. [e] Re-

TABLE II

PHENYLALKYLGUANIDINE DERIVATIVES



No.	R	n	G	HX	Antiinflammatory activity: Rat paw test[a]	Antiinflammatory activity: Ultraviolet erythema test[b]	LD_{50} (mice), mg./kg. p.o.
15	H	1	$NHC(NH_2)=NH$	$0.5H_2SO_4$	2.0	0	125
16	2-Cl	1	$NHC(NH_2)=NH$	$0.5H_2SO_4$	2.5	0	375
17	H	1	$NHC(NHNH_2)=NH$	HI	0.8	0.04	1500
18	2-Cl	1	$NHC(NHNH_2)=NH$	HI	1.0	0.11	1500
19	H	1	$NHC(NHN=CHC_6H_5)=NH$		0.7	0	750
20	2-Cl	1	$NHC(NHN=CHC_6H_5)=NH$		0	0	>2000
21	4-Cl	1	$NHC(NHNH_2)=NH$	HI	0.8	0	>500
22	4-OCH_3	1	$NHC(NHNH_2)=NH$	HI	0.5	0	>500
23	4-CH_3	1	$NHC(NHNH_2)=NH$	HNO_3	1.0	0	1500
24	3,4-$(OCH_3)_2$	2	$NHC(NHNH_2)=NH$	HI	0	0	>500
25	H	1			0	0	>1000

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] F. N. Fastier and F. H. Smirk [*J. Pharmacol. Exptl. Therap.*, **89**, 256 (1947)] quote m.p. 204°. [d] The Wellcome Foundation Ltd., Belgian Patent 598,428 (1961), quotes m.p. 237–240°. [e] Lit.[23] m.p. 127–128°.

nitrogen (**10**), or formation of the Schiff base (**11**) led to a decline of antiedema activity. The related aminotriazole (**16**) was inactive. The isomeric aminoguanidine (**12**) and the related diaminoguanidine (**13**) had considerable antiedema activity.

The phenoxyalkylguanidine derivatives also inhibited formation of edema in the rat paw when kaolin[14] was used as irritant. Compound **1** had approximately one-third of the activity of phenylbutazone in this test. Compounds **2**–**5** were active at 200 mg./kg. *p.o.*

Of phenylalkylguanidines (Table II), benzylguanidine (**15**) and 2-chlorobenzylguanidine (**16**) were most active in inhibiting edema (using yeast as irritant). Also active were the aminoguanidines (**17** and **18**) related to these compounds and the guanyl hydrazone (**19**) derived from **17**. The 1-amino-3-benzylguanidines, containing chloro, methyl, and methoxy substituents in the 4-position of the benzene ring (**21**–**23**), were also active in this test. The aminotriazole **25** was inactive. Using kaolin as irritant in the edema assay, **18** was active at 120 mg./kg., while **15**, **19**, **22**, and **23** had only slight activity at 200 mg./kg. 1-Amino-3-ethylguanidine (Table III, **29**) and the aminoguanidine **30** derived from primaquine[15] were inactive in the yeast-edema assay.

The ultraviolet erythema test[16] was used as an addi-

(14) D. Lorenz, *Arch. Exptl. Pathol. Pharmakol.*, **241**, 516 (1961).

(15) R. C. Elderfield, *et al.*, *J. Am. Chem. Soc.*, **68**, 1524 (1946).

(16) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. intern. pharmacodyn.*, **116**, 261 (1958).

M.p., °C.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...
112–115[d]	$C_{11}H_{18}N_4O \cdot HI$	37.72	37.40	5.47	5.67	16.00	16.03
87–89[d]	$C_9H_{14}N_4O \cdot HI$	33.55	33.30	4.62	4.87	17.39	17.54
99–102[d]	$C_{12}H_{20}N_4O \cdot HI$	39.59	39.83	5.82	5.88	15.59	15.51
89–92[d]	$C_{13}H_{22}N_4O \cdot HI$	41.28	41.17	6.13	6.05	14.81	14.96
140–141[d]	$C_9H_{13}BrN_4O \cdot HI$	26.95	27.12	3.52	3.41	13.95	13.54
149–151[d]	$C_{15}H_{26}N_4O \cdot HI$	44.34	44.15	6.70	6.92	13.79	14.11
164–166[e]	$C_{12}H_{20}N_4O \cdot HI$	39.57	39.44	5.81	5.67	15.38	15.32
99–100[f]	$C_{17}H_{22}N_4O \cdot HI$	47.89	47.68	5.44	5.30	13.15	13.40
184–188	$(C_{13}H_{22}N_4O)_2 \cdot H_2SO_4 \cdot H_2O$	58.67	58.84	6.57	6.56	15.59	15.15
211–213[g]	$[C_{11}H_{18}N_4O]_2 \cdot H_2SO_4$	48.69	48.68	7.06	7.26	20.66	20.70
150–152[e]	$C_{11}H_{19}N_5O \cdot HI$	36.17	36.44	5.52	5.62	19.18	19.41
248–250[h]	$C_{12}H_{16}N_4O$	62.04	62.31	6.94	6.91	24.13	24.40

crystallized from isopropyl alcohol. [f] Recrystallized from ethanol–ether. [g] Lit.[8] m.p. 214–216°. [h] Recrystallized from *n*-butyl alcohol.

M.p., °C.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
207–210[e]	$C_8H_{11}N_3 \cdot 0.5H_2SO_4$	...	...	...	...	...	...
234–237[d]	$C_8H_{10}ClN_3 \cdot 0.5H_2SO_4$	...	...	...	...	...	...
125–127[e]	$C_8H_{12}N_4 \cdot HI$	...	...	...	...	...	...
141–144[f]	$C_8H_{11}ClN_4 \cdot HI$	17.16	17.33	29.42	29.48	3.71	3.56
114.5–119[g]	$C_{15}H_{16}N_4$	71.40	70.99	6.57	6.39	22.12	21.95
115.5–118.5[g]	$C_{15}H_{15}ClN_4$	62.81	62.46	5.27	5.35	19.45	19.18
128–130[h]	$C_{15}H_{15}ClN_4$	...	...	...	...	17.16	17.21
130.5–136[f]	$C_9H_{14}N_4O \cdot HI$	33.55	33.79	4.69	4.70	17.39	17.36
109–115[i]	$C_9H_{14}N_4 \cdot HNO_3$	...	...	...	...	29.03	28.87
127.5–131[f]	$C_{11}H_{18}N_4O_2 \cdot HI$	36.08	36.47	5.23	5.20	15.30	15.08
216–218[k]	$C_9H_{10}N_4$	62.05	62.17	5.79	5.69	32.17	32.22

[f] From isopropyl alcohol. [g] From benzene–petroleum ether (60–80°). [h] From isopropyl alcohol–ether. [i] From hydriodide by reaction with silver nitrate. [j] From ethanol–ether. [k] Lit.[10] m.p. 206–209°; from *n*-butyl alcohol.

tional assay for antiinflammatory activity. Phenylbutazone and most other nonsteroidal antiinflammatory drugs are active in this test. The only compounds found to have significant activity in this series were aminoguanidine derivatives and of particular interest were 1-amino-3-[2-(2,6-xylyloxy)ethyl]guanidine (Table I, **3**), with activity 0.14 times phenylbutazone, and 1-amino-3-(2-chlorobenzyl)guanidine (Table II, **18**), 0.11 times phenylbutazone. Compound **3** was also active in the Randall and Selitto test[17] for analgesic and antipyretic activity at 200 mg./kg. *p.o.*

Examination of the aminoguanidine **3** for other biological activities showed that the compound had sympathetic blocking activity[1] at 20 mg./kg. s.c. *In vitro* assays revealed that **3** also had weak anti 5-hydroxytryptamine (5-HT) activity (0.01 times lysergic acid diethylamide when measured by inhibition of 5-HT-induced contraction of the rat uterus) and monoamine oxidase inhibitory activity at 0.3 mg./ml.[18] The relevance of any of these actions to the antiinflammatory activity is unknown at present.

(17) L. O. Randall and J. J. Selitto, *Arch. intern. pharmacodyn.*, **111**, 409 (1957).

Experimental Section[19]

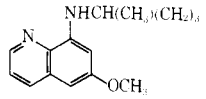
Preparation of 1-Amino-3-substituted Guanidines.—Compounds **3–8, 17, 18, 21–24,** and **27–30** (see tables) were prepared from the appropriate amine and 2-methyl-2-thioisosemicar-

(18) (a) A. A. Waynes, Y. C. Gladish, and J. D. Taylor, *Federation Proc.*, **18**, 462 (1959). (b) The 2,6-dichloro analog of **3** is stated by Augstein, *et al.*,[8] to be an inhibitor of dopamine β-oxidase *in vitro*.

TABLE III

MISCELLANEOUS AMINOGUANIDINE DERIVATIVES

$RNHC(NHNH_2)=NH\cdot HI$

No.	R	Antiinflammatory activity: Rat paw test[a]	Antiinflammatory activity: Ultraviolet erythema test[b]	LD_{50} (mice), mg./kg. p.o.	M.p., °C.	Formula	C, %: Calcd.	C, %: Found	H, %: Calcd.	H, %: Found
27	$(CH_2)_6N(CH_2)_2$	...	0	...	97–98[c]	$C_9H_{21}N_5\cdot HI$[d]	33.03	32.90	6.78	7.00
28	$(CH_2)_7N(CH_2)_2$	...	0	>500	120–122[c]	$C_{10}H_{23}N_5\cdot HI$[e]	35.18	35.20	7.09	7.23
29	C_2H_5	0	0	>2000	81–83.5[f]	$C_5H_{10}N_4\cdot HI$[g]	15.66	15.64	4.82	4.49
30		0	0	>2000	189–191[c]	$C_{14}H_{26}N_6O\cdot HI$[h]	43.24	43.48	5.69	5.88

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] From isopropyl alcohol. [d] *Anal.* Calcd.: equiv. wt., 163.6. Found: equiv. wt., 165.0. [e] *Anal.* Calcd.: equiv. wt., 170.6. Found: equiv. wt., 167.0. [f] Lit.[4] m.p. 84.5–86°. [g] *Anal.* Calcd.: I, 55.16. Found: I, 54.90. [h] *Anal.* Calcd.: N, 18.95. Found: N, 18.80.

bazide hydriodide in ethanol. The experimental procedure is typified as follows.

1-Amino-3-[2-(2,6-xylyloxy)ethyl]guanidine Hydriodide (3).—A mixture of 2-(2,6-xylyloxy)ethylamine (42.5 g., 0.26 mole) and 3-methyl-2-thioisosemicarbazide hydriodide (60.1 g., 0.26 mole) in ethanol (200 ml.) was heated under reflux for 2 hr. Concentration to about 50 ml., followed by the careful addition of dry ether afforded the crude aminoguanidine. Purification was achieved by allowing a solution of this material in isopropyl alcohol to stand at room temperature overnight. Crystals separated out which were removed by filtration (3.3 g.) affording needles from ethanol; m.p. 191.5–192°. This material is presumably 3,4,5-triamino-1,2,4-triazole hemihydriodide (lit.[6] m.p. 192–193°). The sulfate salt, prepared by using silver sulfate, had m.p. ~280° dec.

Anal. Calcd. for $(C_2H_6N_6)_2\cdot H_2SO_4$: C, 14.71; H, 4.33; N, 51.52. Found: C, 14.90; H, 4.52; N, 51.50.

Concentration of the filtrate and addition of ether yielded the aminoguanidine in 2 crops, m.p. 102–112° (29 g.) and m.p. 95–100° (19 g.). Further recrystallizations of the combined material from isopropyl alcohol yielded the pure product, m.p. 111–114.5° (23.7 g., 26%).

1-[2-(2,6-Xylyloxy)ethyl]thiourea.—Benzoyl chloride (14.2 g., 0.1 mole) was added dropwise to a solution of ammonium thiocyanate (7.8 g., 0.1 mole) in dry acetone (50 ml.). The resulting mixture was heated under reflux for 5 min., and 2-(2,6-xylyloxy)ethylamine (16.6 g., 0.1 mole) was added, maintaining a gentle reflux. After addition, the mixture was heated under reflux for 1 hr. and added to water (500 ml.). The crude benzoylthiourea which precipitated was separated and hydrolyzed directly with 350 ml. of boiling 2.5 *N* NaOH for 5 min. The solid so obtained was filtered off and recrystallized from ethanol affording the pure thiourea (15.2 g., 68%), m.p. 192–194°.

Anal. Calcd. for $C_{11}H_{16}N_2OS$: C, 58.89; H, 7.19; N, 12.45; S, 14.29. Found: C, 58.88; H, 7.04; N, 12.59; S, 14.16.

1-[3-(2,6-Xylyloxy)propyl]thiourea was prepared in an identical manner from 3-(2,6-xylyloxy)propylamine[1] in 45% yield. It had m.p. 117–120°.

Anal. Calcd. for $C_{12}H_{18}N_2O_2S$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.14; H, 7.45; N, 11.97.

1-Methyl-1-[2-(2,6-xylyloxy)ethyl]thiourea.—The intermediate benzoylthiourea, m.p. 135–136°, was prepared in the usual manner from 1-methyl-2-(2,6-xylyloxy)ethylamine [synthesized from 2-(2,6-xyloxy)ethylamine and chloral by the method of Blicke and Lee[20]]; HCl m.p. 141–142°.

Anal. Calcd. for $C_{11}H_{17}NO\cdot HCl$: C, 61.24; H, 8.41; N, 6.49. Found: C, 61.26; H, 8.35; N, 6.64.

The benzoylthiourea being derived from a secondary amine was resistant to hydrolytic cleavage,[21] but 13% conversion to the thiourea was achieved in refluxing 10% ethanolic KOH for 30 min. (yield was not improved by increasing the hydrolysis time to 22 hr.). The product had m.p. 165.5–167°.

Anal. Calcd. for $C_{12}H_{18}N_2O_2S$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.70; H, 7.66; N, 11.99.

1-Phenyl-3-[2-(2,6-xylyloxy)ethyl]thiourea.—2-(2,6-Xylyloxy)ethylamine (16.6 g., 0.1 mole) dissolved in dry ethanol (25 ml.) was added to a warm solution of phenyl isothiocyanate (13.4 g., 0.1 mole) in dry ethanol (25 ml.). The mixture was boiled for 2 hr. and cooled. The crystalline product obtained was recrystallized from isopropyl alcohol yielding the thiourea (24.4 g., 85%), m.p. 113–115°.

Anal. Calcd. for $C_{17}H_{20}N_2OS$: C, 67.92; H, 6.49; N, 9.43. Found: C, 67.96; H, 6.71; N, 9.33.

1-Amino-3-[2-(2,6-xylyloxy)ethyl]guanidine Hydriodide (3).—A mixture of 1-[2-(2,6-xylyloxyethyl]thiourea (12.9 g., 0.06 mole) and methyl iodide (7.8 g., 0.06 mole) in ethanol (100 ml.) was heated under reflux for 1 hr. Concentration followed by the addition of ether yielded the 2-methyl-2-thiopseudourea hydriodide which was recrystallized from isopropyl alcohol–ether yielding 13.6 g., m.p. 114–115.5°. Reaction of 9.15 g. of this material with hydrazine hydrate (1.25 g.) in dry ethanol (80 ml.) at reflux for 3 hr. yielded 6.1 g. (48%) of **3**, m.p. 113–115° (from isopropyl alcohol–ether), identical with the product obtained from the amine and 2-methyl-2-thioisosemicarbazide hydriodide.

Anal. Calcd. for $C_{11}H_{18}N_4O\cdot HI$: C, 37.72; H, 5.47; N, 16.00. Found: C, 37.81; H, 5.52; N, 15.79.

1-Amino-3-[3-(2,6-xylyloxy)propyl]guanidine Hydriodide (5).—In a similar manner 1-[3-(2,6-xylyloxy)propyl]thiourea (5.0 g., 0.021 mole) yielded **5** (5.6 g., 76%), m.p. 99–103.5°, identical with the material obtained from the amine and 2-methyl-2-thioisosemicarbazide hydriodide.

1-Amino-3-methyl-3-[2-(2,6-xylyloxy)ethyl]guanidine Hydriodide (9).—In a similar manner 1-methyl-1-[2-(2,6-xylyloxy)-ethyl]thiourea (0.8 g., 3.4 mmoles) yielded **9** (0.8 g., 65%), m.p. 164–166°.

1-Amino-2-phenyl-3-[2-(2,6-xylyloxy)ethyl]guanidine Hydriodide (10).—In a similar manner 1-phenyl-3-[2-(2,6-xylyloxy)ethyl]thiourea yielded **10**, m.p. 99–100°, in 25% yield.

2-(2,6-Xylyloxy)ethylaminoguanidine Sulfate (12).—2-(2,6-Xylyloxy)ethylhydrazine was prepared from 2-(2,6-xylyloxy)-ethyl bromide and hydrazine hydrate in ethanol; hydrochloride m.p. 108–110.5°.

Anal. Calcd. for $C_{10}H_{16}N_2O\cdot HCl$: C, 55.41; H, 7.90; N, 12.93. Found: C, 55.24; H, 8.09; N, 13.04.

Reaction of 4.5 g. (0.025 mole) of the hydrazine with 2-methyl-2-thiopseudourea sulfate (6.3 g., 0.025 mole) in water at reflux temperature for 5 hr. yielded **12**, m.p. 211–213° (from water).[22]

1-Amino-3-[2-(2,6-xylyloxy)ethylamino]guanidine Hydriodide (13).—2-(2,6-Xylyloxy)ethylhydrazine (4.72 g., 0.02 mole) was treated with 2-methyl-2-thioisosemicarbazide hydriodide (4.73 g., 0.02 mole) in ethanol in the usual way. Recrystallization from isopropyl alcohol yielded **15** (2.07 g., 28%), m.p. 150–152°.

1-Benzylideneamino-3-[2-(2,6-xylyloxy)ethyl]guanidine Sulfate Monohydrate (11).—1-Amino-3-[2-(2,6-xylyloxy)ethyl]guanidine hydriodide (5.0 g., 0.014 mole) was dissolved in water and mixed with a solution of silver sulfate (2.25 g., 0.0072 mole) in

(19) Melting points were recorded using an Electrothermal apparatus comprising a gas-heated block and a thermometer calibrated for stem exposure.

(20) F. F. Blicke and C. Lee, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(21) I. B. Douglas and F. B. Dains [*ibid.*, **56**, 1408 (1934)] have reported the resistance to hydrolysis of 1-benzoylthioureas derived from secondary amines.

(22) Independently Augstein, *et al.*,[8] prepared this aminoguanidine by a similar procedure.

water acidified with a few drops of glacial acetic acid. The mixture was set aside at room temperature with intermittent agitation for 2 hr. and filtered, and the filtrate was evaporated to dryness. The crude aminoguanidine sulfate (3.2 g.) so obtained was dissolved in water, filtered from a trace of insoluble material, acidified (H_2SO_4), and, to the resultant solution, benzaldehyde (1.59 g., 0.015 mole) dissolved in ethanol was added. A white solid precipitated which was separated and recrystallized from isopropyl alcohol and finally twice from water to yield the product (1.5 g., 29%) as the monohydrate, m.p. 184.5–186°.

1-Benzyl-3-benzylideneaminoguanidine (19).—In a similar manner 1-amino-3-benzylguanidine hydriodide (20.0 g., 0.069 mole) was converted to the sulfate and treated with benzaldehyde. The benzylideneaminoguanidine sulfate so obtained was converted to the free base by the addition of 40% NaOH. Recrystallization from benzene–petroleum ether (60–80°) yielded pure product (7.3 g., 42%), m.p. 115–119°. The picrate had m.p. 209–212° (lit.[23] m.p. 215–216°).

1-Benzylideneamino-3-(2-chlorobenzyl)guanidine (20).—In a similar manner 1-amino-3-(2-chlorobenzyl)guanidine hydriodide (15.0 g., 0.046 mole) was converted to **20**, and the free base was purified by three recrystallizations from benzene–petroleum ether; yield 4.3 g. (33%), m.p. 115.5–118.5.°

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

3-Amino-4-[2-(2,6-xylyloxyethyl)]-1,2,4-triazole (14).—A suspension of 1-amino-3-[2-(2,6-xylyloxy)ethyl]guanidine hydriodide (5.0 g., 0.014 mole) in formic acid (15 ml.) was boiled under reflux for 2 hr., evaporated to low bulk, diluted with water, and basified with NaOH solution. Solid separated on standing, which was filtered off, washed with water, and recrystallized from *n*-butyl alcohol, affording the triazole (1.9 g., 59%), m.p. 248–250°.

3-Amino-4-benzyl-1,2,4-triazole (25) and 3-Benzylamino-1,2,4-triazole.—A suspension of 1-amino-3-benzylguanidine hydriodide (80.0 g., 0.275 mole) in formic acid (16 ml.) was heated on the steam bath for 1 hr., cooled, diluted with water, and neutralized with $NaHCO_3$ solution. After standing overnight, the precipitated solid was separated, washed with boiling water, and recrystallized from *n*-butyl alcohol affording **25** (22.7 g.) as colorless plates, m.p. 213–215°. From the mother liquors, more of this compound was obtained (6.7 g., m.p. 212–215°) and also 3-benzylamino-1,2,4-triazole[24] (2.2 g.), m.p. 161–163° (lit.[24] m.p. 164–165°).

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(24) M. Pesson and G. Polmanss, *Compt. rend.*, **247**, 787 (1958).

Totally Synthetic Steroid Hormones. V.[1] (±)-2,3-Dimethoxyestra-1,3,5(10)-trien-17β-ol and Some Congeners

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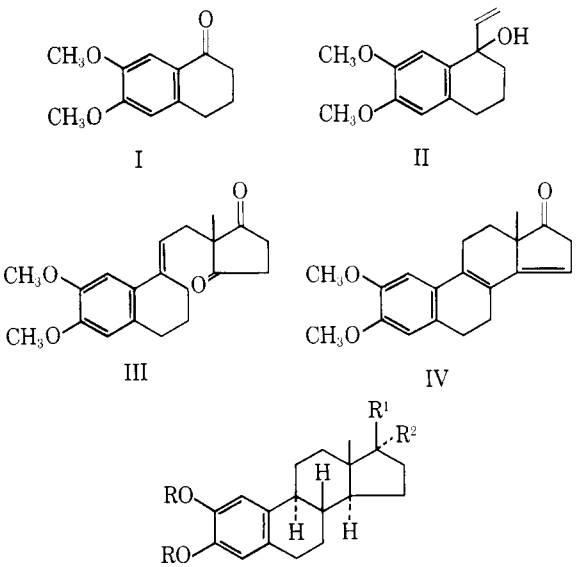
(±)-2,3-Dimethoxy-1,3,5(10)-estratrien-17-one and -17β-ol have been totally synthesized from 6,7-dimethoxy-1-tetralone. Their estrogenic and blood cholesterol lowering properties are recorded.

We[2] have demonstrated the flexibility of our recently described total syntheses of estrone[3] by their extension to a variety of related 13β-alkylgonanes. This paper describes a further application to compounds of the (±)-2,3-dimethoxyestra-1,3,5(10)-triene series which were required for biological evaluation. The project seemed worthwhile in view of the occurrence of 2-methoxyestrone as a metabolite of estradiol in man.[4]

The 6,7-dimethoxy-1-tetralone (I) required as starting material was made, following Haworth and Martin,[5] by cyclodehydrating 4-(3,4-dimethoxyphenyl)butyric acid which was obtained in two stages from veratrole by a modification of the published method,[5] or from 3,4-dimethoxycinnamic acid in five stages, by way of 3-(3,4-dimethoxyphenyl)propyl bromide. Both routes are described in the Experimental Section. The former is the more efficient.

The tetralone (I) was converted into compounds of the (±)-2,3-dimethoxyestra-1,3,5(10)-triene series by the general methods developed earlier.[2,3] Briefly, initial reaction with vinylmagnesium chloride in tetrahydrofuran gave the alcohol II which was condensed with 2-methylcyclopentane-1,3-dione to give the seco steroid III and transformed thence by acid cyclodehydration to the pentaene IV.[6] Catalytic hydrogenation of the



V, Δ^8; R = CH_3; R^1,R^2 = O
VI, Δ^8; R = CH_3; R^1 = OH; R^2 = H
VII, R = CH_3; R^1 = OH; R^2 = H
VIII, R = CH_3; R^1,R^2 = O
IX, $\Delta^{9(11)}$; R = CH_3; R^1,R^2 = O
X, R = H; R^1,R^2 = O

(1) Part IV: J. M. H. Graves, G. A. Hughes, T. Y. Jen, and H. Smith, *J. Chem. Soc.*, 5488 (1964).

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(4) (a) S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 754 (1957); *J. Biol. Chem.*, **229**, 519 (1957); (b) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958).

(5) R. D. Haworth and C. R. Martin, *J. Chem. Soc.*, 1485 (1932).