Imidazole Derivatives. IV. Synthesis and Pharmacologic Activity of Oxygenated Derivatives of Imidazo[1,2-*a*]pyridine

LUIGI ALMIRANTE,* ALFONSO MUGNAINI, NICOLA DE TOMA, AFRO GAMBA, WALTER MURMANN,

Research Department, Selvi and Co., Laboratorio Bioterapico Milanese, Milan, Italy

AND JOHN HIDALGO

Cutter Laboratories, Berkeley, California

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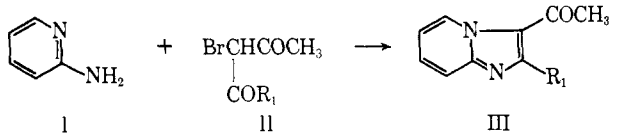
In the course of screening imidazo[1,2-*a*]pyridines, new oxygenated derivatives were synthesized: aldehydes, ketones, their derivatives, and the corresponding alcohols. Some semicarbazones and thiosemicarbazones manifested marked hypotensive activity but pulmonary hemodynamic studies indicate the need for further exhaustive hemodynamic studies of thiosemicarbazones and analogs in several animal species before proceeding to clinical pharmacology tests.

In our previous papers[1-3] on the chemical behavior of the imidazo[1,2-*a*]pyridine ring it was shown that this ring is similar to that of indole. Numerous derivatives of imidazo[1,2-*a*]pyridine and of analogous compounds have been synthesized and a large number of pharmacologic and phytopharmacologic data has been collected in order to determine the biological activity of this ring system. In this paper we report methods of synthesizing aldehydes, ketones, their derivatives, and the corresponding alcohols in which the radical is bound to position 3 of the imidazo[1,2-*a*]pyridine nucleus.

Chemistry.—The aldehydes were prepared by the procedure previously reported[4] for the synthesis of 3-formylimidazo[1,2-*a*]pyridine which employed Vilsmeier's reagent, *viz.*, $POCl_3$–DMF. Table I lists the aldehydes synthesized (**1–7**) and their derivatives: oximes (**8–14**), semicarbazones (**15–21**), thiosemicarbazones (**22–28**), guanylhydrazones (**29–35**), and the phenylhydrazone **36**. By treating 3-formylimidazo[1,2-*a*]pyridine with 3-amino-2-oxazolidone and 5-morpholinomethyl-3-amino-2-oxazolidone, **37** and **38**, respectively, were obtained. The ketones were obtained according to the method of Friedel and Crafts, by treating, in CS_2, derivatives of imidazo[1,2-*a*]pyridine, with Ac_2O and sublimed $AlCl_3$. All the ketones listed in Table II (**39–43**) were obtained in this way, in yields of 18–25%.

It was possible to prove that substitution occurred at position 3 by the classic synthesis of Tchitchibabin,



I II III

i.e., by treating 2-aminopyridine (I) with 2-bromoacetoacetaldehyde (II; R_1 = H) or with 3-bromoacetylacetone (II; R_1 = CH_3).

Attempts to carry out the Friedel–Crafts reaction in solvents other than CS_2, namely $PhNO_2$, $CHCl_3$, and CCl_4, were unsuccessful. Equally unsuccessful were attempts to synthesize the above ketones (as for the analogs of indole) by Grignard reactions or by reaction with $POCl_3$ and $AcNMe_2$.[5]

2-(*p*-Chlorophenyl)imidazo[1,2-*a*]pyridine and 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine did not react according to Friedel and Crafts under the above conditions. Primary alcohols (Table III; **59–65**) and secondary alcohols (**66–70**) were obtained by reducing the corresponding aldehydes and ketones, described earlier, with $NaBH_4$ in aq MeOH.

Pharmacological Studies.—The products synthesized were subjected to pharmacologic screening, according to our test schedule.[1-3] This screening elicited no activity comparable with that of 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine·HCl, which is the most active of the substances derived from imidazo[1,2-*a*]pyridine that we have synthesized.[1]

In the screening of the arterial pressure changes in rats, however, semicarbazones **15**, **18**, **19**, and **20**, thiosemicarbazones **22**, **25**, and **26**, and aminoguanido derivatives **29** and **30** proved to possess pronounced hypotensive activity. Thiosemicarbazone **22**, which from its ED_{50} seemed to be the most promising compound, was subjected to extensive pharmacologic testing, the results of which are summarized here. The effect on mean arterial pressure, mean peripheral pressure, myocardial tension, and central venous pressure was studied in anesthetized dogs. The results obtained with **22** at doses from 2.5 to 10 mg/kg iv in 4 dogs showed a decrease in peripheral resistance and an increase in myocardial tension. The central venous pressure was not appreciably affected. Oral administration of doses ranging from 25 to 100 mg/kg to 4 other, nonanesthetized, dogs caused a decrease in systolic pressure and an increase in heart rate.

The action on isolated rabbit heart shows that probably the slight cardiac stimulation noted *in vivo* is not due to a direct action on the myocardial fiber. The cardiac levels of norepinephrine in guinea pigs were unchanged following dosage with **22**. Simultaneous pulmonary hemodynamic studies were conducted on **22** after pulmonary edema had been observed in dogs, cats, and guinea pigs following administration of the

* To whom correspondence should be addressed.

(1) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. L. Rugarli, A. Biancotti, A. Gamba, and W. Murmann, *J. Med. Chem.*, **8**, 305 (1965).

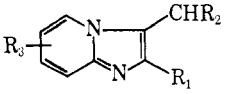
(2) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. L. Rugarli, A. Gamba, A. Olivi, and W. Murmann, *ibid.*, **9**, 29 (1966).

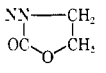
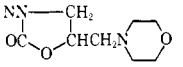
(3) L. Almirante, A. Mugnaini, P. L. Rugarli, A. Gamba, E. Zefelippo, N. De Toma, and W. Murmann, *ibid.*, **12**, 122 (1969).

(4) L. Almirante, A. Mugnaini, L. Polo, and E. Provinciali, *Boll. Chim Farm.*, **105**, 32 (1966).

(5) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).

TABLE I
ALDEHYDES AND DERIVATIVES



No.	R_1	R_2	R_3	Method	Obtained as:	Recrystn solvent	Mp, °C	Formula[a]
1	H	O	H	A	B	H_2O	127–129	$C_8H_6N_2O$
2	CH_3	O	H	A	B	C_6H_6–hexane	122–123	$C_9H_8N_2O$
3	H	O	7-CH_3	A	B	Hexane	83–85	$C_9H_8N_2O$
4	H	O	6-Cl	A	B	C_6H_6-hexane	162–163	$C_8H_5ClN_2O$
5	H	O	6-Br	A	B	C_6H_6–hexane	172–174	$C_8H_5BrN_2O$
6	C_6H_4-Cl(*p*)	O	H	A	B	DMF	213–215	$C_{14}H_9ClN_2O$
7	$C_6H_4SO_2CH_3$(*p*)	O	H	A	B	MeOH	206–207	$C_{15}H_{12}N_2O_3S$
8	H	NOH	H	B	B	50% EtOH	206–207	$C_8H_7N_3O$
9	CH_3	NOH	H	B	B	EtOH	252–254	$C_9H_9N_3O$
10	H	NOH	7-CH_3	B	B	50% EtOH	196–198	$C_9H_9N_3O$
11	H	NOH	6-Cl	B	B	EtOH	269–271	$C_8H_6ClN_3O$
12	H	NOH	6-Br	B	B	EtOH	267–269	$C_8H_6BrN_3O$
13	C_6H_4Cl(*p*)	NOH	H	B	B	DMF	282–284	$C_{14}H_{10}ClN_3O$
14	$C_6H_4SO_2CH_3$(*p*)	NOH	H	B	B	DMF	306–308	$C_{15}H_{13}N_3O_3S$
15	H	$NNHCONH_2$	H	C	HCl	10% HCl	242–244	$C_9H_{10}ClN_5O$
16	CH_3	$NNHCONH_2$	H	C	HCl	37% HCl	249–250	$C_{10}H_{12}ClN_5O$
17	H	$NNHCONH_2$	7-CH_3	C	HCl	37% HCl	256–257	$C_{10}H_{12}ClN_5O$
18	H	$NNHCONH_2$	6-Cl	C	HCl	37% HCl	290–292	$C_9H_9Cl_2N_5O$
19	H	$NNHCONH_2$	6-Br	C	HCl	37% HCl	286–287	$C_9H_9BrClN_5O$
20	C_6H_4Cl(*p*)	$NNHCONH_2$	H	C[b]	HCl	DMF	321–323	$C_{15}H_{13}Cl_2N_5O$
21	$C_6H_4SO_2CH_3$(*p*)	$NNHCONH_2$	H	C	HCl	37% HCl	346–347	$C_{16}H_{16}ClN_5O_3S$
22	H	$NNHCSNH_2$	H	D	HCl	10% HCl	249–250	$C_9H_{10}ClN_5S$
23	CH_3	$NNHCSNH_2$	H	D	HCl	10% HCl	280–281	$C_{10}H_{12}ClN_5S$
24	H	$NNHCSNH_2$	7-CH_3	D	HCl	10% HCl	272–274	$C_{10}H_{12}ClN_5S$
25	H	$NNHCSNH_2$	6-Cl	D	HCl	10% HCl	286–288	$C_9H_9Cl_2N_5S$
26	H	$NNHCSNH_2$	6-Br	D	HCl	10% HCl	289–291	$C_9H_9BrClN_5S$
27	C_6H_4Cl(*p*)	$NNHCSNH_2$	H	D	HCl	10% HCl	312–314	$C_{15}H_{13}Cl_2N_5S$
28	$C_6H_4SO_2CH_3$(*p*)	$NNHCSNH_2$	H	D	B	DMF	379–380	$C_{16}H_{15}N_5O_2S_2$
29	H	$NNHC(NH)NH_2$	H	E	2HCl	75% EtOH	323–324	$C_9H_{12}Cl_2N_6$
30	CH_3	$NNHC(NH)NH_2$	H	E	2HCl	10% HCl	278–279	$C_{10}H_{14}Cl_2N_6$
31	H	$NNHC(NH)NH_2$	7-CH_3	E	2HCl	EtOH	310–312	$C_{10}H_{14}Cl_2N_6$
32	H	$NNHC(NH)NH_2$	6-Cl	E	2HCl	10% HCl	342–344	$C_9H_{11}Cl_3N_6$
33	H	$NNHC(NH)NH_2$	6-Br	E	2HCl	10% HCl	326–328	$C_9H_{11}BrCl_2N_6$
34	C_6H_4Cl(*p*)	$NNHC(NH)NH_2$	H	E	2HCl	10% HCl	311–312	$C_{15}H_{15}Cl_3N_6$
35	$C_6H_4SO_2CH_3$(*p*)	$NNHC(NH)NH_2$	H	E	2HCl	10% HCl	320–322	$C_{16}H_{18}Cl_2N_6O_2S$
36	H	$NNHC_6H_5$	H	F	HCl	10% HCl	289–290	$C_{14}H_{13}ClN_4$
37	H		H	F	HCl	10% HCl	252–253	$C_{11}H_{11}ClN_4O_2$
38	H		H	F	Dimaleate	85% EtOH	181–183	$C_{16}H_{19}N_5O_3 \cdot C_8H_8O_8$

[a] All compounds were analyzed for C, H, N. [b] 95% AcOH was used as solvent. [c] Free base.

substance. In 3 anesthetized dogs an increase in right ventricular pressure, a decrease in left auricular, and an increase in right auricular pressure were observed after iv administration of **22**. These findings agree with the hypothesis that the pulmonary edema seen after administration of **22**, was due, at least in part, to changes in pulmonary hemodynamics. These variations result in an increase of pulmonary resistance and hence of pulmonary pressure. Injection of the substance into the portal vein induced a less marked effect but in the same direction. The action on the lungs has also been elicited in rats. Five animals administered an ip injection of 100 mg/kg of **22** developed pleural effusion and probable edema in 16 hr.

Rhesus monkeys administered orally 100 or 200 mg/kg daily for 10 days or so showed no detectable traces of pulmonary edema at necropsy. The fact remains, however, that the arterial pressure of monkeys with indwelling catheter was unchanged following the oral administration of 25 or 50 mg/kg of **22**.

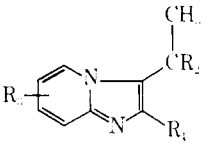
The above results, which applied also to other products of the same series, discourage the use of **22** or of other analogs in man. Clinical trials with thiosemicarbazones and analogs (numerous products of this type are being studied in the antiviral field) should probably be preceded by close study of pulmonary hemodynamics in animals of several species.

Experimental Section[6]

3-Formyl-6-chloroimidazo[1,2-*a*]pyridine (Table I; 4). Method A.—A soln of 45.75 g of 6-chloroimidazo[1,2-*a*]pyri-

(6) All melting points were taken in a capillary apparatus and were corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

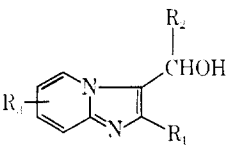
TABLE II
KETONES AND DERIVATIVES



No.	R_1	R_2	R_3	Method	Obtained as:	Recrystn solvent	Mp, °C	Formula[a]
39	H	O	H	G, H	B[b]	Hexane	109–110	$C_9H_8N_2O$
					HBr	95% EtOH	315–316	$C_9H_9BrN_2O$
40	CH_3	O	H	G, H	B	Hexane	110–111	$C_{10}H_{10}N_2O$
41	H	O	7-CH_3	G	B	Hexane	138–140	$C_{10}H_{10}N_2O$
42	H	O	6-Cl	G	B	C_6H_6	133–134	$C_9H_7ClN_2O$
43	H	O	6-Br	G	B	C_6H_6	145–147	$C_9H_7BrN_2O$
44	H	$NNHCONH_2$	H	I	B	DMF	275–277	$C_{10}H_{11}N_5O$
45	CH_3	$NNHCONH_2$	H	I	B	DMF	278–280	$C_{11}H_{13}N_5O$
46	H	$NNHCONH_2$	7-CH_3	I	B	DMF	281–282	$C_{11}H_{13}N_5O$
47	H	$NNHCONH_2$	6-Cl	I	B	DMF	347–348	$C_{10}H_{10}ClN_5O$
48	H	$NNHCONH_2$	6-Br	I	B	DMF	>390	$C_{10}H_{10}BrN_5O$
49	H	$NNHCSNH_2$	H	L	B	DMF	289–290	$C_{10}H_{11}N_5S$
50	CH_3	$NNHCSNH_2$	H	L	B	DMF	267–268	$C_{11}H_{13}N_5S$
					HCl	37% HCl	266–267	$C_{11}H_{14}ClN_5S$
51	H	$NNHCSNH_2$	7-CH_3	L	B	DMF	281–283	$C_{11}H_{13}N_5S$
52	H	$NNHCSNH_2$	6-Cl	L	B	DMF	344–345	$C_{10}H_{10}ClN_5S$
53	H	$NNHCSNH_2$	6-Br	L	B	DMF	379–381	$C_{10}H_{10}BrN_5S$
54	H	$NNHC(NH)NH_2$	H	M	B	EtOH	241–242	$C_{10}H_{12}N_6$
					2HCl	20% HCl	331–333	$C_{10}H_{14}Cl_2N_6$
55	CH_3	$NNHC(NH)NH_2$	H	M	B	EtOH	240–241	$C_{11}H_{14}N_6$
					2HCl	20% HCl	295–297	$C_{11}H_{16}Cl_2N_6$
56	H	$NNHC(NH)NH_2$	7-CH_3	M	B	EtOH	252–254	$C_{11}H_{14}N_6$
					2HCl	20% HCl	324–326	$C_{11}H_{16}Cl_2N_6$
57	H	$NNHC(NH)NH_2$	6-Cl	M	B	EtOH	275–277	$C_{10}H_{11}ClN_6$
					2HCl	20% HCl	333–335	$C_{10}H_{13}Cl_3N_6$
58	H	$NNHC(NH)NH_2$	6-Br	M	B	EtOH	269–271	$C_{10}H_{11}BrN_6$
					2HCl	20% HCl	335–337	$C_{10}H_{13}BrCl_2N_6$

[a] All compounds were analyzed for C, H, N. [b] Free base.

TABLE III
PRIMARY AND SECONDARY ALCOHOLS



No.	R_1	R_2	R_3	Method	Obtained as:	Recrystn solvent	Mp, °C	Formula[a]
59	H	H	H	N	B[b]	C_6H_6	132–134	$C_9H_{10}N_2O$
					HCl	95% EtOH	168–170	$C_9H_9ClN_2O$
60	CH_3	H	H	N	B	H_2O	169–171	$C_{10}H_{12}N_2O$
					HCl	95% EtOH	171–173	$C_{10}H_{11}ClN_2O$
61	H	H	7-CH_3	N	B	$PhCH_3$	134–136	$C_{10}H_{12}N_2O$
62	H	H	6-Cl	N	B	95% EtOH	212–214	$C_9H_7ClN_2O$
63	H	H	6-Br	N	B	95% EtOH	232–234	$C_9H_7BrN_2O$
64	$C_6H_4Cl(p)$	H	H	N	B	95% EtOH	214–216	$C_{14}H_{11}ClN_2O$
65	$C_6H_4SO_2CH_3(p)$	H	H	N	B	DMF	231–233	$C_{15}H_{14}N_2O_3S$
66	H	CH_3	H	N	B	$PhCH_3$	148–150	$C_{10}H_{12}N_2O$
					HCl	95% EtOH	162–164	$C_{10}H_{11}ClN_2O$
67	CH_3	CH_3	H	N	B	C_6H_6	134–135	$C_{10}H_{12}N_2O$
68	H	CH_3	7-CH_3	N	B	$PhCH_3$	149–151	$C_{10}H_{12}N_2O$
69	H	CH_3	6-Cl	N	B	$PhCH_3$	178–179	$C_9H_9ClN_2O$
70	H	CH_3	6-Br	N	B	$PhCH_3$	183–185	$C_9H_9BrN_2O$

[a] All compounds were analyzed for C, H, N. [b] Free base.

dine[4] (0.30 mole) in 80 ml of DMF was added dropwise to a soln of 120 g of $POCl_3$ (0.78 mole) in 200 ml of DMF. The mixture was heated slowly to 105°, an exothermic reaction developed, and dissoln was complete. The temp rose to 120° and the soln was left at 120–125° for 15 min, then cooled to 80°, and left for 3 hr with stirring. The reaction product pptd as the hydrochloride; it was dissolved in H_2O (500 ml) with 35% HCl (20 ml), decolorized with charcoal, and made alkaline with 20% NaOH. The resulting crude product was purified by crystn from C_6H_6 and hexane (13 g, yield 24%).

2-Methyl-3-formylimidazo[1,2-*a*]pyridine Oxime (Table I; 9). Method B.—To a soln of 15 g of 2-methyl-3-formylimidazo-

[1,2-*a*]pyridine (0.094 mole) in 75 ml of EtOH was added a soln of 19.6 g of $NH_2OH \cdot HCl$ (0.28 mole) and 12 g of 95% NaOH (0.28 mole) in 120 ml of H_2O. After refluxing for 1.5 hr flaky crystals were obtained (14.4 g, yield 88%).

3-Formylimidazo[1,2-*a*]pyridine Semicarbazone·HCl (Table I; 15). Method C.—To 7.30 g of 3-formylimidazo[1,2-*a*]pyridine (0.05 mole) dissolved in 31.2 ml of 10% HCl was added a soln of 5.90 g of $H_2NNHCONH_2 \cdot HCl$ (0.053 mole) in 31.2 ml of 10% HCl and 10 ml of H_2O. A bulky ppt formed at once; it was filtered and dried (11 g, yield 92%).

3-Formyl-6-bromoimidazo[1,2-*a*]pyridine Thiosemicarbazone·HCl (Table I; 22). Method D.—To a soln of 1.12 g of 3-formyl-6-bromoimidazo[1,2-*a*]pyridine[4] (0.005 mole) in 10 ml of 10% HCl was added a soln of 0.478 g of $H_2NNHCSNH_2$ (0.053 mole) in 3 ml of 10% HCl. After cooling overnight, the condensation product pptd as a bulky mass; it was filtered and dried (1.5 g, yield 90%).

2-(*p*-Chlorophenyl)-3-formylimidazo[1,2-*a*]pyridine Guanylhydrazone·2 HCl (Table I; 34). Method E.—A soln of 12.8 g of 2-(*p*-chlorophenyl)-3-formylimidazo[1,2-*a*]pyridine (0.05 mole) in 1280 ml of boiling 10% HCl was filtered hot and added to a soln of 8.25 g of $H_2NNHC(=NH)NH_2 \cdot H_2CO_3$ (0.06 mole) in 50 ml of cold 10% HCl. Shiny white crystals pptd which were filtered after cooling (17.5 g) and which after recrystn from 3300 ml of 1% HCl gave 14.2 g (74%).

3-[(Imidazo[1,2-*a*]pyridin-3-ylmethylene)amino]-5-morpholinomethyl-2-oxazolidone Dimaleate (Table I; 38). Method F.—To a soln of 2.01 g of 3-amino-5-morpholinomethyl-2-oxazolidone (0.01 mole) in 20 ml of EtOH, 10 ml of H_2O, and 5 ml of 10% HCl was added a soln of 1.46 g of 3-formylimidazo[1,2-*a*]pyridine (0.01 mole) in 10 ml of EtOH and 5 ml of 10% HCl. The mixture was heated to 70° for 4 hr. The sepd oil was extracted with $CHCl_3$, the solvent evapd, and the residue dissolved in 10 ml of EtOH and treated with 1.32 g of maleic acid in EtOH. On heating on a water bath **38**·dimaleate formed (1.6 g, yield 28%).

2-Methyl-3-acetylimidazo[1,2-*a*]pyridine (Table II; 40). Method G.—To a soln of 39.6 g of 2-methylimidazo[1,2-*a*]pyridine (0.3 mole) in 120 ml of CS_2 was added, very slowly, 90 g of anhyd $AlCl_3$, with external cooling. After stirring for 30 min at room temp the mixture was refluxed gently and 22.5 ml of Ac_2O was added drop by drop, in 30 min. After refluxing for 1 hr, the CS_2 was evapd and the residue mixed with crushed ice, made alkaline with NaOH, and extracted with CH_2Cl_2. The soln was dried (K_2CO_3) and evapd to dryness. The resulting oil was distd under vacuum. Starting product, (14.5 g), bp 92–100° (0.8 mm), and 15 g of the desired product, bp 126–130° (0.8 mm), were obtained. The oil was then crystd from ligroin giving 12 g of the pure product, yield 37% (based on recovered starting material).

3-Acetylimidazo[1,2-*a*]pyridine (Table II; 39). Method H.—To a soln of 17.5 g of 2-aminopyridine (0.185 mole) in 20 ml of EtOH was added 15.2 g of 2-bromoacetoacetaldehyde (0.927 mole).[7] The exothermic reaction was moderated by cooling. The mixture was refluxed for 10 hr, the solvent evapd to dryness, and the residue mixed with H_2O and 20% NaOH and extracted with Et_2O. The soln was dried (K_2CO_3) and evapd. The residue was distd, recovering first 9.6 g of 2-aminopyridine, and then the product, bp 128–130° (1.5 mm). The yield was 4 g (30%), based on 2-aminopyridine consumed.

2-Methyl-3-acetylimidazo[1,2-*a*]pyridine (Table II; 40). Method H.—A soln of 28.5 g of 2-aminopyridine (0.313 mole) in 20 ml of Et_2O was treated as indicated in the previous example with 28 g of crude 3-bromoacetylacetone[8] (0.156 mole). After evapg the solvent, the residue was distd to yield 14 g of 2-aminopyridine and 15 g of product, bp 125–135° (0.6 mm), mp 108–109°.

3-Acetylimidazo[1,2-*a*]pyridine Semicarbazone (Table II; 44). Method I.—To a soln of 20 g of 3-acetylimidazo[1,2-*a*]pyridine (0.125 mole) in 20 ml of H_2O was added a soln of 55.7 g of $H_2NNHCONH_2 \cdot HCl$ (0.5 mole) in 100 ml of 10% NaOH (0.25 mole). The mixture was refluxed for 2 hr, made alkaline with Na_2CO_3, filtered, and washed with H_2O until neutral (21 g, yield 77%). The hydrochloride of this product hydrolyzes very easily.

3-Acetyl-6-chloroimidazo[1,2-*a*]pyridine Thiosemicarbazone (Table II; 52). Method J.—A soln of 2 g of 3-acetyl-6-chloroimidazo[1,2-*a*]pyridine (0.0103 mole), 1.87 g of $H_2NCSNHNH_2$ (0.0206 mole), and 2.6 g of $H_2NCSNHNH_2 \cdot HCl$ (0.0206 mole) in 20 ml of H_2O and 20 ml of EtOH was refluxed for 2 hr, while still hot, the mixture was made alkaline with a satd soln of Na_2CO_3, and the ppt (2.8 g; yield 97%) was filtered and washed with H_2O until neutral.

3-Acetylimidazo[1,2-*a*]pyridine Guanylhydrazone (Table II; 54). Method K.—A soln of 2 g of 3-acetylimidazo[1,2-*a*]pyridine (0.0125 mole) and 6.8 g of $H_2NNHC(=NH)NH_2 \cdot H_2CO_3$ (0.05 mole) in 75 ml of 1 *N* HCl was refluxed for 2 hr; the resulting soln was made strongly alkaline with 20% NaOH and cooled. The thick oil, which was obtained, solidified and was recrystd from C_6H_6 and ligroin (1.5 g, yield 59%).

2-Methyl-3-hydroxymethylimidazo[1,2-*a*]pyridine (Table III; 61). Method L.—A soln of 3.7 g of 2-methyl-3-formylimidazo-[1,2-*a*]pyridine (0.023 mole) in 37 ml of MeOH was cooled to 10° and added to a soln of 0.437 g of $NaBH_4$ (0.0115 mole) in 5 ml of H_2O in 5 min, keeping the temp at 10–15°. The soln was evapd to dryness and the residue recrystd from 30 ml of H_2O (2.9 g, yield 77%).

(7) N. K. Kochetkov, E. E. Nifant'ev, and N. V. Molodtsov, *Zh. Obshch. Khim.*, **29**, 2330 (1959); *Chem. Abstr.*, **54**, 14230*h* (1960).

(8) D. F. Tavares, W. I. O'Sullivan, and C. R. Hauser, *J. Org. Chem.*, **27**, 1251 (1962).

Aralkylaminoguanidines and Related Compounds

JOHN B. BREAM,* CLAUDE W. PICARD, TREVOR G. WHITE,

Research Laboratories, A. Wander Ltd., Kings Langley, Hertfordshire, England

AND HANS LAUENER

Research Institute, Dr. A. Wander S.A., Berne, Switzerland

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A series of substituted aralkylaminoguanidines (I) was synthesized and evaluated for pharmacological activity. The compounds were prepared by catalytic reduction of the guanylhydrazones or by reaction of the aralkylhydrazines with either *S*-methylisothiouronium salts or cyanamide. A method of separating mixtures of I and II obtained by the reaction with *S*-methylisothiouronium salts is described. Some of the aralkylaminoguanidines (**I**) possess adrenergic neurone blocking activity and produce a marked lowering of blood pressure in the hypertensive rat. Some structure–activity relationships are discussed.

During an investigation of compounds containing the hydrazino group, a series of new aralkylaminoguanidines was prepared. Some of these were found to possess marked adrenergic neurone blocking activity similar in character to that of guanethidine. Amongst them, β-(2,6-dichlorophenyl)ethylaminoguanidine hydrochloride (**10**) and γ-phenylpropylaminoguanidine hydrochloride (**26**) proved of special interest as potentially

* To whom correspondence should be addressed.