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The condensation of various halomethyl heterocycles with the potassium salt of the alanine derivative **3**, followed by hydrolysis, gave a series of novel 3-heterocyclic-2-methylalanines.

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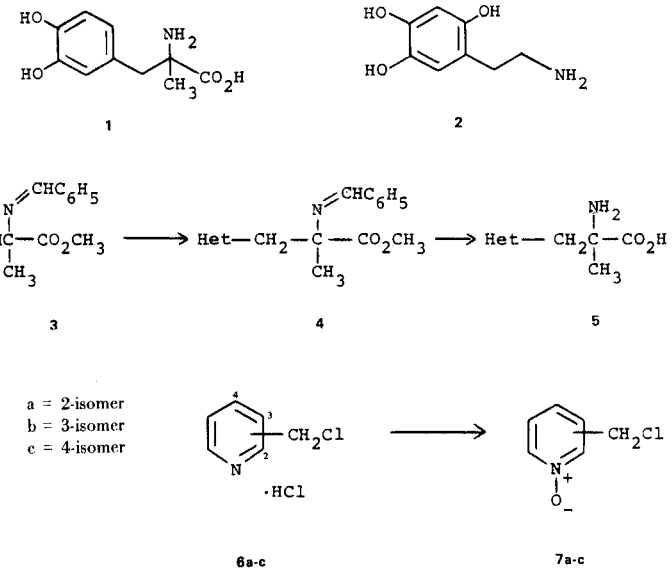
Several workers have recently reported on their efforts to modify the action and turnover of catecholamines through the preparation of various alkylated and homologated derivatives of α-methyldopa, **1** (1-3). In the present study, we have prepared a series of analogs possessing heterocyclic rings in the place of the catechol moiety. These heterocycles have hydroxyl groups and hetero atoms suitably placed about the ring in order to potentially interact with the receptor sites of the enzymes involved in catecholamine recognition and synthesis through hydrogen bonding and electronic interactions. In the case of the six membered ring analogs, these considerations suggested the incorporation of hetero atoms in the positions corresponding to C-3 and C-4 of the catechol nucleus. A hetero atom in the "C-6" position was also considered of interest, since it is well known that 6-hydroxydopamine **2** has great affinity for sympathetic neurons (4).



It appeared that combinations of various halomethyl heterocycles with a suitably protected active hydrogen compound would offer the most general synthetic route to the required series. A convenient approach involved synthesis of the Schiff base **3** from an aqueous solution of methyl alanate and benzaldehyde. The potassium salt of **3** reacted rapidly and cleanly in all cases with the halomethyl heterocycles in tetrahydrofuran-dimethyl sulfoxide mixtures at -30° to give the esters **4**. It is interesting to note that these condensations were very sluggish when the lithium salt of **3** was employed and extensive side reactions occurred.

The crude esters were treated with two equivalents of sodium hydroxide followed by acidification to *p*H 3 and passage through an ion exchange column to remove inorganics. The yields of crude amino acids thus obtained ranged from 50-70% of material sufficiently pure for use in any succeeding steps and a single crystallization generally gave analytically pure **5**. Several of the products were quite hydroscopic and removal of the last traces of water often proved impossible. The results of the condensations and the further transformations of the products are summarized in the table. Since the inception of this work, other groups have reported similar uses of Schiff bases in the synthesis of amino acids (5,6,7).

Synthesis of the three chloromethylpyridine *N*-oxides (**7a-c**) required for the synthesis of **8-10** has been previously described by reaction of the corresponding hydroxymethylpyridine *N*-oxides with thionyl chloride under controlled conditions (8). However, we have found a more convenient alternative, involving treatment of the chloromethylpyridine *hydrochlorides* **6a-c** with an excess of *m*-chloroperbenzoic acid in chloroform giving the *N*-oxides **7** in 60-80% yiels (Method H). This procedure gives a yield of 2-chloromethylpyridine *N*-oxide superior to the process employing hydrogen peroxide-acetic acid (9) and has the further advantage of being applicable to the 3- and 4-isomers as well. The 3-pyridylalanines **11-13** were obtained from the *N*-oxides **8-10** by catalytic reduction over palladium on carbon (Method B).

For the synthesis of the analogs **19-22** the hydroxymethylpyridine **16** (10) was converted to the chloromethyl derivative **17** with thionyl chloride. The 2-chloro substituent rendered the free base relatively stable and it underwent smooth condensation with **3** to give, after hydrolysis, the pyridylalanine derivative **19**. The latter compound was hydrolyzed to the pyridone **20** by treatment with potassium hydroxide at 240° in a stainless steel bomb (Method C). The chloromethylpyridine **17** could also be oxidized to the *N*-oxide **18** which gave on condensation with **3** the corresponding amino acid **21**. The hydrolysis of **21** to **22** was accomplished under milder conditions with sodium hydroxide, as expected for the for the more reactive *N*-oxide system (Method D). We were unable to effect reduction of the *N*-oxide **22** to 20 under a variety of conditions.

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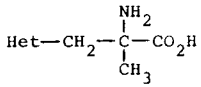
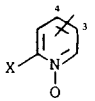
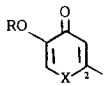
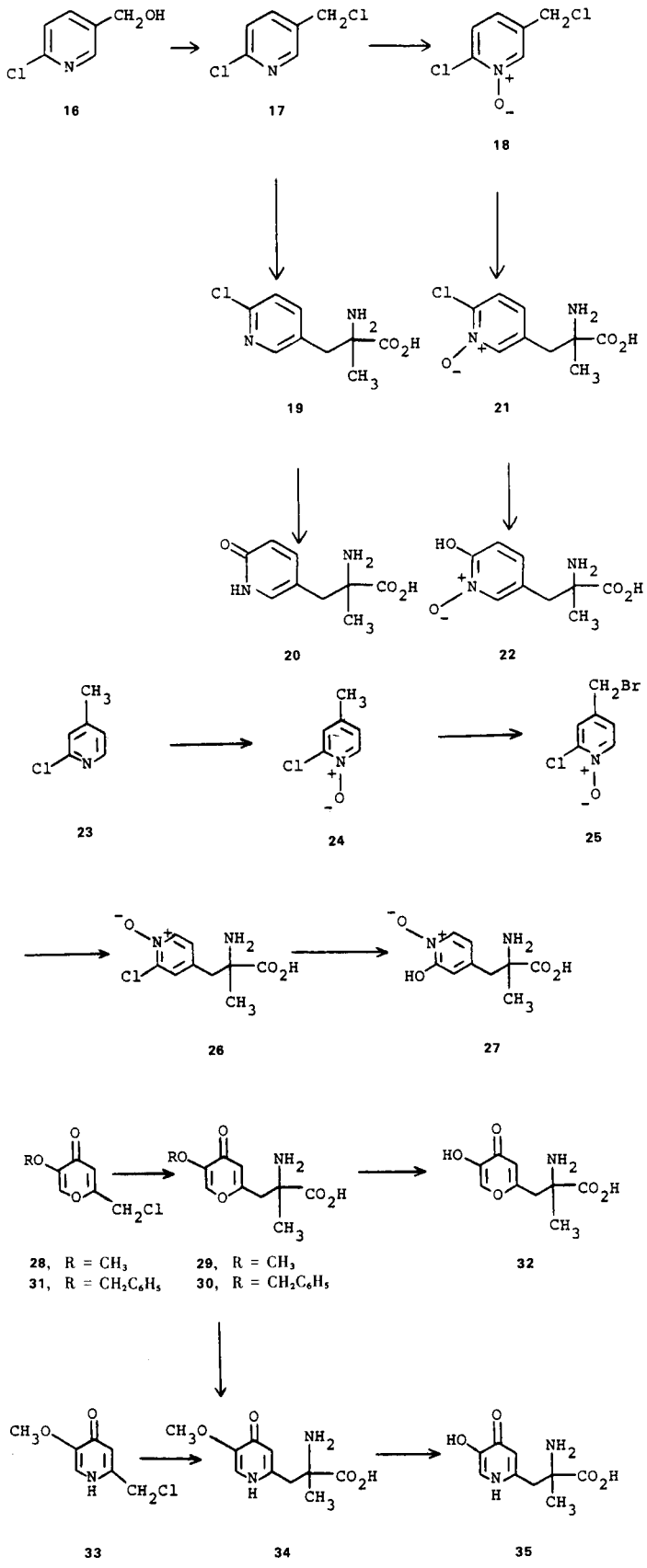
Table I



Heterocycle	Compound No.	Substitution Position	X,R	Method	Yield	M.p. °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	8	2		A	51	244-247	55.10	6.17	14.28	55.06	6.17	14.18
	9	3		A	24	288-289 dec.	55.10	6.17	14.28	55.10	5.93	14.39
	10	4		A	55	202-205 dec.	53.85 (a)	6.28	13.96	53.62	6.02	13.61
	11	2		B	95	247-249	55.99	6.71	15.55	59.74	6.49	15.58
	12	3		B	95	295-296	58.52 (a)	6.82	15.17	58.02	6.97	15.05
	13	4		B	91	259-260	59.99	6.71	15.55	59.82	6.72	15.53
	14 (b)	2		A	31	228-230	47.22 (c)	5.70	6.88	47.04	5.62	6.97
	15 (b)	3		A	39	292-299	51.87	5.99	7.56	51.78	5.83	7.66
	19	3	Cl	A	41	261-263	50.36	5.17	13.05	50.20	5.25	12.98
	20	3	OH	C	52	312-315	52.54 (a)	6.37	13.51	52.57	6.39	13.51
	21	3	Cl	A	21	180-183	38.52 (d)	4.85	9.98	38.25	4.84	9.85
	22	3	OH	D	95	291-293	49.88 (a)	5.81	12.93	49.83	5.81	12.84
	26	4	Cl	A	28	175-178	(e)					
	27	4	OH	D	28	275-280	49.26 (f)	5.84	12.77	49.14	5.91	12.67
	29	2	O, CH_3	A	34	234-238	52.86	5.77	6.16	52.83	5.99	5.96
	30	2	O, C_7H_8	A	29	250-251	63.36	5.65	4.62	63.38	5.68	4.63
	32	2	O, H	E	91	225-227 dec.	50.71	5.20	6.57	50.72	5.16	6.50
	34	2	NH, CH_3	A,F	68,69	236-238	37.99 (g)	5.10	8.86	37.87	5.18	8.86
	35	2	NH, N	G	71	228-230 (h)	36.26	4.58	9.43	36.25	4.51	9.28

(a) Calcd. values include 0.25 mole water of hydration. (b) Starting bromomethylthiophenes were prepared according to K. Dittmar, R. P. Martin, W. Herz and S. J. Cristol, *J. Am. Chem. Soc.*, 71, 1201 (1949). (c) Calcd. values are for the hemi-hydrochloride. (d) Calcd. for 0.75 mole water: H_2O, 4.74. Found: H_2O, 4.57. (e) Sample contained traces of ethanol and water and no satisfactory analysis could be obtained. (f) Calcd. for 0.4 mole water: H_2O, 3.28. Found: H_2O, 3.23. (g) Isolated as hydrobromide salt; calcd. for 0.5 mole water: H_2O, 2.85; Br, 25.28. Found: H_2O, 3.34; Br, 25.88. (h) Isolated as the hydrobromide salt.



Attempted free radical monobromination of 2-chloro-4-methylpyridine **23** was unsuccessful and polybromination always predominated. The reaction could be readily monitored by observation of the nmr signals due to the protons bound to the C-4 methyl group and it was determined that di- and presumably tribrominated products formed during the early stages of the reaction. Similar difficulties have been encountered by other groups working with alkylpyridines (11). In contrast, free radical bromination of the derived *N*-oxide **24** (12) gave a 71% yield of the bromomethylpyridine **25** which led readily to the amino acids **26** and **27**.

In order to prepare analogs derived from kojic acid, the chloromethylpyrone **28** (13) was condensed with **3** to give the methoxypyrone **29**. Attempts to cleave **29** with hydrobromic acid to the hydroxypyrone **32** led only to decomposition, but **32** could be synthesized by selective hydrogenation of the benzyloxy-derivative **30** obtained from **31** (14). The pyrido compound **34** could be isolated from the condensation of **33** (15) with **3** or equally well from the aminolysis of **29** (Method F). Reaction of **34** with refluxing hydrobromic acid gave the final member of the series, **35**.

All of the compounds listed in the table, with the exception of **26** and **32**, were screened in hypertensive rat models. None of these compounds exhibited useful levels of antihypertensive activity.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on Varian XL-100 or HA-100 instruments; ir spectra were determined on Beckmann IR-9 or Digilab FTS-14 instruments. Mass spectra were determined on Varian CH-5 or CEC-21-100 instruments. The spectral data were consistent with the assigned structures in all cases.

Methyl *N*-Benzalalanate (**3**).

An ice cold solution of 70.0 g. (0.50 mole) of methyl alanate hydrochloride in 200 ml. of water was treated with 60.5 g. (0.6 mole) of triethylamine. After 10 minutes, 80 g. (0.75 mole) of benzaldehyde was added and the resulting mixture was allowed to warm to room temperature overnight. The reaction mixture was partitioned between water and benzene, and the brown oil isolated from the benzene layer was distilled to give 56.7 g. (56%) of **3**, b.p. 138-145° (4 mm).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.80; N, 7.32. Found: C, 69.10; H, 6.89; N, 7.31.

Method A is Illustrated by the Synthesis of Racemic 3-(3-Methoxy-4-oxo-4*H*-pyran-6-yl)-2-methylalanine (**29**).

A solution of 11.22 g. (0.100 mole) of potassium *tert*-butoxide in 200 ml. of dry THF was cooled to -30° under an argon atmosphere and a solution of 15.9 g. (0.0835 mole) of **3** in 20 ml. of THF was added. The resulting bright red solution was stirred at -30° for 30 minutes and 17.45 g. (0.1 mole) of **28** (13) was added in 100 ml. of DMSO. The resulting mixture was stirred 3 hours at -20 to -30°. was diluted with 350 ml. of methylene chloride and washed with 5 x 100 ml. of water.

The residue from the methylene chloride layer was dissolved in 100 ml. of ethanol and 84 ml. of 2 *N* sodium hydroxide and was stirred at 25° overnight. The pH of the solution was adjusted to 3 by addition of dilute hydrochloric acid and the mixture was evaporated to drynesss. The residue, 36.4 g., was dissolved in 500 ml. of water, filtered and applied to an ion exchange column containing 350 ml. of Dowex 50W resin in the H^+ form. The column was washed with water until neutral and then with 1-5% aqueous pyridine to elute **29**, 13.1 g. Recrystallizaiton from ethanol gave the analytical sample, 6.5 g. (34%), m.p. 232-234°.

Method B is Illustrated by the Synthesis of Racemic 2-Methyl-3-(2-pyridyl)alanine (**11**).

A solution of 2.50 g. (0.0128 mole) of **8** in 40 ml. of water was hydrogenated over 500 mg. of 10% palladium on charcoal overnight. The reaction mixture was filtered and evaporated to give 2.19 g. (95%) of **11**, m.p. 247-249°.

Method C; Racemic 3-(6-Hydroxy-2-pyridyl)-2-methylalanine (**20**).

A solution of 3.75 g. (0.0175 mole) of **19** in 75 ml. of 4 *N* potassium hydroxide was sealed in a stainless steel bomb and heated to 240° for 30 minutes. On cooling, the mixture was acidified with hydrochloric acid, evaporated to dryness and applied to an ion exchange column as described for Method A. Elution with 5% aqueous pyridine gave 3.0 g. (89%) of **20**, m.p. 312-315° dec.

Method D; Racemic 3-(1,2-Dihydro-1-hydroxy-2-oxo-4-pyridyl)-2-methylalanine (**27**).

A solution of 2.6 g. (0.0113 mole) of **26** and 4.5 g. (0.11 mole) of sodium hydroxide in 36 ml. of water was heated to 110° for 2 hours. On cooling, the reaction mixture was acidified with hydrochloric acid, evaporated to dryness and applied to an ion exchange column as described for Method A. Elution with 5% aqueous pyridine afforded 1.7 g. (71%) of **27**, m.p. 275-280°.

Method E: Racemic 3-(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)-2-methylalanine (**32**).

A suspension of 3.28 g. (0.00927 mole) of **32** as the hydrochloride was hydrogenated over 500 mg. of 10% palladium on charcoal in ethanol. Crystallization of the crude product from methanol gave 2.2 g. (91%) of **32**, m.p. 225-227° dec.

Method F; Racemic 3-(3-Methoxy-4-oxo-1*H*-6-pyridyl)-2-methylalanine (**34**).

A solution of 2.5 g. (0.011 mole) of **29** in 75 ml. of concentrated ammonium hydroxide was heated in a sealed tube at 100° overnight. The resulting solution was evaporated to a tan solid which was acidified with aqueous hydrobromic acid evaporated and crystallized from water to give 2.4 g. (69%) of **34**, as the hydrobromide, m.p. 236-238°.

Method G; Racemic 3-(3-Hydroxy-4-oxo-1*H*-6-pyridyl)-2-methylalanine (**35**).

A solution of 6.5 g. (0.0212 mole) of **34** in 50 ml. of 48% hydrobromic acid was heated to reflux for 19 hours. On cooling, the product separated to give 4.4 g. (71%) of **35**, as the hydrobromide, m.p. 228-230°.

Method H is Illustrated by the Synthesis of 2-Chloromethylpyridine 1-Oxide (**7a**).

To a mixture of 41.0 g. (0.25 mole) of 2-chloromethylpyridine hydrochloride and 35.5 g. of sodium sulfate in 1 l. of chloroform was added a solution of 150 g. (0.75 mole) of *m*-chloroperbenzoic acid in 1500 ml. of chloroform. The resulting mixture was stirred at room temperature for 60 hours and diluted with saturated potassium carbonate solution. The two phase mixture was filtered and the chloroform layer was washed with saturated potassium carbonate and saturated sodium chloride, and was evaporated to give 29.3 g. (82%) of **7a**, m.p. 72-75° (lit. (9) m.p. 75-77°).

The 4-chloromethylpyridine *N*-oxide (**7c**) was not stable as the free base and was isolated in 60% yield as its hydrochloride salt.

2-Chloro-5-chloromethylpyridine (**17**).

To a solution of 82.0 g. (0.57 mole) of **16** (10) in 1 l. of chloroform was added 280 g. (2.3 mole) of thionyl chloride over 1 hour. The resulting solution was refluxed for 24 hours and evaporated to an oil. The last traces of thionyl chloride were removed by azeotropic distillation with benzene to give 76.7 g. (quantitative) of a semi-solid which was suitable for use in the next step.

2-Chloro-5-chloromethylpyridine *N*-Oxide (**18**).

This compound was prepared according to Method H from 38.4 g. (0.24 mole) of crude **17**. Filtration through silica gel and crystallization from THF-hexane gave 15.4 g. (35%) of **18**, m.p. 88-90°.

Anal. Calcd. for $C_6H_5Cl_2NO$: C, 40.48; H, 2.83; N, 7.87. Found: C, 40.65; H, 2.84; N, 8.10.

4-Bromomethyl-2-chloropyridine *N*-Oxide Hydrobromide (**25**).

A solution of 2.00 g. (0.014 mole) of **24** (12), 2.4 g. (0.013 mole) of *N*-bromosuccinimide, and 100 mg. of benzoyl peroxide in 100 ml. of benzene was heated to reflux for 2 hours. An additional 100 mg. of benzoyl peroxide was added and reflux was continued for 4 hours. The mixture was washed with 5% sodium hydroxide and 4% hydrobromic acid, concentrated to 50 ml., diluted with 200 ml. of ether and saturated with gaseous hydrogen bromide to precipitate 3.0 g. (71%) of **25**. Recrystallization from methanol ether gave the analytical sample, m.p. 138-142°.

Anal. Calcd. for $C_6H_5BrClNO \cdot HBr$: C, 23.75; H, 1.99; N, 4.62. Found: C, 23.50; H, 2.21; N, 4.64.

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