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SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLINES FROM α-METHYLDOPA

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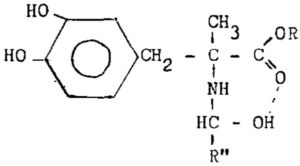
A short time ago some interesting compounds obtained by reactions between α-methyldopa, α-methyldopa esters, and aldehydes (1), (2), (3) were described.

These reactions were said to result in the formation of geminal aminocarbinols of the following type:

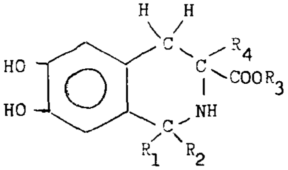


"A"

We tried to reproduce some of these reactions but failed to obtain the results that have been described.

Instead of the expected compounds the tetrahydroisoquinolines I, II, III, and VI (table I) were formed.

It has been known for some time that aminoacids can form tetrahydroisoquinolines according to the Pictet-Spengler synthesis (4)



I - VIII

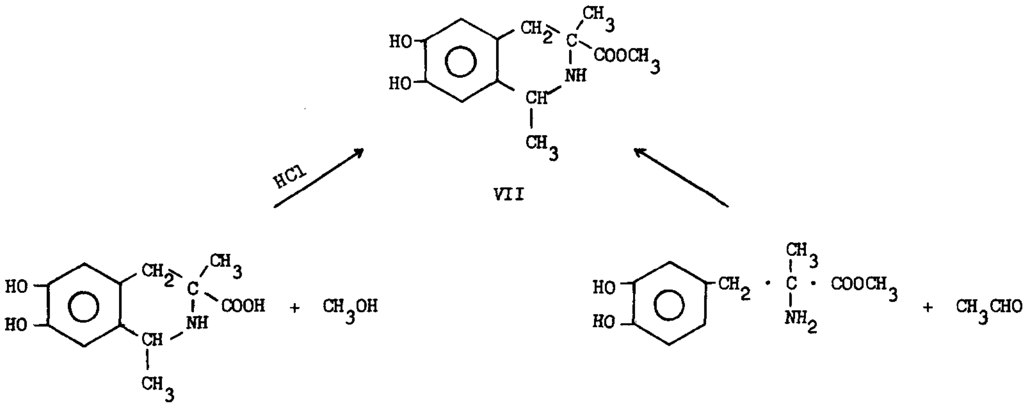
More recently it has been found possible to obtain 6,7-dihydroxy-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid from dopa and formaldehyde (5).

Besides the above mentioned compounds we have isolated products IV and V from condensations of phenylacetaldehyde with α-methyldopa and dopa respectively.

Compound II was suspended in dry methanol and hydrogen chloride was passed in. From this reaction mixture the methyl ester of II was isolated as compound VII. The hydrochloride of the ana-

TABLE I

No.	R_1	R_2	R_3	R_4	Mp. °C	Formula	Calcd. %				Found %			
							C	H	N		C	H	N	
I	H	H	H	CH_3	279-80	$C_{11}H_{13}NO_4$	59.18	5.87	6.28		59.09	6.07	6.24	
II	H	CH_3	H	CH_3	285-87	$C_{12}H_{15}NO_4$	60.75	6.37	5.90		60.63	6.32	5.85	
III	H	C_6H_5	H	CH_3	258-59	$C_{17}H_{17}NO_4$ 1/2 H_2O	66.23	5.89	4.55	2.92 (H_2O)	66.29	5.87	4.37	2.94 (H_2O)
IV	H	$C_6H_5CH_2$	H	CH_3	264-66	$C_{18}H_{19}NO_4$	68.99	6.11	4.47		68.87	6.18	4.44	
V	H	$C_6H_5CH_2$	H	H	221-23	$C_{17}H_{17}NO_4$ H_2O	64.34	6.64	4.41	5.68 (H_2O)	64.26	6.50	4.40	5.46 (H_2O)
VI	H	H	CH_3	CH_3	246-48	$C_{12}H_{15}NO_4$ HCl	52.66	5.88	5.12	12.96 (Cl^-)	52.50	5.97	5.12	13.08 (Cl^-)
VII	H	CH_3	CH_3	CH_3	191-93	$C_{13}H_{17}NO_4$	62.14	6.82	5.57		62.09	6.95	5.44	
VIII	CH_3	COOH	C_2H_5	CH_3	218-20	$C_{15}H_{19}NO_6$	58.24	6.19	4.53		57.16	6.20	4.51	
IX	CH_3	COOH	C_2H_5	CH_3	248-50	$C_{15}H_{19}NO_6$	58.24	6.19	4.53		58.05	6.21	4.41	



VII

II

logus compound VI was formed similarly from compound I. Compound VII can also be obtained by condensation of α-methyldopa methyl ester with acetaldehyde. α-Methyldopa does not react with pyruvic acid, but α-methyldopa ethyl ester reacts to yield two different tetrahydroisoquinolines, VIII and IX, which can be separated by their difference in solubility in water. Thin-layer chromatography on silica gel plates using n-butanol-acetic acid-water (80:20:20) gave R_f values for VIII 0,44 and for IX 0,6.

The physical and chemical properties of compounds I-V are typical for aminoacids. The stability of all compounds is typical for isoquinolines.

The structures were established on the basis of their elemental analysis together with their infrared and NMR spectral properties.

NMR spectra (33% CF_3COOD in D_2O, 60 mc) were obtained with TMS as external standard. Symbols s,d and m represent singlet, doublet, and multiplet respectively. All signals are reported as ppm in δ values, the coupling constants in cps.

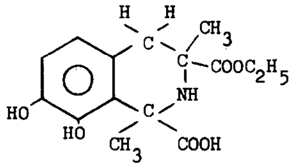
TABLE II

Compound	C_4-H_2	C_5-H	C_8-H	C_3-CH_3
I	2,96 d(17) 3,24 d(17)	6,72 s	6,72 s	1,59
II	3,00 d(17) 3,26 d (17)	6,71 s	6,71 s	1,68
III	3,15 d(17) 3,39 d(17)	6,76 s	6,27 s	1,76
IV	-	6,73 s	6,58 s	1,64
V	-	6,66 or 6,77 s	6,66 or 6,77 s	
VI	2,97 d(17) 3,24 d(17)	6,69 s	6,69 s	1,58
VII	3,04 d(17) 3,30 d(17)	6,72 or 6,74 s	6,72 or 6,74 s	1,68
VIII	3,03 d(15,5) 3,28 d(15,5)	6,79 or 7,11 s	6,79 or 7,11 s	1,83
compound	C_4-H_2	C_5-H	C_6-H	C_3-CH_3
IX	2,93 d(17) 3,27 d(17)	6,58 or 6,87 d(8,2)	6,58 or 6,87 d(8,2)	1,72

The earlier proposed structures of type "A" are excluded primarily on the basis of NMR data. Thus, compounds I, II, VI - IX, all show only two aromatic protons rather than three as expected for structure "A". Similarly, compounds III - V, which contain phenyl or benzyl substituents, have seven, rather that eight, aromatic protons. Taken together with the other data, these results indicate the formation of dihydroxy-1,2,3,4-tetrahydroisoquinolines.

For all compounds the pattern of signals for the two aromatic protons is two singlets. In compounds I, II and VI the singlets are almost identical. This result is also consistent with the formulation of compounds I - VIII as 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines.

For compound IX the aromatic protons show an A,B pattern (j=8,2 cps) consistent in this case, with a 7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline structure.



IX

REFERENCES

(1) a) A. Hajos and P. Sohar, Experientia 21, 434 (1965).
b) A. Hajos and P. Sohar, Acta Chim. Hung. 49, 417 (1966).
(2) A. Hajos and P. Sohar, Acta Chim. Hung. 53, 295 (1967).
(3) Egyesült Gyogyszer es Tapszer-gyar, Neth.Appl. 6,4o8,o34. Ref.: C.A. 63, 1866 E.
(4) W.M. Whaley and T.R. Govindachari, Organic Reactions, Vol. VI, p.151. John Wiley and Sons, INC, New York (1951).
(5) P.J. Shan, D.D. Vaghani, and I.R. Merchant, J.Org.Chem., 36, 3533 (1961).