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A Novel Synthesis of L-(−)-α-Methyl-3,4-dimethoxyphenylalanine

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Numerous synthetic approaches to L-(−)-α-methyldopa manifest the importance of this antihypertensive drug. The original processes utilize variations of the classical amino acid syntheses, starting from 3,4-dimethoxyphenylacetone.[1-3] More recent and also more elaborate syntheses introduce the amino group in the penultimate step by either displacing halogen with ammonia,[4] by Curtius rearrangement[5] or by Schmidt reaction.[6] In all these cases the racemic α-methyldopa has to be resolved with optically active acids or bases or by selective crystallization.[7] Weinges, *et al.*,[8] were able to obtain, however, in an elegant asymmetric Strecker synthesis, α-methyldopa in optically pure form.

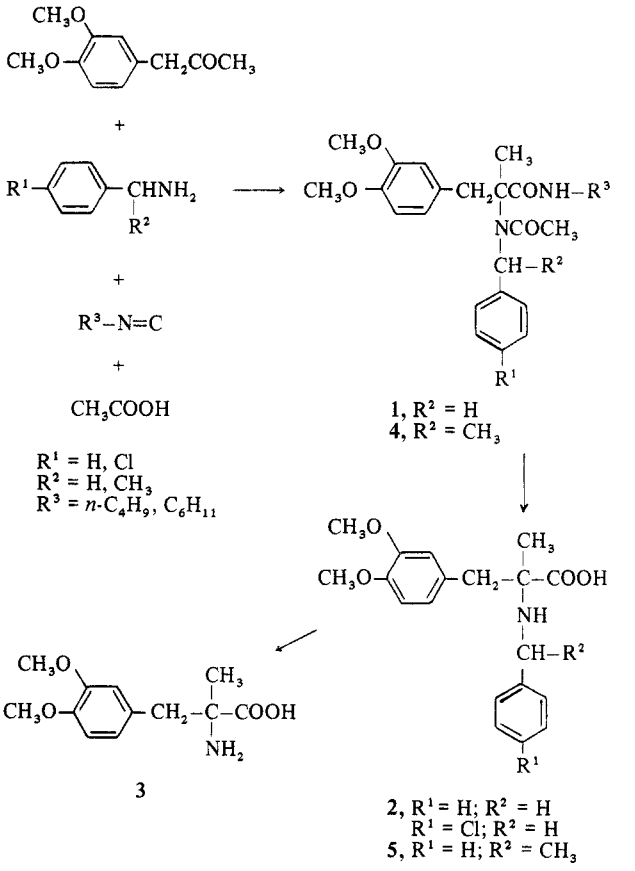
We wish to report a novel synthesis of 3,4-dimethoxyphenylalanine, the precursor of α-methyldopa, unrelated to those reported previously, which combines the simplicity of the Ugi reaction[9] with a facile separation of the resulting diastereoisomeric L-(or D)-α-methylbenzyl-DL-amino acids.

Model studies with optically inactive materials showed that the four component reaction (Scheme I) easily yielded the benzylamino acids (**2**) after saponification of the uncharacterized α-acetylamino acid amides (**1**). The DL-α-methyl-3,4-dimethoxyphenylalanine (**3**) was obtained by hydrogenolytic cleavage.

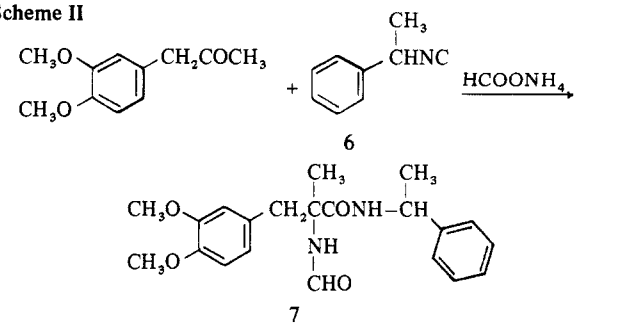
This reaction sequence was repeated with L-(−)-α-methylbenzylamine, and the resulting diastereoisomers (**4**) were—again without isolation—saponified to the amino acid (**5**). From the mixture of diastereoisomeric hydrochlorides of **5**, one isomer crystallized in optically pure form as judged by the specific rotation, which remained unchanged on recrystallization. On hydrogenolysis of the methylbenzyl moiety the desired L-(−)-α-methyl-3,4-dimethoxyphenylalanine (**3**) was obtained, which demonstrates that the crystalline diastereoisomer **5** had the LL configuration.

The loss of the optically active benzylamine on hydrogenolysis is clearly a disadvantage of this method. It therefore appeared attractive to introduce the second asymmetric center with an optically active isonitrile (**6**). On hydrolysis of the Ugi product (**7**), optically active amine could be recovered, which then could be reconverted into the isonitrile (Scheme II). This approach proved to be unrewarding, however, in view of persistent low yields in all reaction steps and was therefore abandoned.

Scheme I



Scheme II



Experimental Section

DL-*N*-Benzyl-α-methyl-3,4-dimethoxyphenylalanine (2, R¹ = H). A mixt of 3,4-dimethoxyphenylacetone (38.8 g, 0.2 mole), benzylamine (21.4 g, 0.2 mole), and C_6H_6 (200 ml) was refluxed under stirring for 2 hr; at that time H_2O sepn in a Dean–Stark tube had stopped. The solvent was evapd *in vacuo*, and the residue stirred with butylisonitrile (16.6 g, 0.2 mole) and AcOH (12 g, 0.2 mole) in MeOH (150 ml) at room temp for 1 week. The mixt was evapd to dryness, and the residue heated with H_2SO_4 (30%) (100 ml) to reflux for 24 hr. H_2O (200 ml) was added, and the soln washed with $CHCl_3$. On neutralization, the amino acid pptd. It was recrystd from water: yield 20 g (30.5%); mp 233–235°. *Anal.* ($C_{19}H_{23}NO_4$) C, H, N.

DL-*N*-(4-Chlorobenzyl)-α-methyl-3,4-dimethoxyphenylalanine (2, R¹ = Cl). This compd was obtained exactly as **2**, R¹ = H, using 4-chlorobenzylamine and cyclohexylisonitrile: yield 27.6%; mp 234–236°. *Anal.* ($C_{19}H_{22}ClNO_4$) C, H, Cl, N.

DL-α-Methyl-3,4-dimethoxyphenylalanine (3-DL). Both compds (**2**) were hydrogenated in EtOH with Pd/C (5%) at room temp and 25 psi in the usual way. The amino acid crystd as the hydrochloride monohydrate: yield 75.0%; mp 223–225°.

DL-α-Methyl-*N*-L-(−)-α-methylbenzyl-3,4-dimethoxyphenylalanine (5-DL-L). This compd was prepd like **2**, using 3,4-dimethoxyphenylacetone (38.8 g, 0.2 mole), L-(−)-α-methylbenzylamine (24.2 g, 0.2 mole), and *n*-butylisonitrile (16.6 g, 0.2 mole): yield 30.5 g (44.5%); mp 212–214°; $[\alpha]^{25}D$ −44° (*c* 0.5, 0.5 *N* NaOH). *Anal.* ($C_{20}H_{25}NO_4$) C, H, N.

L-α-Methyl-*N*-L-(−)-α-methylbenzyl-3,4-dimethoxyphenylalanine Hydrochloride (5-L-L·HCl). The above mixt of diastereoisomers (13.1 g) was converted to the hydrochlorides in EtOH (150 ml) with dry HCl. On concn and trituration with Et_2O the pure

L,L diastereoisomer crystd: yield 6.0 g (41.4%); mp 207–210°; $[\alpha]^{25}D$ −66° (*c* 0.4, 0.5 *N* NaOH).

The filtrate, contg the isomer **5**-D-L·HCl in impure form, did not crystallize. The amorphous material had a specific rotation of $[\alpha]^{25}D$ −15° (*c* 0.4, 0.5 *N* NaOH).

L-(−)-α-Methyl-3,4-dimethoxyphenylalanine (3-L). This compd was obtained as the hydrochloride by hydrogenation of (**5-L-L**) as described for **3**-DL: yield 77.3%; first mp 160–165°; solidifies at 170°; second mp 227–229°; $[\alpha]^{25}D$ −2.88° (*c* 1, 1 *N* HCl); lit.[10] $[\alpha]D$ −2.6° (*c* 1.01, 1 *N* HCl).

D-(+)-α-Methyl-3,4-dimethoxyphenylalanine (3-D). This compd was obtained as the hydrochloride, using the same procedure as for **3**-L replacing L-(−)-α-methylbenzylamine in the preparation of **5** by the D enantiomer: yield 69.5%; first mp 160–165°; second mp 227–229°; $[\alpha]^{25}D$ 2.01° (*c* 1, 1 *N* HCl).

DL-*N*-Formyl-α-methyl-3,4-dimethoxyphenylalanyl-*N*^{1}-D-(+)-α-phenylethylamine (7). A mixt of 3,4-dimethoxyphenylacetone (46.5 g, 0.24 mole), ammonium formate (31.5 g, 0.5 mole), and D-(+)-α-phenylethylisonitrile (**6**)[11] (38.8 g, 0.24 mole) was refluxed in MeOH–H_2O (4:1) (250 ml) for 24 hr. The residue from evapn was extd with $CHCl_3$, washed with H_2O, dried, and evapd. The residue was crystd from Me_2CO: yield 17.8 g (20%); mp 138–139°; $[\alpha]^{25}D$ 28.5° (*c* 1, EtOH). *Anal.* ($C_{21}H_{26}N_2O_4$) C, H, N.

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Synthesis of Insect-Repellent Amino Analogs of 2-Ethyl-1,3-hexanediol (Rutgers 612)†

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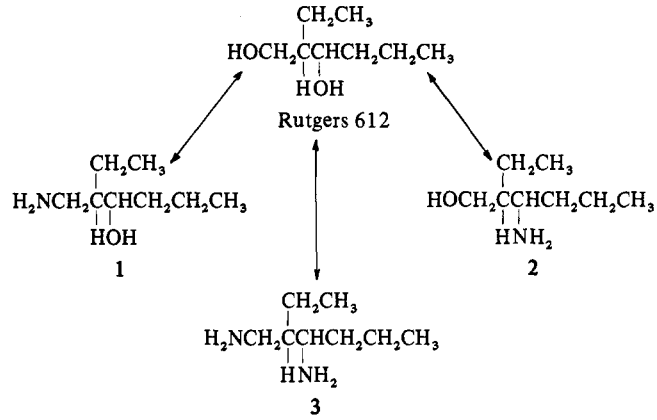
Received March 12, 1972

As an extension of our work on the development of insect repellents with dermophilic characteristics and long-lasting efficacy,[1-11] we designed and prepared amino analogs (**1–3**) of the standard repellent 2-ethyl-1,3-hexanediol (Rutgers 612). Since the latter's duration of effectiveness is known to be limited by volatilization from and absorption through the skin,[12] it was envisioned that interaction of the novel compounds' amino groups with acidic functions in the matrix of the epidermis[13] would extend insectifugal activity. The basic groups provide, also, means for linking the new agents to established anchoring components used in precursor molecules, capable of sustained repellent activity.[8]



Chemistry. Amino alcohol **1** was prepared by LAH reduction of 3-cyano-4-heptanone (**4**); the latter was obtained following the procedure described by Ziegler, *et al.*[14] In the synthesis of compds **2** and **3**, 3-amino-2-ethylhexanenitrile (**6**) constituted the key intermediate; it was prepared by the method of Grandberg and Golubeva.[15] LAH reduction of **6** afforded **3**, while ethanolysis of **6** and LAH reduction of the resulting aminoester (**7**) gave **2**. Characterization of compds **1–3** included their conversion to the respective hexachlorophene [2,2′-methylenebis(3,4,6-trichlorophenol)] salts (**8–10**).

Insect Repellency. Comparative evaluation of the repellency of several of the novel compds against *Aedes aegypti* (L.) mosquitoes was performed employing methodologies described in preceding communications.[1,3] Forearms of human volunteers, treated with the evaluants or with the standard repellent, were exposed (3 min) to caged mosquitoes at 30-min intervals until a confirmed bite was received. While the data from "round-robin" tests (Table I) reflect the fact that compds **1** and **2** elicit activities paralleling that of 2-ethyl-1,3-hexanediol (Rutgers 612), results from *paired* tests indicate for compd **1** an efficacy surpassing that of the standard Rutgers 612 (Table II). In other paired evaluations, repellency indices for compd **2** and for ethyl 3-amino-2-ethylhexanoate (**7**) were computed at 0.68 and 0.67, respectively, using Rutgers 612 as the standard. Compd **3** was ineffective; the lack of activity was probably associated with the formation of a solid carbonate derivative upon exposure to the atmosphere.

Based upon the results summarized above, amino alcohol **1** appears to offer prominent potentialities as a component of precursor-type repellents. Field tests have been projected

Table I. Protection Effected by Repellents against Biting by *A. aegypti*[a]

Repellent[b]	Protection time, min: Range	Protection time, min: Average[c]	Repellency index[d]
1	30–210	127	0.88
2	60–180	120	0.83
2-Ethyl-1,3-hexanediol	60–270	144	1.00

[a] In standard "round-robin" repellency tests on skin (ref 16). [b] One-half g of the respective repellents in ethanol was applied to the entire forearm of a human volunteer. [c] Average of 8 tests; least significant difference (0.05 level) = 34. [d] The repellency index = average protection time effected by the evaluant:average protection time effected by the 2-ethyl-1,3-hexanediol standard.

†This investigation was supported by the U. S. Army Medical Research and Development Command, Washington, D. C., through Research Contract DA-49-193-MD-2636.