Tetrahedron Letters No.24, pp. 1597-1600, 1964. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF HYDROECHINULINE .

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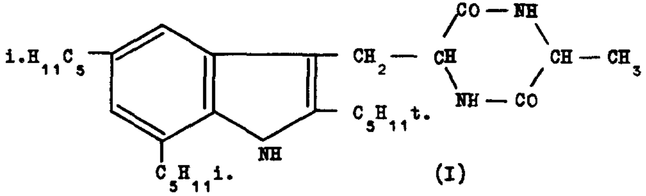
(Received 23 April 1964)

The structures of echinuline $C_{29}H_{39}N_3O_2$ and hydroechinuline $C_{29}H_{45}N_3O_2$ have been definitively elucidated by A.Quilico and coworkers (1), so that the latter is expressed by (I) :



(I)

We wish now to report the total synthesis of the optically inactive hydroechinuline .

Isophtalaldehyde has been converted, by reaction with isobutylmagnesium bromide, into the carbinole (II) (m.p. 78°-79°) and this reduced catalytically on Pd-C/$HClO_4$ to 1,3-diisoamyl-benzene (III) (liquid, b.p. 110°/0,7 mmHg). Reaction with diethyl azodicarboxylate in the presence of BF_3 afforded N,N'-dicarbethoxy-2,4-diisoamyl-phenylhydrazine (IV) (m.p. 66°-67°), which after alkaline hydrolysis was submitted to the Fischer indole synthesis with polyphosphoric acid (PPA) and 3,3-dimethyl-pentanone-2: the raw product was enriched by chromatography on alumina and purified by preparative gas-liquid chromatography, giving

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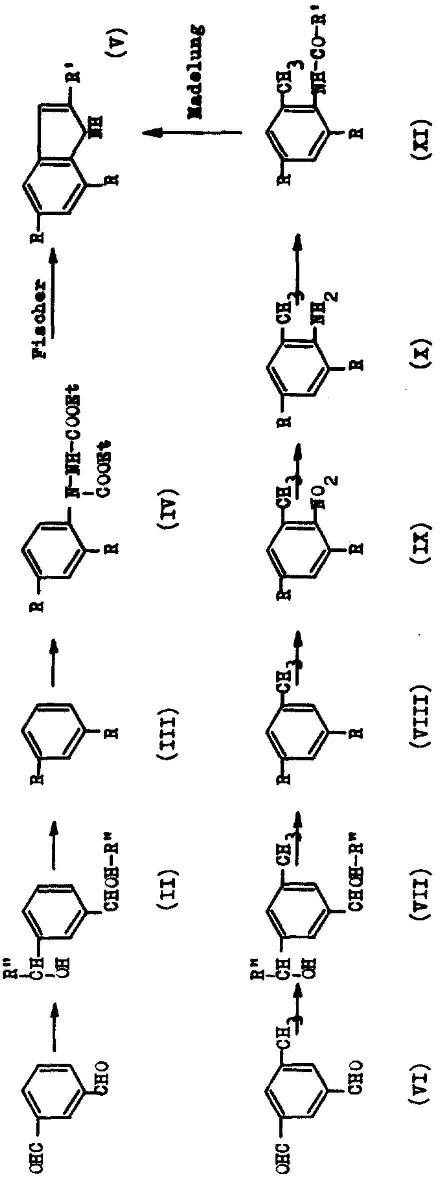
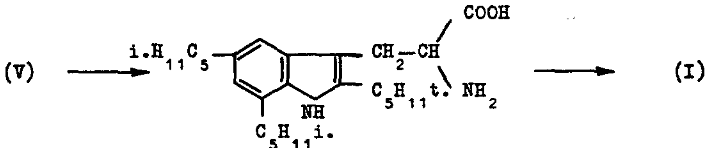
(+) In alphabetic order.



R = isoamyl R' = tert.amyl R" = isobutyl in poor yield pure 2-*tert.*amyl-5,7-diisoamyl-indole $C_{23}H_{37}N$ (V) which was recognized by physical and chemical methods to be identical with the product obtained by alkaline pyrolysis of saponified hydroechinuline (2).

The same 2,5,7-trisubstituted indole was obtained in better yield by the following pathway: mesitylene submitted to chromic oxidation in acetic acid - acetic anhydride solution afforded 5-methyl-isophtalaldehyde (VI) (m.p. 96°-97°) which was treated with isobutylmagnesium bromide: the resulting carbinol (VII) (m.p. 99°-100°) was reduced catalytically on Pd-C/$HClO_4$ to 3,5-diisoamyl-toluene (VIII), which was purified by preparative GLC (liquid, b.p. 85°/0,3 mmHg). Nitration of this compound in acetic acid - acetic anhydride solution yielded mainly 2-nitro-3,5-diisoamyl-toluene (IX) (liquid, b.p. 160°/2 mmHg) which was reduced catalytically to 2,4-diisoamyl-6-methyl-aniline (X) (purified by preparative GLC: liquid, b.p. 120°/0,3 mmHg). The amine was treated with butyllithium and then with α,α-dimethylbutyroyl -chloride, giving N-α,α-dimethylbutyroyl -2,4-diisoamyl-6-methyl-aniline (XI) (m.p. 89°-90°): the latter submitted to the Madelung indole synthesis with potassium *tert.* butoxide yielded 2-*tert.*amyl-5,7-diisoamyl-indole (V), which was also purified by preparative GLC.

As the indole (V) obtained by degradation of natural hydroechinuline had been already converted by means of an Erlenmeyer synthesis into the optically inactive DL-hydroechinine (XII) (3), and this latter transformed into hydroechinuline (I) (4), this constitutes also the first total synthesis of the hydroderivative of echinuline.



(XII)

Analytical results, infrared and ultraviolet spectra agree with the expected structures of all the products described.

We thank Prof. Quilico for the encouragement and helpful discussions.

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