Tetrahedron Letters No.44, pp. 5353-5356, 1966. Pergamon Press Ltd.
Printed in Great Britain.

PHOTOCHEMICAL SYNTHESIS OF APORPHINES

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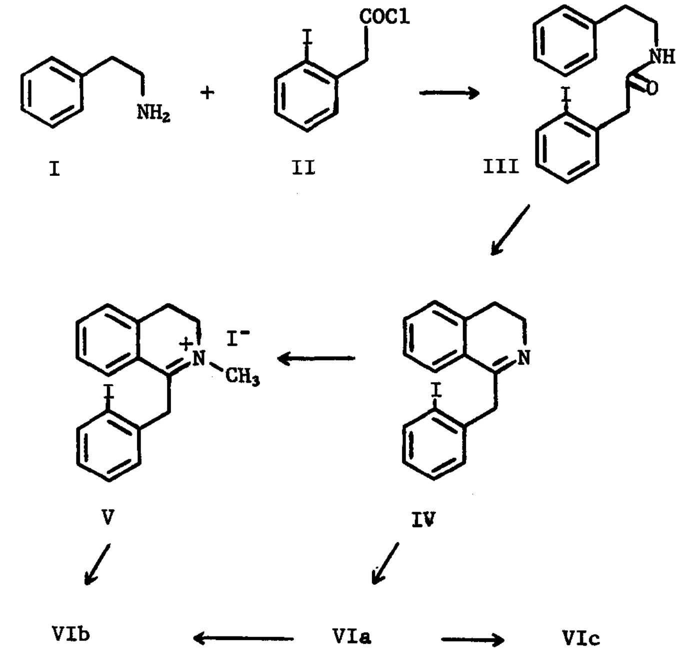
(Received 4 August 1966)

Two recent reports have described a synthetic approach to aporphines which proceeds via photochemical conversion of benzylidene-tetrahydroisoquinolines to dehydroaporphanes (1,2). The appearance of the latter reports prompts us to record an alternative photochemical synthesis of noraporphines and aporphines, which involves photocyclization of 1-(2-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline derivatives.

Photolysis of iodoaromatic compounds has been shown to yield biphenyl and polyphenyl derivatives (3). An earlier study in this Laboratory showed that the reaction could be used to effect photocyclization of substituted 2-iodostilbenes to phenanthrene derivatives (such as aristolochic acid) not readily accessible by other approaches (4).

The present report concerns a new application of the photolysis of iodoaromatic compounds in an intramolecular reaction, to effect photocyclization to aporphines. The 1-(2-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline derivatives (VI a-h) were prepared in very good yield by the procedure exemplified by Scheme 1. Condensation of phenethylamine (I) with the acid chloride (II) prepared from 2-iodophenylacetic acid (5) gave N-(β-phenethyl)-2-iodophenylacetamide (III, m.p. 124-125°, $\lambda_{max}^{chf.}$ 2.90 μ (NH), 5.99 μ (CONH)). Bischler-Napieralski ring closure with polyphosphate ester (cf. 6) smoothly afforded 1-(2-iodobenzyl)-3,4-dihydroisoquinoline (IV, m.p. 87-89°, $\lambda_{max}^{chf.}$ 6.13 μ (C=N); hydrochloride, m.p. 202-203°). Reduction of IV with sodium borohydride in methanol yielded 1-(2-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline (VIa), characterized as its

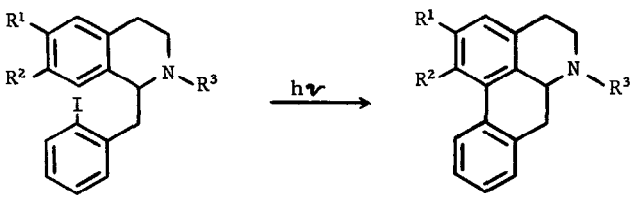
Scheme 1



hydrochloride salt (m.p. 249-251°). 2-Acetyl-1-(2-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline (VIc, amorphous, $\lambda_{max}^{chf.}$ 6.10 μ (CON)) was prepared by treatment of VIa with acetic anhydride. 1-(2-Iodobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (VIb, hydrochloride, m.p. 201-203°, λ_{max}^{EtOH} 226 mμ (ε 10,300)) was prepared either by reducing the methiodide V (m.p. 205-207°) with sodium borohydride in methanol or by treating Va with formaldehyde and sodium borohydride.

Photolysis of VIa in cyclohexane for 3 hr. at room temperature with a Nester-Faust NFUV-300 ultraviolet source gave a complex intractable mixture of products which showed negligible UV absorption in the region characteristic of

TABLE 1



VI VII

	Substituents	Medium	% Yield of the isolated aporphine
a	$R^1=R^2=H$; $R^3=H$	hydrochloride in H_2O	33 (hydrochloride, m.p. 275-280°)
b	$R^1=R^2=H$; $R^3=CH_3$	" " "	13 (hydrochloride, m.p. 253-255°)
c	$R^1=R^2=H$; $R^3=-\overset{O}{\overset{\|\|}{C}}-CH_3$	cyclohexane	15 (m.p. 214-215°)
d	$R^1=R^2=H$; $R^3=-\overset{O}{\overset{\|\|}{C}}-C_6H_5$	"	20 (m.p. 201-202°)
e	$R^1=R^2=OCH_3$; $R^3=H$	hydrochloride in H_2O	21 (hydrochloride, m.p. 260-262° dec.)
f	$R^1=R^2=OCH_3$; $R^3=CH_3$	" " "	16 (hydrochloride, m.p. 256-257° dec.)
g	$R^1=R^2=OCH_3$; $R^3=-\overset{O}{\overset{\|\|}{C}}-CH_3$	cyclohexane	20 (m.p. 232-233°)
h	$R^1=R^2=OCH_3$; $R^3=-\overset{O}{\overset{\|\|}{C}}-C_6H_5$	"	21 (m.p. 192-193°)

aporphines (270 mμ). Apparently the presence of the free electron pair on nitrogen was detrimental to the desired photocyclization of VIa, and other reactions predominated. However, when the N-acyl derivatives VIc and VId were irradiated in cyclohexane solution as described, the corresponding acylnoraporphines were obtained in the yields indicated (Table 1). An alternative approach which circumvented the detrimental effect of the basic nitrogen consisted of irradiating the hydrochloride salt of VIa in aqueous solution, whereupon photocyclization to noraporphine hydrochloride (VIIa) was effected.

Photocyclization of the appropriate precursors (VIe and VIf respectively) yielded dl-nornuciferine (VIIe) and dl-nuciferine (VIIf) in the best yields reported to date (cf. 1, 7).

Acknowledgment. - This investigation was supported in part by a research grant from the National Heart Institute (HE-02952). We thank Spang Microanalytical Laboratory, Ann Arbor, Michigan, for satisfactory analyses for all new compounds reported.

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