

INSERTION OF ISOPRENE UNITS INTO INDOLE SYSTEMS.

G. Casnati, M. Francioni, A. Guareschi and A. Pochini

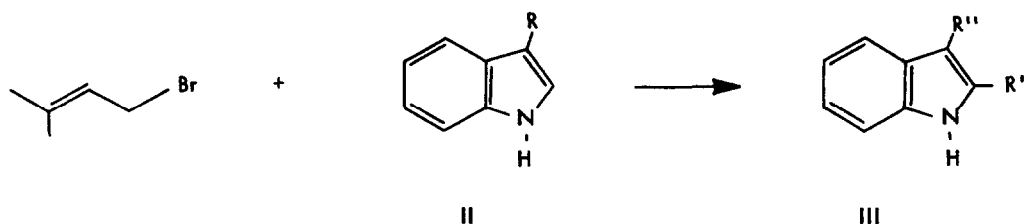
Istituto di Chimica Organica dell'Università di Parma

43100 - PARMA (Italy)

(Received in UK 20 April 1969; accepted for publication 23 May 1969)

We wish to report preliminary results of work directed to insert an isoprene unit into an indole system simulating biological conditions. We have investigated the reaction between indoles and γ, γ -dimethylallyl bromide (I) in acetic acid-water medium buffered with sodium acetate¹ at room temperature under nitrogen.

The main products from indole (IIa) and skatole (IIb) were 3- γ, γ -dimethylallylindole (IIIa) and 3-methyl-2- γ, γ -dimethylallylindole (IIIb).



IIa : R = H

IIb : R = CH₃

IIIa : R' = H; R'' = CC(C)=CC

IIIb : R' = CC(C)=CC; R'' = CH₃

The experimental results are summarized in table I.

The reaction products IIIa and IIIb were separated by absorption chromatography (silicagel, n-hexane/ethyl acetate 9:1 in vol.). IIIa, a white solid, mp 43-5⁰2, shows resonances in the pmr spectrum in CDCl₃ at δ 6.72 (1H, broad singlet, α -H), 6.9-7.7 (5H, ar-H and H on N), 5.41 (1H, broad triplet, en-H), 3.41 (2H, broad doublet, methylene H, J=7 cps) and 1.73 (6H, singlet, methyl H) and maxima in the uv (95% ethanol) at 223.5 (log ϵ =4.59), 282 (3.76) and 290.5 m μ (3.69). IIIb is an air sensitive oil whose pmr spectrum in CDCl₃ exhibits resonances at δ 7.0-7.6 (5H, ar-H and H on N), 5.21 (1H, broad triplet, en-H), 3.29 (2H, doublet, methylene H, J=7.5 cps), 1.7 (6H, broad singlet, methyl H) and 2.19 (3H, singlet, ring methyl). The position of the methyl group in IIIb was ascertained by taking its pmr spectrum in trifluoroacetic acid³ which causes protonation of the 3-position of the ring

with the appearance of a new quartet at δ 4.32 (1H) and the shielding and the splitting of the methyl group on the ring whose signal shows up at δ 1.87 (3H, doublet, $J=7.5$ cps.). The methylene hydrogens are also influenced by the protonation moving to δ 3.96. The uv spectrum of IIIb recorded in 95% ethanol exhibits maxima at 228 ($\log \epsilon$ 4.41), 285 (3.80) and 291 $m\mu$ (3.37).

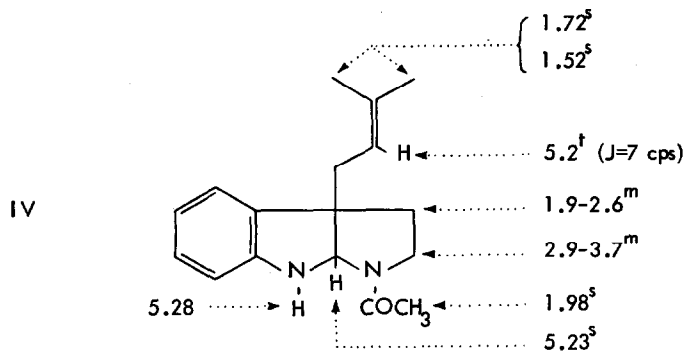
Table I
Reaction of I with Indole and Skatole^(a)

	Relative Composition ⁴		
	Unreacted	Monoalkylated	Unidentified
Indole	43.3	55.8	0.9
Skatole	28.3	61.5	10.2

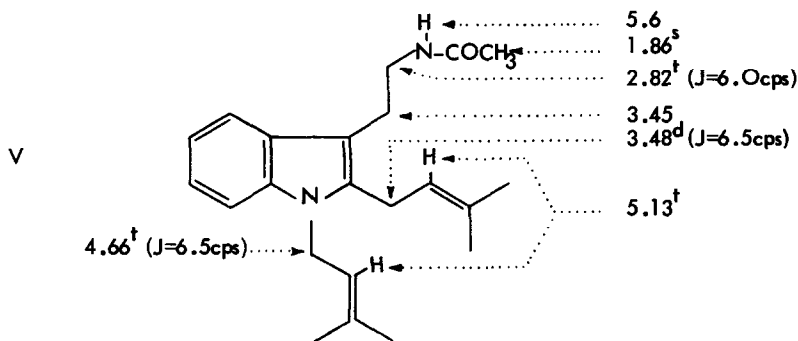
(a) 0.042 mol IIa or IIb, 0.05 mol I, 100 ml acetic acid (13N) and 10 g sodium acetate; reaction time : 1 hr. The relative compositions were established by glc using 20% SE 30 on 60-80 mesh Chromosorb W at 205°.

The interaction of I with tryptophane, its cupric complex and N-acetyltryptophane⁵ did not yield any new compound in the same experimental conditions. N-acetyl-tryptamine, though, reacted with I to a white solid, separated by two successive preparative tlc's, mp 94-5°, which was the main reaction product. The uv spectrum is suggestive of an indoline structure: (EtOH 95%) 229.5 ($\log \epsilon = 4.59$), 282 (3.76), 290.4 $m\mu$ (3.69). Molecular weight determined by mass spectrometry (molec. ion at 270 mass units) and elemental analysis agree with the formula $C_{17}H_{22}N_2O$, which corresponds to a 1:1 adduct with elimination of hydrogen bromide. The main ions in the mass spectrum showed up at 270, 201 (elimination of C_5H_9), 159 (less - $CH_2 = CO$) and 130 (less $CH_2 = NH$). This fragmentation pattern is analogous with that of physostigmine⁶.

The pmr spectrum from a deuteriochloroform solution provided a definitive evidence for structure IV. In particular, the expected singlet for the proton on the carbon attached to two nitrogen atoms falls at δ 5.23^{7,8}.



A byproduct was isolated to which the structure V corresponding to 1,2 (γ, γ -dimethylallyl)-N-acetyltryptamine was assigned on the basis of its uv and pmr spectra : uv max.at 230 ($\log \epsilon = 4.48$), 287 (3.85), 295 $m\mu$ (3.84).



The formation of the above products are rationalized with a primary electrophilic attack at the 3 position of the indole ring⁹: the intermediary indolenine thus formed may either rearrange to indoles (IIIa and b, V) or cyclize on the nucleophilic site of a suitably located ring substituent (IV), a phenomenon recently uncovered with other substrates.^{7,8,10}

Acknowledgements - We wish to thank Mr.A.Arnone for the NMR spectra and Dr.A.Selva for the mass spectra.

This work was supported in part by the Consiglio Nazionale delle Ricerche.

References

- 1) - Positive results are also obtained in aprotic solvents.
- 2) - A.H.Jackson and A.E.Smith, *Tetrahedron* 21, 989 (1964).
- 3) - R.L. Hinman and E.B.Whipple, *J.Am.Chem.Soc.* 84, 2534 (1962).
A.H.Jackson and A.E. Smith, *J.Chem.Soc. (Suppl.I)* 5510, 1964.
- 4) - The reported relative percentages are referred only to gaschromatographabile fraction.
- 5) - Positive results are obtained with N-acetyltryptophane esters; the research in this field are in progress.
- 6) - R.Robinson in R.H.E.Manske and H.L.Holmes. *The Alkaloids: Chemistry and Physiology*, Academic Press, Vol.X, pag.383.
- 7) - T.E.Spande, M.Wilchek and B.Witkop, *J.Am.Chem.Soc.* 90, 3256 (1968).
- 8) - B.Gaffney Mc Farland, Jasuo Jnoue and Koji Nakanishi, *Tetrahedron Letters* 857, 1969.
- 9) - A.H.Jackson, B.Naidov and P.Smith, *Tetrahedron* 24, 6119 (1968).
- 10) - Motonori Ohno, T.F. Spande and B.Witkop, *J.Am.Chem.Soc.*, 90, 6521 (1968).