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FORMATION OF APPARENT PARA-BENZIDINE REARRANGEMENT PRODUCTS DURING INDOLE SYNTHESES

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In order to obtain new quinolizidinyl derivatives of pharmacological interest, a series of 2-methyl-3-quinolizidinyl-5-R'-indoles was prepared(1). Attempts to obtain the indole with R'=H through ethanolic hydrogen chloride cyclization of quinolizidinyl-acetone phenylhydrazone (Ia) afforded as main product, instead of the expected indole (which was isolated in a small amount), a compound (IIIa; m. p. 198-199°) *corresponding to the formula* $C_{18}H_{26}N_2O$ and differing from the starting material by the replacement of a NH group with an oxygen atom.

The chemical properties (diazotisation, iodoform formation) and I. R. spectrum ($\bar{\nu}_{max}$= 3350, 1705, 1623, 1511 and 826 cm^{-1}) of this compound agree with the presence of a primary amino group, a carbonyl next to a methyl group and a para disubstituted benzene ring(2).

N. M. R. spectrum of IIIa, in $CDCl_3$ solution with TMS internal standard, supports the presence of a methyl adjacent to a carbonyl group (singlet at δ2. 1), of an amino group (singlet at δ3. 67 that broadens at 50° and moves *to higher field) and of a para disubstituted benzene* ring (two doublets centered at δ7. 1 and δ6. 65; J=7. 5cps(3)). One doublet centered at δ4. 05 suggests the presence of one H on a carbon between the carbonyl group and the aromatic ring.

The U. V. spectrum in ethanol (λ_{max}: 252 and 294. 5 nm; lg ε =3, 94 and 3. 58) is different from those of p-aminoacetophenone and of p-toluidine, while in 1N HCl the spectrum (λ_{max}: 218. 3; 255; 260. 4; 268 and 285. 7 nm; lgε =3. 88;2. 74; 2. 77; 2. 77 and 2. 81) is similar to that of phenylacetone (λ_{max}: 252. 5; 258. 7; 265. 3 and 284 nm; lgε =2. 38; 2. 41; 2. 33 and 2. 19) supporting further the presence of a CH between *the carbonyl group and the aromatic ring.*

After reduction of IIIa with $NaBH_4$, the 1705 cm^{-1} carbonyl band disappears and U. V. spectrum in ethanol becomes (λ_{max}=238 and 288 nm; lg ε =4. 01 and 3. 09) practically overlapping with that of p-toluidine.

The reduction product (IVa) is amorphous, but it is possible to obtain a well crystallized dihydrochloride (m. p. 250-255°) whose analysis agrees with the expected formula $C_{18}H_{28}N_20+2HCl$.

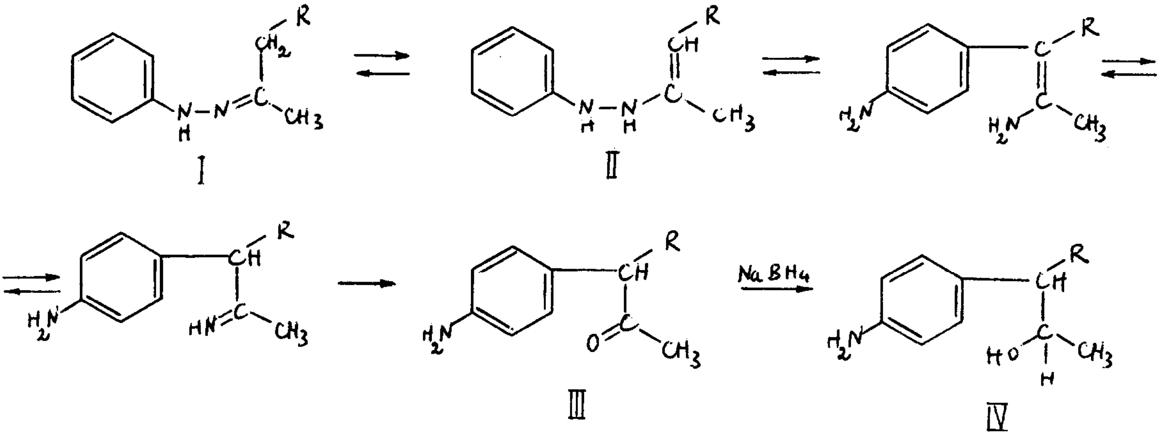
The available data support the structure (IIIa) of 1-p-aminophenyl -1-quinolizidin-1'-yl-acetone.

Similarly, *during the cyclisation of* β-*methyl-campholenone* phenylhydrazone (Ib) there was obtained, together with the expected indole, a compound $C_{17}H_{23}NO$ (very viscous oil, b. p. ~120° at 0. 02 torr) that from chemical reactivity, U. V., I. R. and N. M. R. spectra appears to be a para substituted aniline with a methyl next to a carbonyl group.

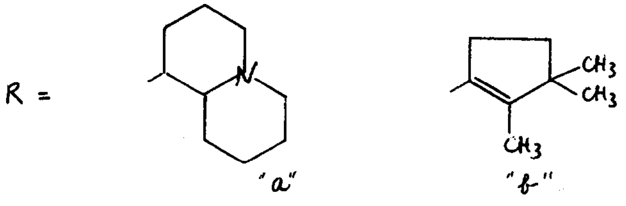
For this compound could be proposed a structure IIIb, with which the N. M. R. spectrum is however not fully consistent.

Quite probably these exceptional compounds are originated through formal para-benzidinic rearrangements of the ene-hydrazines (IIa) and (IIb) collateral to the ortho-benzidinic ones that give place at last to the indoles. Para rearrangement should be favoured since it produces a relief of intramolecular steric interactions and (although the reported examples so far are the only known) it should be expected in all cases of Fischer indole syntheses involving ketones carrying bulky substituents on the methylene contiguous to the carbonyl group.

Work is progressing in order to check this possibility and fully elucidate the structure of compound $C_{17}H_{23}NO$.



I II III IV



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