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SYNTHESIS OF INDAZOLES FROM ACETOPHENONE p-NITRO-PHENYLHYDRAZONES USING POLYPHOSPHORIC ACID AS A CONDENSING AGENT

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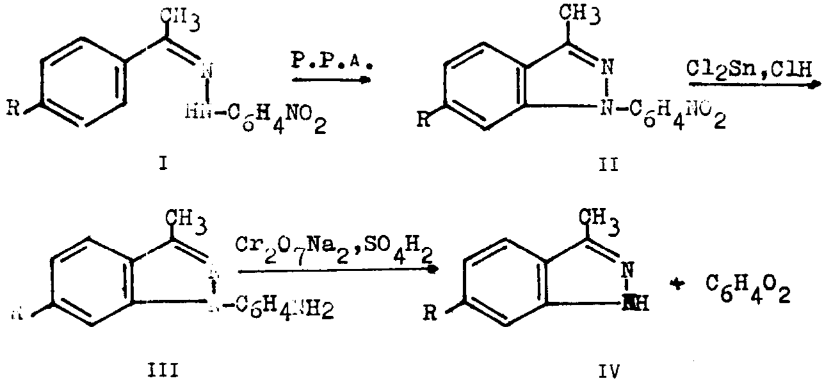
IN this communication, a synthesis of indazoles is described by the reaction of polyphosphoric acid on acetophenone p-nitrophenylhydrazones. As is outlined in the sequel, this transformation appears to take place in a novel manner.

In experiments devoted to study the preparation of nitroindoles by the Fischer method employing polyphosphoric acid (PPA), the nitrophenyllhydrazones were usually heated to 110-130° with ten times their weight of the acid. Under these conditions, acetophenone p-nitrophenylhydrazone did not produce any appreciable amount of the expected indole. The heating temperature was then increased to 160° and it yielded a compound melting at 150°, which analyzed for $C_{14}H_{11}N_3O_2$, with an U.V. spectrum (λ max. 232 mμ log ε 4.30; 355, 4.25) different from the nitroindoles. The I.R. spectrum of the p-nitrophenylhydrazone (Potassium bromide) showed the typical band of the nitro group at 1528, 1335 and 840 cm^{-1}. That the nitro group was present in the new compound was shown by the presence of a strong band at 840 cm^{-1} in the I.R. spectrum. Only a shoulder was noticeable at 1530 cm^{-1} and the original band at 1335 cm^{-1} has merged with other, giving a strong broad band with a maximum at 1320 cm^{-1}. The NMR spectrum although poor, because of the low solubility of the compound, showed a peak at τ = 7.36, that could be assigned to a methyl group, no doubt derived from the one originally present in the acetophenone.

The new compound was stable in concentrated sulfuric acid and not changed by boiling with acetic anhydride. When treated with N KOH in 90% ethanol, a product $C_{28}H_{22}N_6O$, m.p. 223-224°, with the properties of an azoxybenzene was obtained. The last compound could be reduced with stannous chloride in acetic-hydrochloric acids, to give an amine $C_{14}H_{13}N_3$, m.p. 136-137°, which could also be obtained by direct reduction of the original compound m.p. 150° with the same reagent.

That the compound formed by the action of PPA on acetophenone p-nitrophenylhydrazone contained an indazole nucleus, was shown as follows: If the amine $C_{14}H_{13}N_3$ is carefully oxidised with 0.5 mol. of sodium bichromate in 25% sulfuric acid solution, p-quinone is produced and the 3-methylindazole of Fischer and Tafel[1], m.p. 110-111°, can be separated in good yield. The 3-methylindazole was identified by comparison with an authentic sample, I.R.



spectra and preparation of its picrate, m.p. 198-199°(Auwers[2] gives m.p. 198.5-199.5°).

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[1] E. Fischer and J. Tafel, Liebigs Ann. **227**, 317 (1885).

[2] K.v. Auwers, Ber. Dtsch. Chem. Ges. **52**, 1338 (1919).

The reactions describing the production of the 3-methylindazole are indicated in the sequence I → IV. They could be extended to other p-nitrophenylhydrazones of substituted acetophenones, as indicated in Table I.

TABLE I

Indazoles obtained from p-nitrophenylhydrazones of different acetophenones.

Hydrazone (I)		1-p-Nitrophenyl-3-methylindazole (II)		Amine (III)	3-Methylindazole (IV)
R	M.p.	Yield %	M.p.	M.p.	M.p.
H	180°	29	150°	136-137°	110-111°
CH_3	188-189°	42	158-159°	114-115°	148-149°
CH_3O	197-198°	47	209-210°	111-112°	168-169°
Br	241-242°	8	180-181°	124-125°	191-192°

When the p-nitrophenylhydrazones were treated with the usual condensing agents (20% sulfuric acid or hydrochloric acid) they were recovered and did not condense to indoles or indazoles. On the other hand, the phenylhydrazones of the same acetophenones, when the nitro group was absent, gave the expected indoles on treatment with PPA, following the lines of the typical Fischer synthesis.

Only general mechanisms for the reaction can be discussed as indicated in the sequences V → VIII → X or V → VII → IX → XI → X[3]. Nucleophilic substitution by the nitrogen atom takes place at the carbon atom of the benzene ring, that has the largest positive charge in relation to the others. The intermediate compound (VII) can then be transformed into the indazole (X) by elimination of a proton and a hydride ion, by the electronic displacements shown in (VIII).

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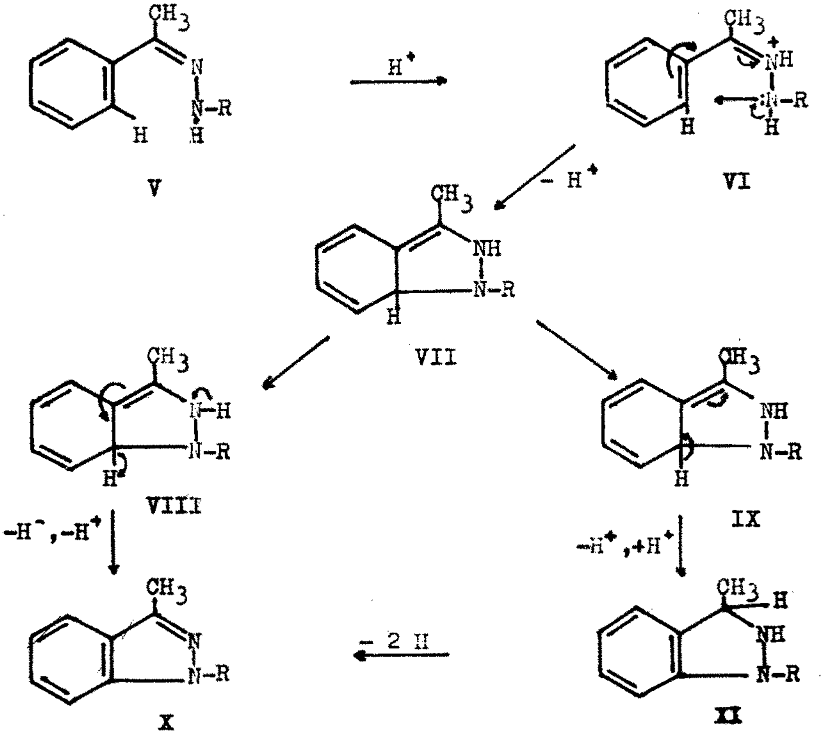
[3] The mechanism that includes stages IX and XI has been suggested by a referee.

The synthesis of indazoles from hydrazones, by nucleophilic substitution with displacement of a negative group from the benzene ring, has been described in several cases. In all of them the leaving group (halide ion, NO_2^-, CH_3O^-) is more electronegative than the hydrogen and it must be, with a few exceptions, properly activated by a nitro group in the adequate place[4].



$R = C_6H_4NO_2$, (p)

In the other mechanism, proton addition and elimination from (VII) favored by the displacements indicated in (IX), produce a dihydroindazole

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[4] V. Meyer, Ber. Dtsch. Chem. Ges. 22, 319 (1883); M. Dittrich and V. Meyer, Liebigs Ann. 264, 131 (1891); W. Borsche, Ber. Dtsch. Dhem. Ges. 42, 601 (1909); S. Reich and G. Gaigailin, Ber. Dtsch. Chem. Ges. 46, 2380 (1913); J. Meisenheimer and O. Senn, Ber. Dtsch. Chem. Ges. 59, 199 (1926); W. Borsche and K. Diacont, Liebigs Ann. 510, 287 (1934); W. Borsche and W. Scriba, Liebigs Ann. 540, 83 (1939).

(XI) which is oxidized to the indazole (X).

The two atoms of hydrogen eliminated in passing from the acetophenone p-nitrophenylhydrazones to the indazoles, must be accepted by other hydrazone molecules, and possibly by the nitro group.

Correct analyses were obtained for all new compounds mentioned in Table I. I wish to thank the Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina for a fellowship and to E.R. Squibb and Sons, Argentina, for a grant.