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ACTION OF NITROUS ACID ON N-SUBSTITUTED-ISATINIC ACIDS. DISPROPORTIONATION TO INDAZOLOLS.

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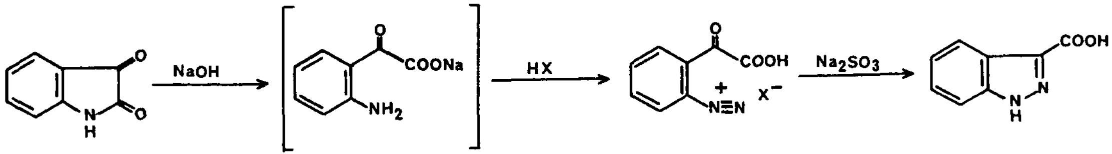
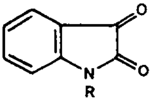
SUMMARY: By reacting N-substituted-2-isatinic acids with nitrous acid, indazolols, N-nitroso-N-substituted anthranilic acids and the esters of said acids with the above mentioned indazolols were obtained through disproportionation of the N-nitroso-N-substituted-isatinic acids.

It is well known that the diazonium salt of the isatinic (2-amino-phenyl-glyoxylic) acid **1** is obtained from isatin and nitrous acid through the sodium salt of the acid **2**.
Although this diazonium salt was isolated only twenty years ago[1] it had already been used in the last century by Schad as raw intermediate for the preparation of the indazole-3-carboxylic acid **3** by a sodium sulfite reduction[2].



2 **1** **3**

Since Schad himself asserted that he had isolated the N-methyl-N-nitroso-isatinic acid by the action of nitrous acid on the sodium salt of the N-methyl-isatinic acid, we tried to apply the same sequence to the synthesis of 1-substituted-indazole-3-carboxylic acids. Therefore, 1-phenyl-isatin **4a** (0.1 mole) was dissolved in 2N NaOH (0.15 mole), $NaNO_2$ (0.1 mole) was added to the solution which, cooled at 5°C, was then acidified dropwise with 2N HCl (0.25 mole) in about half an hour. Instead of the expected N-nitroso-N-phenyl-isatinic acid, the gummy precipitate was shown to consist in an approximatively equimolecular mixture of 1-phenyl-indazol-3-ol **5a**, N-nitroso-N-phenyl-anthranilic acid **6a**, and a neutral substance (dec. above 67°C, UV (n-Heptane), λmax_1 at 249 nm (ε = 28,100), λmax_2 at 304 nm (ε = 12,750); IR (CCl_4), $\nu_{C=0}$ = 1763 cm^{-1}) to which we assigned the structure **7a**. (Yields - **5a**: 23.2%; **6a**: 23.6%; **7a**: 52.8%).



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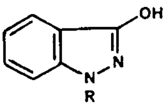

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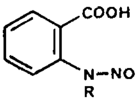

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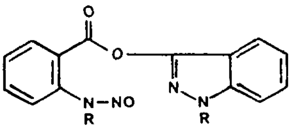

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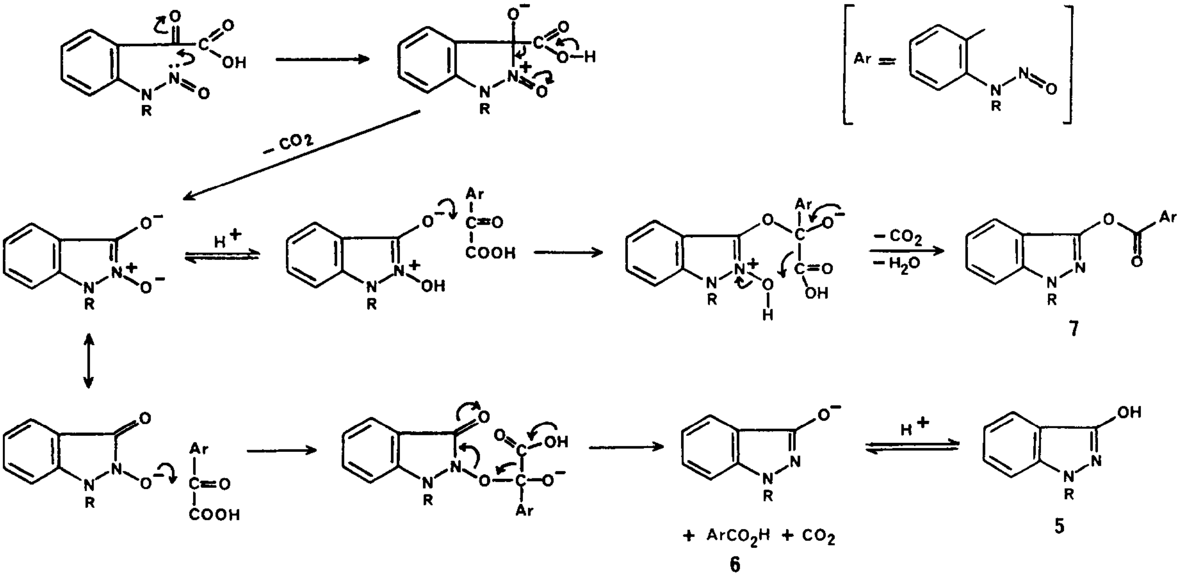
a) R = Ph; b) R = 4-ClPh; c) R = $PhCH_2$; d) R = CH_3.

5a and **6a** were well known products[3,4] while the structure of **7a** was deduced from spectroscopic properties and from independent synthesis (nitrosation of the ester of 1-phenyl-anthranilic acid with 1-phenyl-indazol-3-ol, m.p. 60-62°C) as well as from the fact that it exclusively gives **5a** and **6a** when refluxed in 2N NaOH for 3 hours.

Compounds similar to **7a**, in yields very near to 50%, were obtained as neutral components of the mixtures obtained starting from different N-substituted isatins (**7b**: m.p. 147°C (dec.); **7c**: m.p. 128-130°C; **7d**: m.p. 121-123°C).

Three points must be taken into account when considering the following reaction mechanism, which postulates the disproportionation of the intermediate N-nitroso-N-substituted-isatinic acid.



1) The nitroso anthranilic acid is not an intermediate in the formation of the indazole nucleus. In fact starting from N-phenyl-isatin, when a molecular amount of N-nitroso-N-benzyl-anthranilic acid was added to the reaction mixture, after hydrolysis, only 1-phenyl-indazol-3ol was obtained without any trace of 1-benzyl-indazol-3-ol. On the other hand, similarly starting from 1-benzyl-isatin, only 1-benzyl-indazol-3-ol was obtained whether or not one molecular equivalent of the N-nitroso-N-phenyl-anthranilic acid was added.

2) 2-oxo-ketoacids do not react at all with the N-nitroso-amines under these conditions.

3) The reaction conditions are too mild for the transformation of **5** + **6** into **7** or of **7** into **5** + **6**.

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