ADDITION PRODUCTS OF INDAZOLE AND NITRILIMINES. SYNTHESIS OF 1-PHENYL-5-(o-AMINO-PHENYL)-1,2,4-TRIAZOLES AND THEIR ANNELATION TO 1,2,4-TRIAZOLO[1,5-f]PHENANTHRIDINES.

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Treatment of indazole with nitrilimines (IIIa-c) afforded the corresponding phenylhydrazone adducts (Va-c), which undergo an acid-catalysed transformation to give the hitherto unknown 1-phenyl-5-(o-amino-phenyl)-1,2,4-triazole derivatives (XIa-c). Diazotization of (XIa-c) followed by treatment with hypophosphorous acid gave 1,2,4-triazolo[1,5-f]phenanthridines (XIIa-c).

In a previous paper[1] we pointed out the tendency of the C=N bond of 1-methylindazole (I) to react as dipolarophile with the nitrilimine (IIIa). The reaction investigated, which appears to have no precedent in the indazole series, is also interesting with regard to the synthetic point of view. In fact, the acid-catalysed transformation of the cycloadduct (IVa) into (Xa) furnishes an interesting alternative route to synthetize 1,2,4-triazole derivatives.

In this paper we have treated the indazole itself with the nitrilimines (IIIa-c) but, owing to the presence of an hydrogen

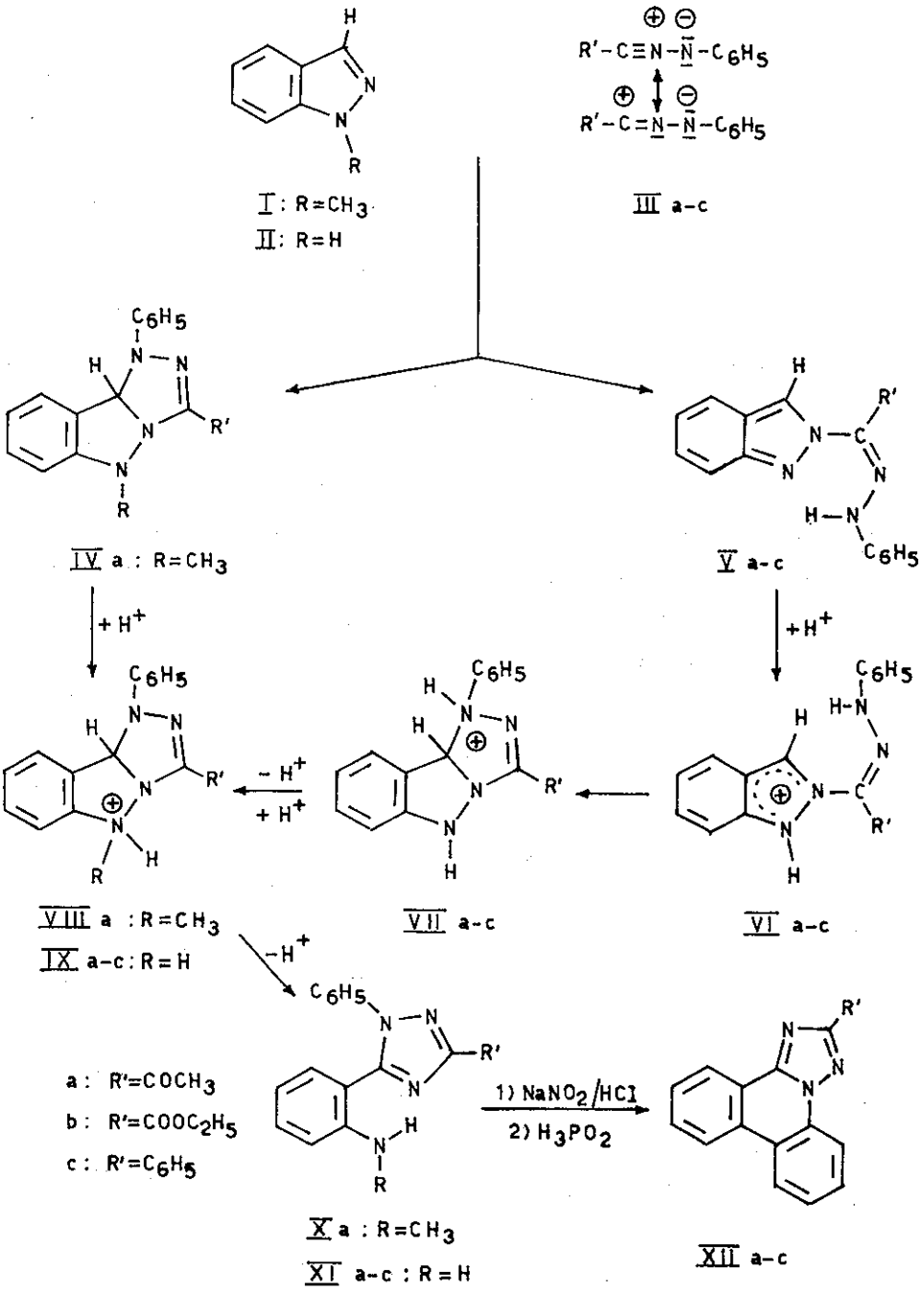
atom instead of a methyl group at the position 1, a 1,3-addition reaction was observed. This reaction pathway, already observed for imidazole derivatives[2,3] not substituted at the position 1, leads to the phenylhydrazones (Va-c), whose structures were supported by elemental[4] and spectroscopic[5] analysis and by chemical properties.

Although the reaction of indazole with nitrilimines failed to give cycloaddition products, the related phenylhydrazones(Va-c) proved useful in the synthesis approach to 1,2,4-triazole derivatives. Compounds (Va-c) in fact are converted in good yields into 1-phenyl-5-(o-amino-phenyl)-1,2,4-triazole derivatives (XIa-c) when refluxed in ethanol with conc. HCl.

It seems reasonable to assume that N_2-substituted indazoles (Va-c), which have a fixed quinoid structure as a basic formula, under influence of the acidic catalyst cyclize into (VIIa-c) through an intramolecular attack of the phenyl-nitrogen atom to the strong electrophilic center C_3 of (VIa-c). Prototropic equilibria involving (IXa-c), analogous of (VIIIa), leads to the above products whose structures have been assigned on the basis of analytical, spectroscopic and chemical data.

Diazotization of (XIa-c) followed by treatment with hypophosphorous acid in an attempt to effect deamination, gave the internuclear cyclization to (XIIa-c), accordingly to their analytical and spectroscopic data.

A synthesis of (XIIb) via another route was recently reported[6], but the above reaction is of considerable interest since it constitutes a new method for the preparation of substituted 1,2,4-triazolo[1,5-f]phenanthridines.


I: R=CH3
II: R=H
III a-c
IV a : R=CH3
V a-c
+H+
VIII a : R=CH3
IX a-c: R=H
- H+
+ H+
VII a-c
VI a-c
-H+
a: R'=COCH3
b: R'=COOC2H5
c: R'=C6H5
1) NaNO2/HCl
2) H3PO2
X a : R=CH3
XI a-c : R=H
XII a-c

EXPERIMENTAL SECTION

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 257. *Nmr* spectra were measured using tetramethylsilane as internal standard, with a Jeol C-60H spectrometer. Uv spectra were recorded on a Beckmann DB spectrometer.

General procedure for the phenylhydrazone adducts (Va-c).- A solution of equimolar amounts of indazole (0.017 mol) and α-chloro-α-(N-phenylhydrazono)acetone (XIIIa)[7], or ethyl α-chloro-α-(N-phenylhydrazono)acetate (XIIIb)[8], or α-chloro-benzaldehyde-phenylhydrazone (XIIIc)[9], in dry THF (50 ml), was treated with a threefold excess of triethylamine. The reaction mixture was allowed to stand at room temperature for 4 days (in the case of (XIIIc) the mixture was refluxed for two days), and then triethylamine hydrochloride was filtered off and the solvent evaporated under reduced pressure. The residue was taken up with ethanol (20 ml) (methanol in the case of XIIIc) and the insoluble material crystallized from ethanol to yield (Va-c) [*in the case of Vc, a preliminary purification on Merk silica gel deactivated with water (15%), eluent cyclohexane/ethyle acetate 9:1, was necessary*]

2-pyruvoyl-indazole 2[1]-(phenylhydrazone) (Va): 3.85 g (82% yield), m.p. 140°.

2-ethoxalyl-indazole 2[1]-(phenylhydrazone) (Vb): 4 g (76.60% yield), m.p. 128°.

2-benzoyl-indazole(phenylhydrazone) (Vc): 1.67 g (31.7% yield), m.p. 104-105°.

Taking up again with ethanol, the residue obtained by evaporation of the methanol solution of (Vc), gave a secondary product[10]

(0.24 g), m.p. 218°.

Transformation of phenylhydrazones (Va-c) into 1,2,4-triazole derivatives (XIa-c).- By refluxing (Va-c) (0.5 g) with conc. HCl (0.5 ml) in ethanol (20 ml) for two days (two hr in the case of Vc), evaporation of the solvent in vacuum, repeated additions of benzene to the residue and further evaporation under reduced pressure, (XIa-c) are obtained as hydrochlorides:

1-phenyl-5-(o-amino-phenyl)-3-acetyl-1,2,4-triazole (XIa) hydrochloride: 95% yield, m.p. 182-185°; free base: m.p. 139-141° (cyclohexane/ethyle acetate 4:1); uv λ_{max}^{EtOH} nm (log ε) 217 (4.45), 252s(4.10), 322 (3.60); ir ν max (nujol mull) 3360, 3445 (NH_2), 1695 (C=O); nmr ($CDCl_3$) δ: 2.62 (s,3H,$COCH_3$), 5.17 (br s,2H,NH_2), 6.26-7.35 (m,4H,Ar-H), 7.37 (s,5H,C_6H_5).

1-phenyl-5-(o-amino-phenyl)-3-ethoxycarbonyl-1,2,4-triazole (XIb) hydrochloride: 72% yield, m.p. 176-180°; free base: m.p. 141-142° (cyclohexane); uv λ_{max}^{EtOH} nm (log ε) 217 (4.45), 255s (4.03), 324 (3.65); ir ν max (nujol mull) 3328, 3430 (NH_2), 1720 (C=O); nmr ($CDCl_3$) δ: 1.49 (t,3H,$OCH_2\underline{CH_3}$,J=6.9 Hz), 4.57 (q,2H,$O\underline{CH_2}CH_3$,J=6.9 Hz), 5.23 (br s,2H,NH_2), 6.30-7.45 (m,4H, Ar-H), 7.53 (s,5H,C_6H_5).

1,3-diphenyl-5-(o-amino-phenyl)-1,2,4-triazole (XIc) hydrochloride: 97% yield, m.p. 179-184°; free base: m.p. 121-123° (petroleum ether/ethyle acetate 4:1); uv λ_{max}^{EtOH} nm (log ε) 222 (4.59), 322 (3.62); ir ν max (nujol mull) 3322, 3437 (NH_2); nmr ($CDCl_3$) δ: 5.21 (br s,2H,NH_2), 6.25-7.60 [m,12H,Ar-H ($\underline{1}$-C_6H_5,s,7.47)], 8.18 (m,2H,o-Ar-H at position $\underline{3}$).

1,2,4-triazolo[1,5-f]phenanthridine derivatives (XIIa-c).- To a stirred solution of (XIa-c) hydrochlorides (0.9 mmoles in 3M HCl (4 ml) (XIa) or conc. HCl (4 ml) (XIb-c), water (4 ml) and

then (at 0-5°) a solution of $NaNO_2$ (0.5 g) in water (4 ml) were added. After 0.5 hr, H_3PO_2 (50%, 2 ml) was added and the mixture was stirred for 12 hr. After overnight, the products were isolated by filtration and purified by crystallization:

2-acetyl-1,2,4-triazolo[1,5-f]phenanthridine (XIIa): 0.2 g (85% yield), m.p. 207-208° (ethanol); uv λ_{max}^{EtOH} nm (log ε) 240 (4.76), 247 (4.85), 278s (4.18), 297s (3.52), 312 (3.51), 326 (3.54); ir ν max (nujol mull) 1699(C=O); nmr ($CDCl_3$) δ: 2.85 (s,3H,$COCH_3$), 7.40-7.90 (m,4H,6,7,10,11-H), 8.15-8.80 (m,4H,5,8,9,12-H).

2-ethoxycarbonyl-1,2,4-triazolo[1,5-f]phenanthridine (XIIb): 0.25 g (94% yield), m.p. 180-182° (ethanol); uv λ_{max}^{EtOH} nm (log ε) 241s (4.81), 247 (4.89), 278s (4.12), 299 (3.22), 311 (3.48), 326 (3.60).

2-phenyl-1,2,4-triazolo[1,5-f]phenanthridine (XIIc): 0.22 g (84% yield), m.p. 189-191° (ethanol); uv λ_{max}^{EtOH} nm (log ε) 246s (4.76), 252 (4.88), 260s (4.77), 285s (4.23), 302s (3.44), 317 (3.54), 331 (3.58); nmr ($CDCl_3$) δ: 7.25-7.85 (m,7H,6,7,10,11-H and meta and para-H of C_6H_5), 8.15-8.60 (m,6H,5,8,9,12-H and ortho-H of C_6H_5).

REFERENCES and NOTES

1) M.Ruccia, N.Vivona, and G.Cusmano, Heterocycles, 4, 1655 (1976).

2) M.Ruccia, N.Vivona, G.Cusmano, and M.L.Marino, Gazz.Chim. Ital., 100, 358 (1970).

3) A 1,3-addition reaction has been also observed for some pyrazoles not substituted at position 1 (unpublished results).

4) All new compounds give right analytical values.

5) A full account of spectroscopic data (uv, ir, and nmr) will be published in a forthcoming paper.

6) L.Garanti, A.Scandroglio, and G.Zecci, J.Heterocyclic Chem., 13, 1339 (1976).

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9) P.Wolkoff, Can.J.Chem., 53, 1333 (1975).

10) Work is in progress to clarify the structure of this product.

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