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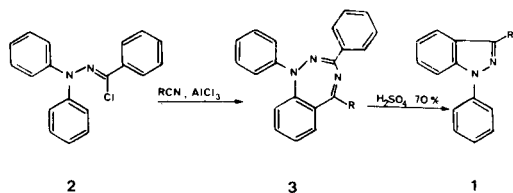
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The action of polyphosphoric acid on some *N*-phenylhydrazidoyl chlorides has been studied. Indazoles, dihydrophthalazines or Hoffmann-Martius rearranged products were obtained depending on the particular substrate employed.

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Conde, Corral and Madronero (1) disclosed in 1974 a new synthesis of 1-arylidazoles **1** starting from *N,N*-diphenylbenzhydrazidoyl chlorides (**2**) **2** through 1,2,4-benzotriazepines **3**. Our interest in the field of indazoles

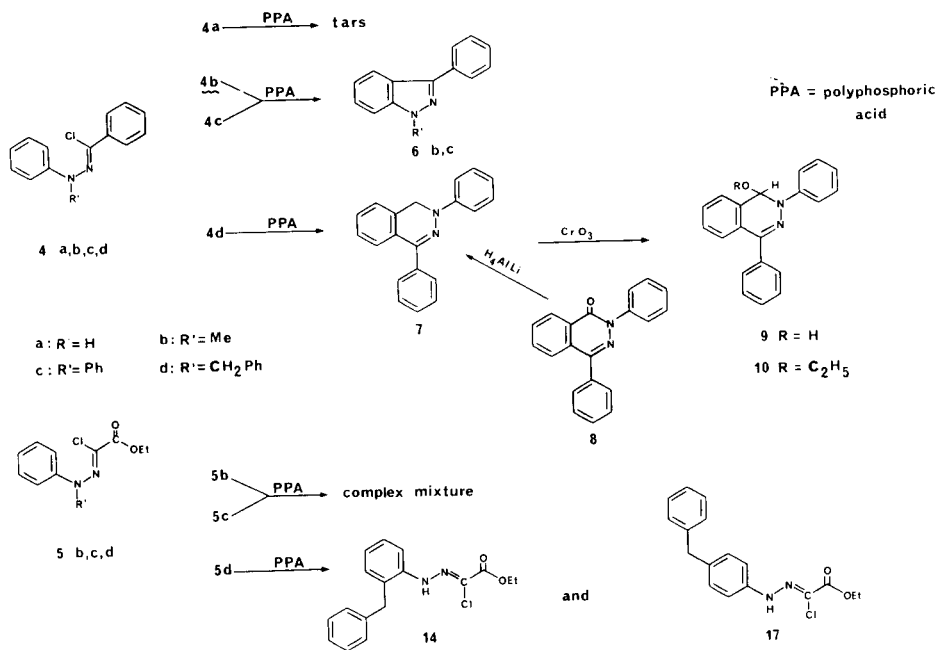


(**3**) prompted us to test the possibility of obtaining indazoles directly starting from phenylhydrazidoyl chlorides by means of acidic condensing agents.

Two distinct series of *N*-phenylhydrazidoyl chlorides derived from benzoic and ethoxalic acid **4** and **5**, respectively were investigated; the latter has been studied in the hope of obtaining 1-substituted-3-indazolecarboxylic acids or their esters which are the substances we are intensively studying in our laboratories in relation with their antispermatogenic properties (4).

Polyphosphoric acid was chosen as the condensing agent for both series after some discouraging results were obtained with aluminum chloride and zinc chloride. Four different derivatives of the benzoic acid **4a,b,c,d**, in which $\text{R}' = \text{H, Me, Ph, CH}_2\text{-Ph}$, were chosen. Compound **4a** was obtained as described by Huisgen *et al.* (5), **4b** and **4c** with the method of Conde (1) which was also found useful in order to obtain **4d**.

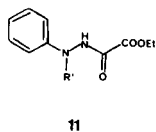
No definite reaction product was obtained when polyphosphoric acid was reacted with **4a**, whereas **4b** and **4c**, under the same conditions, gave the expected and already known 3-phenylindazoles **6b** (**6**) and **6c** (**7**) although in very low yields. We obtained different results starting from **4d**. This latter compound lost hydrogen chloride by the action of polyphosphoric acid to give, in moderate yields, a substance which is isomeric with 1-benzyl-3-phenylindazole. The uv and nmr spectra suggested the structure of 2,4-diphenyl-1,2-dihydrophthalazine **7** for this substance. This structure was confirmed by an independent synthesis. In fact the same compound was obtained by LAH reduction of the known 2,4-diphenyl-1(2*H*)-phthal-



azinone **8** (**8**). In an effort to obtain **8** by chromic oxidation of **7** the cyclic amino-hemiacetal **9** was isolated. When crystallized from ethanol it is transformed into the amino-acetal **10**. This fact is not surprising since the methylene group in **7** is a benzylaminic one and benzylamines gave, by chromic oxidation, the corresponding aromatic aldehydes (**9**).

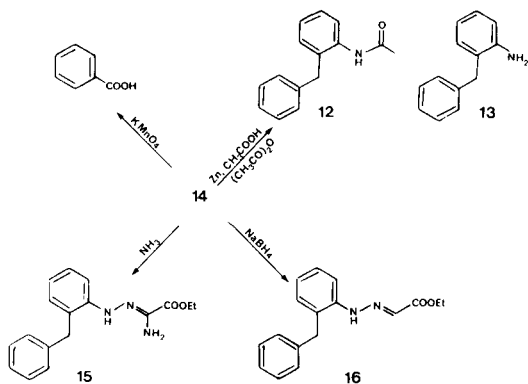
We did not further explore this new synthesis of dihydrophthalazines but it seems to compete well with the ones already described (**10**).

Concerning the series **5**, three different products **5b**, **5c** and **5d** were chosen (b, c and d having the same meaning as above), which were obtained in the same way as **4**, starting from the appropriate *N,N*-disubstituted ethoxalyl hydrazines **11**. From none of them did we obtain indazole derivatives.

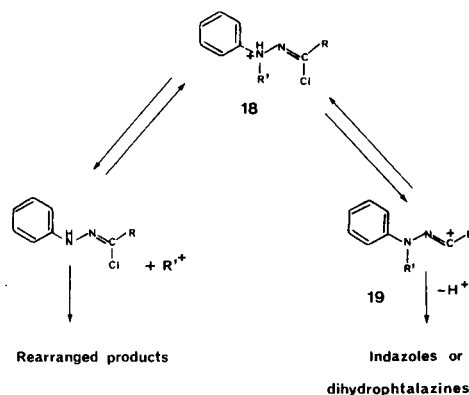


Compound **5d**, when treated with polyphosphoric acid, gave two products in about equal amounts, which could be separated by column chromatography. Both products were isomeric with the starting **5d** based upon elemental analysis and their mass spectra. The product having the lower retention time exhibits in the nmr spectrum one proton interchangeable with deuterium oxide, two benzylic, nine aromatic and five ethoxy protons. It gave benzoic acid by permanganate oxidation. Its chlorine atom could be replaced by an amino group upon treatment with ethanolic ammonia and by hydrogen upon reduction with sodium borohydride. Its reduction with zinc, acetic acid and acetic anhydride gave the acetyl derivative **12** of the *o*-benzylaniline **13** (**11**), as confirmed by an undepressed mixed melting point with an authentic sample prepared through an independent synthesis.

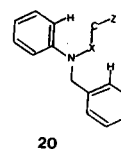
From the above results, the structure **14** of *N*-(*o*-benzyl)phenylcarbethoxyhydrazidoyl chloride was assigned to the substance having the lower retention time and the structures **15** and **16** to its derivatives. The following scheme shows the above described transformations:



Since the isomeric substance with the higher retention time showed rather similar spectroscopic properties (nmr, ir, uv), the structure of the *para*-isomer of **14**, i.e. *N*-(*p*-benzyl)phenylcarbethoxyhydrazidoyl chloride **17** was assigned to it. Both from **5b** and **5c**, by action of polyphosphoric acid, a complex reaction mixture was obtained as shown by a tlc analysis. From these mixtures and by working up using accepted procedures only a small amount of the corresponding ethoxalyl hydrazides **11b** and **11c**, respectively was isolated. As a rationalization of the above reported results the following scheme is proposed:



Under the reaction conditions the cation **18** reacts according to two different pathways. Depending on the electronic nature of R it either forms or does not form the carbocation **19**. When R = carbethoxy, the positive charge on the carbon atom is destabilized and consequently **19** does not form and no definite product is obtained, but in the particular case in which R' = benzyl, **18** undergoes fragmentation to give a Hoffmann-Martius (12) like rearrangement. When R = phenyl, **18** loses hydrogen chloride to give the carbocation **19**, which then undergoes a ring closure through the expulsion of H⁺. The formation of the phthalazine ring instead of the formation of an indazole system, when **4d** was heated with PPA, is rather unexpected. It is, in fact, well known that from *N*-benzylaniline derivatives of the general formula **20**,



in which ZH can be lost to give a heterocyclic ring, a five member heterocyclic ring is always obtained, both under acidic and neutral conditions, while the formation of a six member heterocyclic ring (**13**) was never observed. This probably is due to the easier attack on the activated aniline ring rather than on the benzylic moiety. An eventual explanation of the unusual behaviour of the cation **19**, as regards the preferred closure to the dihydrophthalazine ring starting with **4d** and the poor yields of the indazoles

obtained from **4b** and **4c**, must take into account a particular geometrical constriction induced by the presence of the C=N double bond in **19**.

EXPERIMENTAL

The melting points were determined on a Büchi apparatus and are uncorrected. The nmr spectra were taken with a Perkin Elmer Hitachi R 24 (60 MHz) spectrometer (with TMS as the internal standard), the ir and uv spectra, respectively, with a Perkin Elmer 257 and a Perkin Elmer 550 Spectrometer, the Mass spectra were measured in DIS at 70 eV with a LKB 9000 apparatus. It was used polyphosphoric acid (85% P₂O₅) obtained from Aldrich. The reactions carried out with the above-mentioned reagents were monitored through tlc analyses and stopped when no more starting products were detectable.

N-Methylphenyl-*N*-phenylcarboxyhydrazonoyl Chloride (**4d**).

Phosphorus pentachloride (30 g) was added to a solution of *N*-benzoyl-*N'*-benzyl-*N'*-phenylhydrazine (**22 g**) (14) in ethyl ether (220 ml). The mixture was stirred at room temperature for two hours, then poured into crushed ice (about 300 g). The organic layer was separated, washed with cold water and dried. After evaporation of the solvent the residue was crystallized from *n*-hexane to give 13 g of **4d** mp 58-59°, yield 56%; nmr (deuteriochloroform): δ 5.00 (s, 2H, CH₂-Ph).

Anal. Calcd. for C₂₀H₁₇ClN₂: C, 74.88; H, 5.34; N, 8.73. Found: C, 75.08; H, 5.35; N, 8.70.

1-Methyl-3-phenylindazole (**6b**).

Compound **4b** (4 g) was added to polyphosphoric acid (25 g). After stirring for 1 hour at 90° the reaction mixture was poured into crushed ice. The oil which separated was taken up with ethyl ether. The residue which was obtained after removal of the solvent was extracted with hot petroleum ether (40-60°). The solvent was evaporated and the residue crystallized from *n*-hexane to give 0.25 g of **6b**, mp 78-80° (Lit (6) 78.5-80°) yield 7%.

1,3-Diphenylindazole (**6c**).

This compound was obtained starting from **4c**, as above described for **6b**, mp 96-98° (Lit (7) 100-101°), yield 6%.

2,4-Diphenyl-1,2-dihydrophthalazine (7) (8) from **4d**.

Compound **4d** (1 g) was added to polyphosphoric acid (6.5 g) and the mixture was heated under stirring at 90° for 10 minutes, then cooled and poured into ice. After extraction with ethyl ether and removal of the solvent the residue was crystallized from hexane to give 0.25 g of **7**, mp 83-85°, yield 28%; nmr (deuteriochloroform): δ 4.70 (s, 2H, CH₂-Ph); uv (ethanol): λ max 247, 373 nm (ε = 22180, 12440).

Anal. Calcd. for C₂₀H₁₆N₂: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.34; H, 5.65; N, 9.69.

2,4-Diphenyl-1,2-dihydrophthalazine (7) by Independent Synthesis.

Lithium aluminum hydride powder (0.2 g) was added to a suspension of 2,4-diphenyl-1(2*H*)-phthalazinone **8** (8) (1 g) in anhydrous ethyl ether (30 ml) at room temperature and under stirring. After 30 minutes the excess of lithium aluminum hydride was decomposed with water, the organic phase was separated and evaporated to give **7** (0.5 g), yield 52%, mp 81-84°, also in mixture with the sample obtained as above.

2,4-Diphenyl-1,2-dihydrophthalazin-1-ol **9** and 1,2-Dihydro-2,4-diphenyl-1-ethoxyphthalazine **10**.

A solution of **7** (0.24 g) in acetic acid (4 ml) was added to a solution of chromic anhydride (0.17 g) in water (0.5 ml) and acetic acid (1.0 ml). After 10 minutes at 60° the resulting solution was cooled, diluted with water (100 ml) and the mixture was extracted with chloroform ethanol free. The residue obtained after removal of the solvent was crystallized from benzene to give **9** (0.12 g), mp 174-177°, yield 47%; nmr (deuteriochloroform): δ 6.40 (d, 1H, J = 4 Hz, s after deuterium oxide, PhCH-OH); ir

(potassium bromide): 3400 (broad), 1600, 1390 cm⁻¹.

Anal. Calcd. for C₂₀H₁₆N₂O: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.18; H, 5.19; N, 9.05.

In another identical preparation the residue obtained from the removal of chloroform was recrystallized from ethanol to give **10** (0.09 g), mp 99-100°, yield 33%; nmr (deuteriochloroform): δ 1.00 (t, 3H, J = 7 Hz, -CH₂-CH₃), 3.20 (q, 2H, J = 7 Hz, -CH₂-CH₂-), 6.70 (s, 1H, Ph-CH-OC₂H₅).

Anal. Calcd. for C₂₂H₂₀N₂O: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.26; H, 5.97; N, 8.47.

Chloro(phenylhydrazono)acetic Acid Ethyl Esters (**5b**, **5c** and **5d**).

Compounds **5b**, **5c** and **5d** were obtained as described above for **4d** starting from the appropriate *N,N*-disubstituted ethoxalyldiazine. From *N*-methyl-*N*-phenylethoxalyldiazine (15), *N*-methyl-*N*-chloro(phenylhydrazono)acetic acid ethyl ester **5b** was obtained, bp 130° (0.2 mm Hg) in 74% yield; nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7 Hz, CH₂-CH₃), 3.75 (s, 3H, CH₃-N), 3.80 (q, 2H, J = 7 Hz, CH₂-CH₃).

From *N,N*-diphenylethoxalyldiazine (16), *N*-phenyl-*N*-chloro(phenylhydrazono)acetic acid ethyl ester **5c** was obtained in 47% yield, mp 67-70°; nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7 Hz, -CH₂-CH₃), 4.35 (q, 2H, J = 7 Hz, -CH₂-CH₃), 6.95-7.65 (m, 10 H aromatics).

Anal. Calcd. for C₁₆H₁₅ClN₂O₂: C, 63.48; H, 4.99; N, 9.25. Found: C, 63.27; H, 4.92; N, 9.07.

From *N*-methylphenyl-*N*-phenylethoxalyldiazine, (mp 60-62°; nmr (deuteriochloroform): δ 1.20 (t, 3H, J = 7 Hz, CH₂-CH₃), 4.15 (q, 2H, J = 7 Hz, CH₂-CH₃), 4.60 (s, 2H, CH₂-Ph), 8.95 (s, 1H, NH)).

Anal. Calcd. for C₁₇H₁₈N₂O₂: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.25; H, 6.06; N, 9.57.

N-Methylphenyl-*N*-chloro(phenylhydrazono)acetic acid ethyl ester **5d** was obtained in 50% yield, mp 57.5-58.5°; nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7 Hz, CH₂-CH₃), 4.35 (q, 2H, J = 7 Hz, CH₂-CH₃), 5.48 (s, 2H, CH₂-Ph); uv (ethanol): λ max 225, 290, 313 nm (ε = 12000, 8400, 3500).

Anal. Calcd. for C₁₇H₁₇ClN₂O₂: Cl, 11.19. Found: Cl, 11.09.

N-(2-Methylphenyl)phenylcarbethoxyhydrazidoyl Chloride (**14**) and *N*-(4-Methylphenyl)phenylcarbethoxyhydrazidoyl Chloride (**17**).

Compound **5d** (0.5 g) was added to polyphosphoric acid (3.3 g), and the mixture was heated at 90° for 30 minutes then cooled and poured into ice. After extraction with ethyl ether and removal of the solvent, the residue, which showed two spots on tlc analysis, was chromatographed on II/III grade alumina column (50 g). The elution with hexane-ethyl acetate = 8:2 afforded 0.17 g of the compound with the lower retention time to which the structure of *N*-(2-methylphenyl)phenylcarbethoxyhydrazidoyl chloride **14** was assigned, mp 93-95°; nmr (deuteriochloroform): δ 1.30 (t, 3H, J = 7 Hz, CH₂-CH₃), 4.00 (s, 2H, CH₂-Ph), 4.35 (q, 2H, J = 7 Hz, -CH₂-CH₃), 8.20 (s, 1H, NH); ir (potassium bromide): 3420 (broad), 3290 (sharp), 1720 cm⁻¹; uv (ethanol): λ max 230, 292, 319 nm (ε = 10700, 9500, 17900); ms: m/e 318 (M + 2, 20), 316 (M⁺, 54), 282 (54), 276 (5), 254 (30), 236 (100), 226 (24), 152 (30).

Anal. Calcd. for C₁₇H₁₇ClN₂O₂: C, 64.56; H, 5.38; N, 8.86. Found: C, 64.61; H, 5.48; N, 8.78.

After several mixed fractions the product with the higher retention time was eluted and the structure of *N*-(4-methylphenyl)phenylcarbethoxyhydrazidoyl chloride **17** was assigned to it, mp 85-86°; nmr (deuteriochloroform): δ 1.32 (t, 3H, J = 7 Hz, -CH₂-CH₃), 3.90 (s, 2H, CH₂-Ph), 4.35 (q, 2H, J = 7 Hz, CH₂-CH₃), 8.32 (s, 1H, -NH); ir (potassium bromide): 3440 (broad), 3270 (sharp), 1710 cm⁻¹; uv (ethanol): λ max 230, 295, 321 nm (ε = 12100, 13000, 21470).

Anal. Calcd. for C₁₇H₁₇ClN₂O₂: C, 64.56; H, 5.38; N, 8.86. Found: C, 64.36; H, 5.34; N, 8.71.

Reactions of **14**.

a) With an ethanolic solution of ammonia at room temperature, **15** was obtained from **14** in 68% yield, mp 106-108.5° (from hexane-isopropyl ether); nmr (deuteriochloroform): δ 1.30 (t, 3H, J = 7 Hz, CH₂-CH₃), 3.90

(s, 2H, CH_2 -Ph), 3.95 (s, 2H, $-NH_2$), 4.20 (q, 2H, $J = 7$ Hz, CH_2 - CH_3), 6.30 (s, 1H, NH); ir (potassium bromide): 3460 (sharp), 3320 (sharp), 3200 (broad), 1725, 1630 cm^{-1} .

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.61; H, 6.47; N, 13.97.

b) By the action of sodium borohydride in methanol on **14**, **16** was obtained in 57% yield, mp 97-100° (from hexane); nmr (deuteriochloroform): δ 1.35 (t, 3H, $J = 8$ Hz, CH_2 - CH_3), 4.02 (s, 2H, CH_2 -Ph), 4.30 (q, 2H, $J = 8$ Hz, CH_2 - CH_3), 6.80 (s, 1H, $CH=C$); ir (potassium bromide): 3420 (broad), 3260 (sharp), 1695 cm^{-1} .

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.03; H, 6.44; N, 9.84.

c) By the action of an aqueous solution of potassium permanganate 8% in aqueous sodium hydroxide, a mixture was obtained which showed in glc analysis, after treatment with diazomethane, a principal peak due to the methyl ester of benzoic acid.

d) Compound **14** (0.3 g) was added to a suspension of zinc powder (0.5 g) in a mixture of acetic acid:acetic anhydride = 2:1 (2.4 ml) and the mixture was refluxed for 12 hours, cooled and poured into ice. After extraction with ethyl ether and evaporation of the solvent, the residue was crystallized from aqueous ethanol to give **12** (**11**) (0.04 g), yield 60%, mp 124-125°, also in mixture with an authentic sample obtained from acetylation of *o*-benzylaniline (**11**).

REFERENCES AND NOTES

(1) S. Conde, C. Corral and R. Madronero, *Tetrahedron*, **30**, 195 (1974).

(2) The exact nomenclature of these compounds according to *Chem. Abstr.* is too complicated to be currently used, nevertheless it is reported

in the experimental part.

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(4) G. Corsi, G. Palazzo, C. Germani, P. S. Barcellona and B. Silvestri, *J. Med. Chem.*, **19**, 778 (1976).

(5) R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, **17**, 18 (1962).

(6) K. V. Auwers and K. Huttenes, *Chem. Ber.*, **55b**, 1112 (1922).

(7) W. Borsch and W. Scriba, *Ann. Chem.*, **540**, 83 (1939).

(8) The phthalazinone **8** was described for the first time by Roger (*Chem. Ber.*, **18**, 805 (1885)). The dihydrophthalazine **7** is reported in the *Chem. Abstr.*, Ninth Collective Subject Index, Vol. **76-85** (1972-1976) and referred to Vol. **83**, 178862j but in the corresponding original paper (*Indian J. Chem.*, **13**, 652 (1975)) only the phthalazinone **8** is cited, whereas no mention is found of the dihydrophthalazine **7**.

(9) Houben-Weyl "Methoden der Organischen Chemie", G. Thieme, Verlag Stuttgart, Band IV/1b, 463, 1975.

(10) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 2715 (1969).

(11) O. Fischer, Schutte, *Chem. Ber.*, **26**, 3086 (1893).

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(13) Several examples of this fact can be found in the literature, *i.e.* the synthesis of 1-benzyl-3-hydroxyindazoles according to Stollè (R. Stollè, H. Nieland, M. Merkle, *J. Prakt. Chem.*, **116**, 192 (1927)) or to Milrath (G. Milrath, *Monatsh. Chem.*, **29**, 920 (1920)), the synthesis of 1-benzylindole according to Palazzo (G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.*, **83**, 211 (1953)) and the synthesis of 1-benzylisatin according to Baiocchi (L. Baiocchi, *Ann. Chim. (Rome)*, **57**, 492 (1967)).

(14) Franzen, *Chem. Ber.*, **42**, 2467 (1909).

(15) I. S. Berdinskii, *Zh. Obshch. Khim.*, **33**, 1219 (1963).

(16) I. S. Berdinskii and P. A. Petyunin, *ibid.*, **26**, 2592 (1956).