Advances in
HETEROCYCLIC CHEMISTRY

A. R. KATRITZKY

A. J. BOULTON

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CHEMISTRY

Edited by

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Volume 8

Academic Press · New York and London · 1967

ACADEMIC PRESS INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

PRINTED IN THE UNITED STATES OF AMERICA

Preface

The eighth volume of this serial publication comprises eight contributions from international authors. Four of these deal with well-defined groups of compounds: thiopyrones (R. Zahradník, R. Mayer, and W. Broy), phenoxazines and phenothiazines (M. Ionescu and H. Mantsch), diazepines (F. D. Popp and A. Catala Noble), and benzisoxazoles (anthranils and indoxazenes) (K.-H. Wünsch and A. J. Boulton). J. M. Tedder has surveyed the field of the heteroaromatic diazo compounds which are derived from a variety of heterocyclic ring systems, and M. Schulz and K. Kirschke discuss heterocyclic peroxides. The remaining two chapters survey well-known reactions: the Hilbert–Johnson reaction is covered by J. Pliml and M. Prystaš, and heterocyclic Claisen rearrangements by B. S. Thyagarajan.

We are grateful to the publishers and the authors for their cooperation, which has enabled this volume to be produced more quickly than some of the earlier volumes in this serial publication. We hope to improve this schedule still further in future volumes.

A. R. Katritzky
A. J. Boulton

Norwich, England
December, 1966

Contents

PREFACE vii

Heterocyclic Diazo Compounds

J. M. TEDDER

I. Introduction 1
II. Methods of Preparation 3
III. Heterocyclic Diazo Compounds 8
IV. Applications of Heterocyclic Diazo Compounds 18

The Chemistry of Diazepines

F. D. POPP and A. CATALA NOBLE

I. Introduction 21
II. 1,2-Diazepines 22
III. 1,3-Diazepines 38
IV. 1,4-Diazepines 52

Phenoxazines

MARIA IONESCU and HORST MANTSCH

I. Introduction 83
II. Methods of Preparation 84
III. Physical Properties 91
IV. Chemical Properties 96
V. Biologically Important Phenoxazines and Industrial Uses . . 108

The Hilbert-Johnson Reaction of 2,4-Dialkoxypyrimidines with Halogenoses

JIŘÍ PLIML and MIROSLAV PRYSTAŠ

I. Introduction 115
II. Scope and Limitations 118
III. Modifications 122
IV. Side Reactions 124

V. Miscellaneous Uses of the Hilbert–Johnson Products 127
VI. Configuration of the Hilbert–Johnson Products 127
VII. Related Reactions 128
VIII. Mechanism 131
IX. Stereochemistry 133
X. Experimental Conditions 136
XI. Comparison with Other Methods of Nucleoside Synthesis . . . 137
XII. Tabular Survey of Reactants (Tables I–III) 139

Claisen Rearrangements in Nitrogen Heterocyclic Systems

B. S. Thyagarajan

I. Introduction 143
II. Synthesis of the Allyl Ethers 144
III. General Conditions of Rearrangements 146
IV. Rearrangements and Mechanistic Features 146

Cyclic Peroxides

Manfred Schulz and Klaus Kirschke

I. Introduction 165
II. Syntheses of Cyclic Peroxides with Hydrogen Peroxide . . . 167
III. Syntheses of Cyclic Peroxides with Ozone 187
IV. Syntheses of Cyclic Peroxides with Oxygen 203

Monocyclic Sulfur-Containing Pyrones

R. Mayer, W. Broy, and R. Zahradník

I. Introduction 219
II. Nomenclature 220
III. Syntheses 220
IV. Properties of Thiopyrones 243

Indoxazenes and Anthranils

K. H. Wünsch and A. J. Boulton

I. Introduction 277
II. 1,2-Benzisoxazoles (Indoxazenes) 278
III. 2,1-Benzisoxazoles (Anthranils) 303
IV. Note Added in Proof 339
V. Tables I–XVIII 343

Author Index 381

Heterocyclic Diazo Compounds

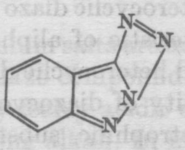
J. M. TEDDER

Queen's College, Dundee, Scotland

I. Introduction 1
II. Methods of Preparation 3
III. Heterocyclic Diazo Compounds 8
A. Diazopyrroles 8
B. Diazoindoles 11
C. 3-Diazocarbazole 13
D. Diazopyrazoles 13
E. Diazoindazole 15
F. Diazoimidazole 16
G. Diazopurines 16
H. Diazotriazoles and Diazotetrazole 18
IV. Applications of Heterocyclic Diazo Compounds 18

I. Introduction

Stable five-membered heterocyclic diazo compounds form an interesting group of compounds. The first example, 3-diazoindazole, was reported by Bamberger in 1899.[1] To reinterpret Bamberger's suggestion for its structure in modern terms is difficult since the structure proposed for indazole itself would be unacceptable. However Bamberger regarded the diazoindazole as an anhydride of the diazonium hydroxide and he suggested it contained a four-membered ring (which he called a triazolen ring). We can therefore depict his structure as in 1.



(1)

"Indazoletriazolen," Bamberger, 1899

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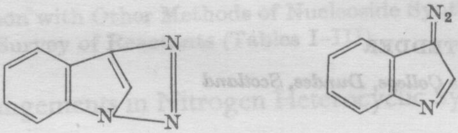
[1] E. Bamberger, *Ber. Deut. Chem. Ges.* **32**, 1773 (1899).

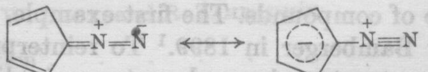
In their first paper on diazoindoles some 5 years later Angeli and D'Angelo again regard the diazo compound as the anhydride of the diazonium hydroxide.[2] They offered two structures (**2** and **3**) one of which is very close to today's picture.



(2) **(3)**

Structures for diazoindole, Angeli and D'Angelo, 1904

It is interesting that Taylor and Baker in their brilliant rewriting of Sidgwick's "Organic Chemistry of Nitrogen" should have written of 3-diazodi- and triphenylpyrroles: "the composition of these so-called diazopyrroles resembles that of the aliphatic diazocompounds but their structure is not fully known."[3] The real interpretation of the structure and stability of heterocyclic diazo compounds was not forthcoming until 1959. In 1953 Doering and De Puy reported the synthesis of diazocyclopentadiene (4), apparently unaware that heterocyclic analogs had been known 50 years before.[4] Formula **4b** is supposed to represent a combination of the four possible canonical



(4a) **(4b)**

forms with a negative charge on unsubstituted carbon atoms. The cyclopentadienyl ring then contains six π electrons necessary to make a closed aromatic shell. In fact, the infrared spectrum of diazocyclopentadiene, and of most heterocyclic diazo compounds, shows absorption at 2100 cm^{-1} characteristic of aliphatic diazo compounds (cf. 2200 cm^{-1} for aromatic and heterocyclic diazonium salts). Nevertheless, the exceptional stability of diazocyclopentadiene and the fact that it will undergo electrophilic substitution suggest that the

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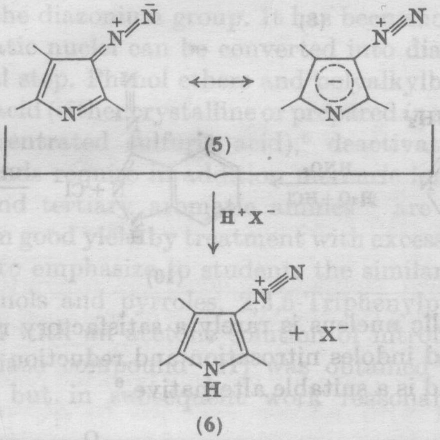
[2] A. Angeli and A. D'Angelo, *Atti Reale Accad. Lincei* **13**, 258 (1904)

[3] T. W. J. Taylor and W. Baker, "The Organic Chemistry of Nitrogen," p. 480. Oxford Univ. Press, London and New York, 1937.

[4] W. von E. Doering and C. H. De Puy, *J. Am. Chem. Soc.* **75**, 5955 (1953).

canonical forms represented by formula **4b** do contribute to the over-all structure of the molecules.

The heterocyclic diazo compounds such as diazopyrroles bear the same relation to diazocyclopentadiene that pyridine does to benzene. Just as pyridine is a base and forms a pyridinium ion, in acid solution, so diazopyrroles (**5**) form pyrrole diazonium salts (**6**).



We shall first discuss the preparation of heterocyclic diazo compounds as a class and shall then consider separately the individual characteristics of the various types, e.g., diazopyrroles, diazopyrazoles, etc.

II. Methods of Preparation

3-Diazoindazole (**11**) was first prepared by the diazotization of 3-aminoindazole (**9**) followed by the treatment of the resulting diazonium salt (**10**) with base,[1,5] This remains the most important method of synthesis for the whole class of heterocyclic diazo compounds. (See p. 4.)

Pyrrole and indole diazonium salts are acidic and lose a proton even in dilute acid to yield the diazo compound. Pyrazole diazonium salts, on the other hand, are only feebly acidic and the diazo compound is liberated only in quite strong alkali. In many cases the difficulty in obtaining the heterocyclic diazo compound has mainly centered round the preparation of the preceding amino compound. Nitration

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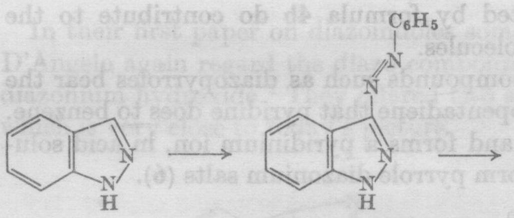
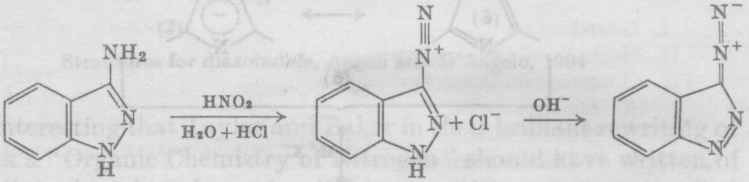
[5] E. Bamberger, *Ann. Chem.* **305**, 289 (1899).

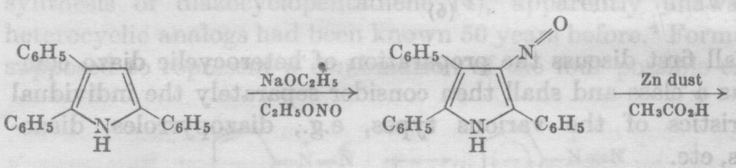


(7) (8)

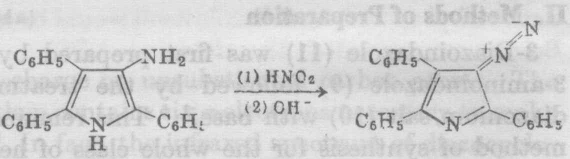


(9) (10) (11)

of the heterocyclic nucleus is rarely a satisfactory reaction and for diazopyrroles and indoles nitrosation and reduction of the resulting nitroso compound is a suitable alternative.[6]



(12) (13)



(14) (15)

Another route extensively used in the pyrazole series goes via a Curtius rearrangement (16→19).[7]

One of the factors which stimulated recent interest in heterocyclic diazo compounds was the application of the technique of direct

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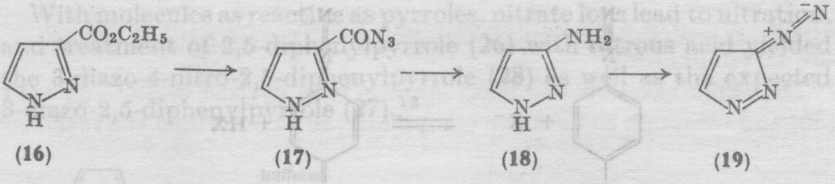
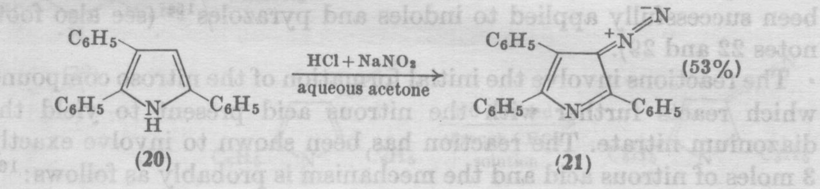
[6] F. Angelico, *Atti Reale Accad. Lincei* **14**, 167 (1905).

[7] H. Reimlinger, A. v. Overstraeten, and H. G. Viche, *Chem. Ber.* **94**, 1036 (1961).



introduction of the diazonium group. It has been shown that a wide variety of aromatic nuclei can be converted into diazonium salts in one experimental step. Phenol ethers and polyalkylbenzenes require nitrosyl sulfuric acid (either crystalline or prepared *in situ* from sodium nitrite and concentrated sulfuric acid),[8] deactivated nuclei such as nitro compounds require in addition mercuric ions as catalysts,[9] but phenols[10] and tertiary aromatic amines[11] are converted into diazonium salts in good yield by treatment with excess of nitrous acid. It is customary to emphasize to students the similarity in chemical reactions of phenols and pyrroles. 2,3,5-Triphenylpyrrole (**20**) was therefore treated with an acetone solution of nitrous acid and the corresponding diazo compound (**21**) was obtained[12] (initially the yield was poor but in subsequent work reasonable yields were obtained).[13]



The analogy between phenols and pyrroles is particularly apt in this case because the equilibrium between a phenol diazonium salt (**22**) and a diazooxide (**23**) is exactly analogous to that between a pyrrole diazonium salt (**24**) and a diazopyrrole (**25**). (See p. 6.)

At first it was believed that the reaction could not be applied to pyrroles in which the 2-position was vacant,[12] but subsequent work

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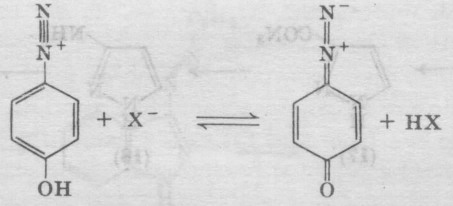
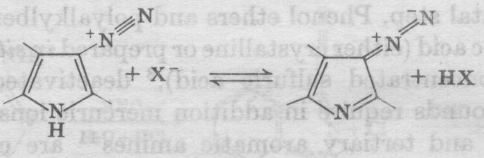
[8] J. M. Tedder, *J. Chem. Soc.* p. 4003 (1957).
[9] J. M. Tedder and G. Theaker, *J. Chem. Soc.* p. 4008 (1957).
[10] J. M. Tedder and G. Theaker, *J. Chem. Soc.* p. 2573 (1958).
[11] H. P. Patel and J. M. Tedder, *J. Chem. Soc.* p. 4889 (1963).
[12] J. M. Tedder and B. Webster, *J. Chem. Soc.* p. 3270 (1960).
[13] H. P. Patel, Ph.D. Thesis, University of Sheffield, 1963.



(22) (23)

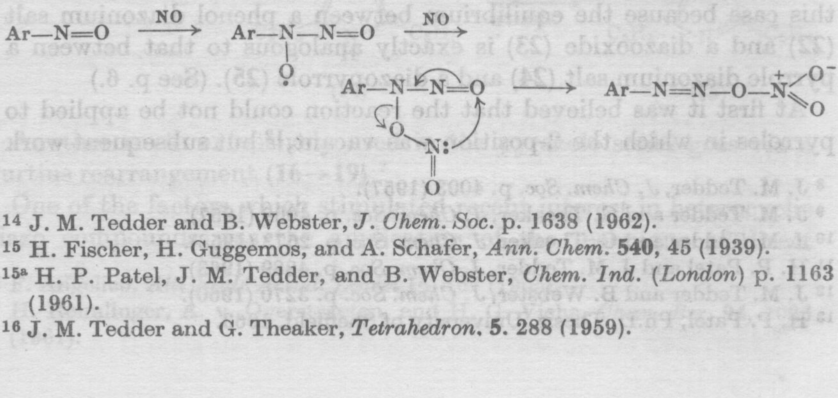


(24) (25)

showed that such compounds could be converted into 2-diazopyrroles.[14] This was the first synthesis of this class of compound and in view of the known instability of 2-aminopyrroles it may well prove to be the only route. Certainly the only reported reactions of unstable 2-aminopyrroles with nitrous acid led to decomposition.[15] The technique of the direct introduction of the diazonium group has also been successfully applied to indoles and pyrazoles[15a] (see also footnotes 22 and 29).

The reactions involve the initial formation of the nitroso compound which reacts further with the nitrous acid present to yield the diazonium nitrate. The reaction has been shown to involve exactly 3 moles of nitrous acid and the mechanism is probably as follows:[16]

$$\mathrm{ArH} \xrightarrow{\mathrm{HNO_2}} \mathrm{Ar{-}N{=}O} \xrightarrow{\mathrm{2HNO_2}} \mathrm{Ar{-}\overset{+}{N}{\equiv}N}\quad \mathrm{NO_3^-}$$



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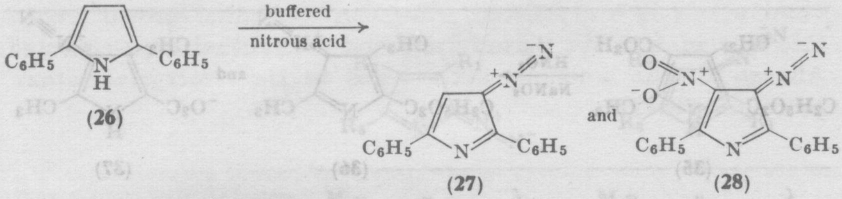
[14] J. M. Tedder and B. Webster, *J. Chem. Soc.* p. 1638 (1962).

[15] H. Fischer, H. Guggemos, and A. Schafer, *Ann. Chem.* **540**, 45 (1939).

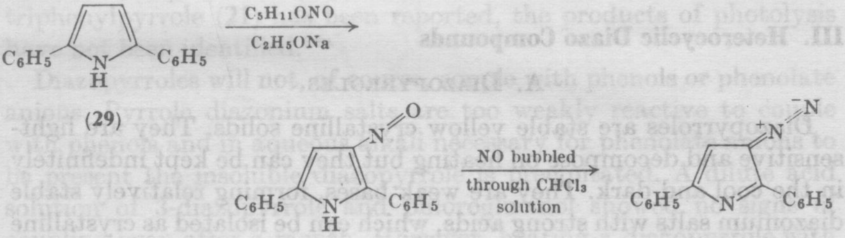
[15a] H. P. Patel, J. M. Tedder, and B. Webster, *Chem. Ind.* (*London*) p. 1163 (1961).

[16] J. M. Tedder and G. Theaker, *Tetrahedron*. **5**. 288 (1959).

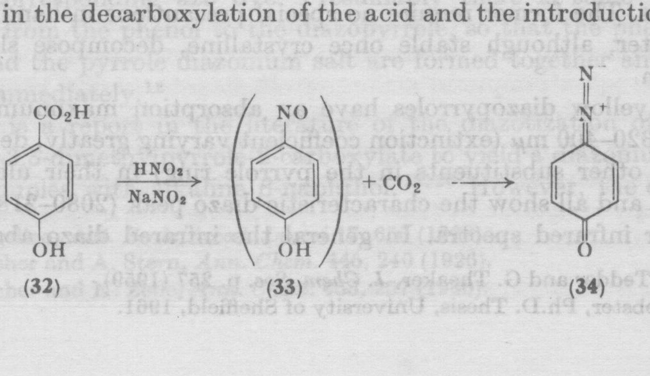
With molecules as reactive as pyrroles, nitrate ions lead to nitration, and treatment of 2,5-diphenylpyrrole (**26**) with nitrous acid yielded the 3-diazo-4-nitro-2,5-diphenylpyrrole (**28**) as well as the expected 3-diazo-2,5-diphenylpyrrole (**27**).[12]



The nitration was avoided by employing a two-step process. The pyrrole (**29**) was converted into 3-nitroso-2,5-diphenylpyrrole by treatment with pentylnitrite and sodium ethoxide. The resulting nitroso compound was converted into the diazo compound (**31**) by treatment with gaseous nitric oxide. Exactly the same problem was encountered in the preparation of 2-diazo-3,5-diphenylpyrrole.[12]

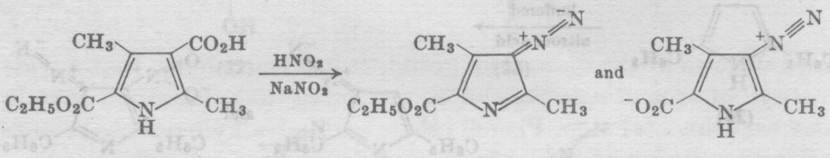


Treatment of *o*- or *p*-hydroxybenzoic acids with buffered nitrous acid resulted in the decarboxylation of the acid and the introduction of a



nitroso group or a diazonium group in the site originally occupied by the carboxyl group.[17]

The same reaction has been applied to a pyrrole carboxylic acid (**35**) and although some diazo compound (**36**) was formed the reaction



(35) (36) (37)

was complicated by side reactions and the yield was too small for this to be considered as a practicable method of preparing diazo compounds.[14]

An obvious alternative route to heterocyclic diazo compounds would be that employed by Doering and De Puy for the synthesis of diazocyclopentadiene. However, attempts to do this have not been very successful.[18]

III. Heterocyclic Diazo Compounds

A. DIAZOPYRROLES

Diazopyrroles are stable yellow crystalline solids. They are light-sensitive and decompose on heating but they can be kept indefinitely in the cool and dark. They are weak bases, forming relatively stable diazonium salts with strong acids, which can be isolated as crystalline solids. Soluble in organic solvents such as acetone, ethanol, or chloroform, diazopyrroles are insoluble in water. There is a very marked difference in the stability of the 3-diazopyrroles and the 2-diazopyrroles. The former require no special precautions in handling but the latter, although stable once crystalline, decompose slowly in solution.

The yellow diazopyrroles have an absorption maximum in the region 320–400 mμ (extinction coefficient varying greatly, depending on the other substituents in the pyrrole ring) in their ultraviolet spectra and all show the characteristic diazo peak (2080–2180 cm^{-1}) in their infrared spectra. In general the infrared diazo absorption

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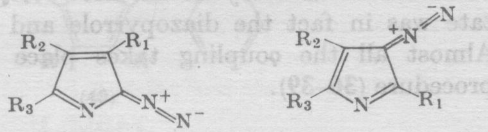
[17] J. M. Tedder and G. Theaker, *J. Chem. Soc.* p. 257 (1959).

[18] B. Webster, Ph.D. Thesis, University of Sheffield, 1961.

occurs at slightly shorter wavelengths for the 2-diazopyrroles than for the corresponding 3-diazo compounds (see Table I).

TABLE I

SPECTRAL CHARACTERISTICS OF SOME TYPICAL DIAZOPYRROLES[12, 14]



R_1	R_2	R_3	M.p. (°C)	ν_{max} (cm^{-1})	λ_{max} ($m\mu$)	M.p. (°C)	ν_{max} (cm^{-1})	λ_{max} ($m\mu$)
C_6H_5	H	C_6H_5	104	2138	345	122	2095	387
C_6H_5	NO_2	C_6H_5	116.5	2172	—	145	2150	339
CH_3CO	C_6H_5	CH_3	102	2146	351	—	—	—
C_6H_5	H	CH_3	—	—	—	81	2062	360
CH_3	CH_3	CO_2Et	—	—	—	79.5–80	2155	333

Although a preliminary study of the effect of light on 3-diazo-2,4,5-triphenylpyrrole (**21**) has been reported, the products of photolysis have not been identified.[18a]

Diazopyrroles will not, of course, couple with phenols or phenolate anions. Pyrrole diazonium salts are too weakly reactive to couple with phenols and in aqueous alkali necessary for phenolate anions to be present the insoluble diazopyrrole is precipitated. A dilute acid solution of 3-diazopyrrole and phloroglucinol showed no signs of coupling even after a month. However, heating a diazopyrrole with a phenol (either fusing them together, or better refluxing a solution of them in an organic solvent, e.g., chloroform) results in the formation of the corresponding azo dye. Presumably there is some proton transfer from the phenol to the diazopyrrole, so that the phenolate anion and the pyrrole diazonium salt are formed together and then couple immediately.[12]

There is a report in the literature of the diazotization of ethyl 4-amino-3,5-dimethylpyrrole-2-carboxylate to yield a diazonium salt which couples with alkaline β-naphthol.[19, 20] However, the experi-

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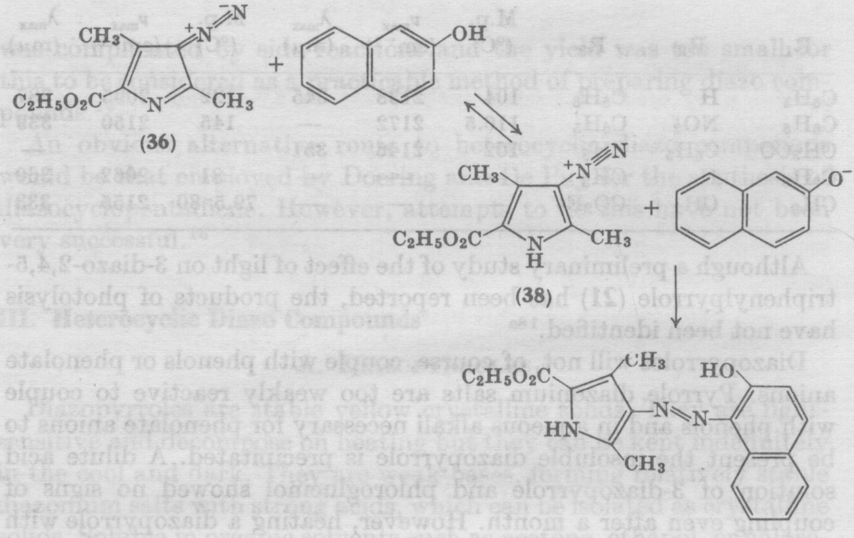
[18a] F. Angelico, *Atti. Reale Accad. Lincei* **17**, 655 (1908).

[19] H. Fischer and A. Stern, *Ann. Chem.* **446**, 240 (1926).

[20] H. Fischer and K. Zeile, *Ann. Chem.* **483**, 257 (1930).

mental section of this paper[20] clearly describes the formation of a brown precipitate when the coupling was carried out in sodium bicarbonate solution. When the product was recrystallized from chloroform the solution turned red and the correct azo dye was obtained. Repetition of this work confirmed the experimental observations in every detail. However, the initial brown precipitate was in fact the diazopyrrole and β-naphthol coprecipitated. Almost all the coupling takes place in the "recrystallization" procedure (**36–39**).



(**36**) (**38**) (**39**)

The azo dyes are typical red crystalline compounds; those derived from 2-diazopyrroles (**40**) form lakes with the transition metals.[14]

Although attempts to make pyrrole diazonium salts couple intermolecularly have been unsuccessful, 3-diazo-2,4,5-triphenylpyrrole (**21**) on prolonged heating in dilute sulfuric acid undergoes internal coupling (**21**→**41**).[21] That coupling occurred with the phenyl group in the 4-position rather than the 2-position is shown by the formation of the diketone (**42**) on oxidation with nitric acid.

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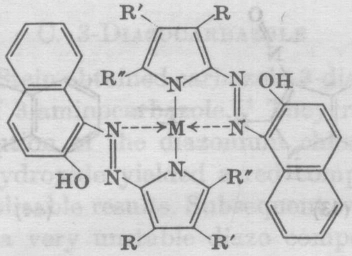
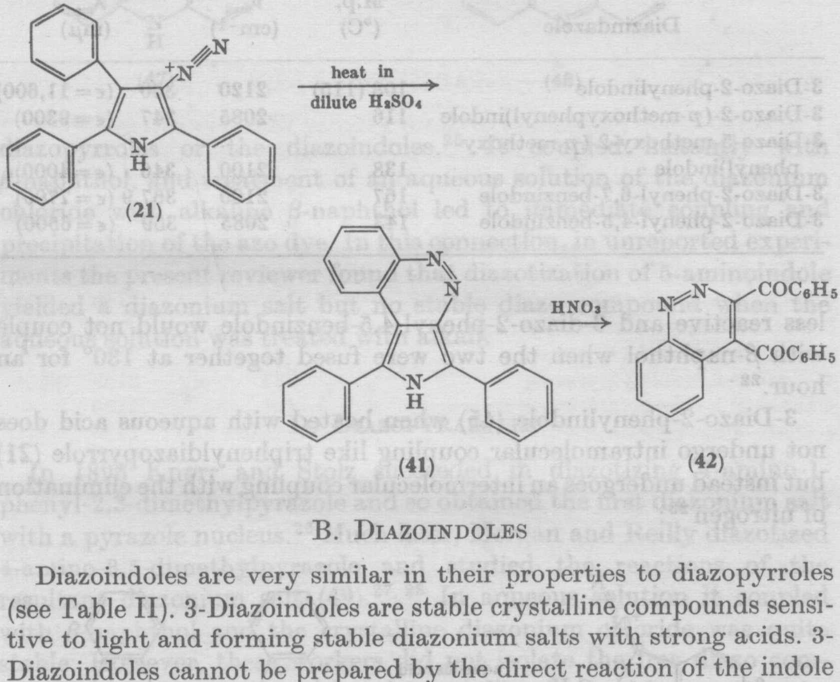
[21] F. Angelico and F. Monforte, *Gazz. Chim. Ital.* **53**, 795 (1923).



(40)

Possible structure of complex formed between transition metal cations and azo dyes derived from 2-diazopyrroles.



B. DIAZOINDOLES

Diazoindoles are very similar in their properties to diazopyrroles (see Table II). 3-Diazoindoles are stable crystalline compounds sensitive to light and forming stable diazonium salts with strong acids. 3-Diazoindoles cannot be prepared by the direct reaction of the indole with nitrous acid, presumably because the nitroso compound (43) completely rearranges to the oximoimine form (44).[22] (See p. 12.)

3-Diazoindoles will couple with phenols under the same conditions as those described for diazopyrroles. The benzindoles were very much

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[22] H. P. Patel and J. M. Tedder, *J. Chem. Soc.* p. 4593 (1963).