

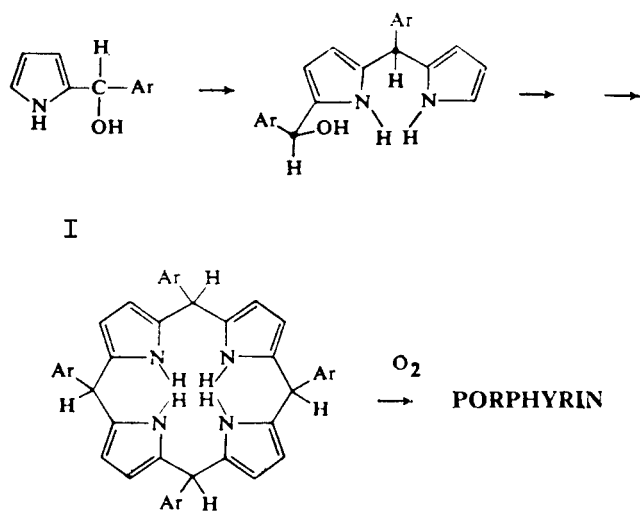
Robert G. Little

Department of Chemistry, University of Maryland Baltimore County, Catonsville, Maryland 21228
Received December 16, 1980

Aryl pyrrol carbinols have been found to readily cyclize to *meso*-substituted tetraarylporphyrins in yields which are consistent with the intermediacy of the pyrrol carbinols in the Rothmund reaction. Acidic solutions of the pyrrol carbinols show absorption bands characteristic of pyrrolylmethenes. It is suggested that pyrrolylmethenes are likely intermediates in the Rothmund reaction.

J. Heterocyclic Chem., **18**, 833 (1981).

In the Rothmund reaction (1,2) pyrrole is condensed under acidic conditions with aryl or alkyl aldehydes to give, in one step, *meso*-substituted porphyrins in yields as high as 40%. The mechanism of this reaction has been studied by several investigators, (2-7). Adler, Longo and Shergalis (5) have suggested that the cyclization reaction most likely proceeds *via* the carbinol, I (see Scheme I). In order to test this hypothesis we have prepared a series of pyrrol carbinols and examined their cyclization to *meso*-substituted porphyrins.



Scheme I

The yields obtained with several different pyrrol carbinols are listed in Table I. Also listed are the yields obtained in two mixed-carbinol syntheses of unsymmetrically substituted porphyrins (8,9). As the data show the yields are essentially the same as those obtained in the Rothmund reaction. This result is consistent with the intermediacy of the carbinols in that reaction. Since the pyrrol carbinols were oils which could not be distilled the yields reported here are based on the amount of ketone.

We have observed that propionic acid solutions of the carbinols become bright red in the early stages of the cyclization reactions. We have briefly investigated the

nature of these species. Cold propionic acid solutions of phenyl, 4-nitrophenyl, 3-pyridyl, and methyl pyrrol carbinols show absorption maxima at 475, 478, 481 and 498 nm, respectively. Similar intense absorptions are observed in the early stages of the Rothmund reaction. For example, a hot propionic acid solution of 3-pyridinecarboxaldehyde and pyrrole has a particularly long-lived absorption at 481 nm. We note that these absorptions are characteristic of pyrrolylmethenes, II (11-13), and we suggest that they are likely intermediates in the Rothmund reaction (14). Their intermediacy is entirely consistent

with the rate of water formation during the reaction (5). It has been previously demonstrated that pyrrolylmethenes will react with pyrroles to give dipyrrolylmethenes (13).

The reactivity of pyrrol ketones was briefly examined. They showed no tendency to cyclize and could be nearly quantitatively recovered from reaction mixtures. This rules out their proposed role in the Rothmund reaction (4).

EXPERIMENTAL

The nmr spectra in deuteriochloroform solutions were obtained in a Perkin-Elmer R24B spectrometer operating at 60 MHz. The shifts, δ , are given in ppm from TMS and the coupling constants are in Hz. Analyses were performed by Gallbraith Laboratories, Inc., Knoxville, Tenn. The chromatographic separations were effected by the dry-column procedure using either alumina (Fisher Scientific A-540), silica gel (Baker, 5-3405), silica gel (Woelm-04526; obtained through ICN Pharmaceuticals, Inc.).

All solvents and reagents were purchased commercially and used as supplied except as follows. Pyrrole was distilled from calcium hydride and 1,2-dichloroethane was distilled from phosphorus pentoxide. The following aryl pyrrol ketones were synthesized by the method of White and McGillivray (15): 2-benzoylpyrrole: mp 78°, lit. 77.5-78.0° (15), 2-(4-chlorobenzoyl)pyrrole: mp 118°, lit. 118.5-119.5° (15), 2-(4-nitrobenzoyl)pyrrole: mp 161°, lit. 160-162° (15).

Table I

Yields Obtained in Porphyrin Syntheses From Carbinols and From Aldehydes

Porphyrin (a)	Ref.	Yield (%) from Carbinol	Yield (%) from Aldehyde
TPP	(18)	41	35
T-3-PyP	(8)	18	17
<i>p</i> -Cl-TPP	(18)	19	18
TMP	(18)	0	0
Mixed Syntheses of <i>p</i> -Nitrophenylporphyrins			
TPP	(18)	5.8	6.0
mono-4-NO ₂ -TPP	(19)	6.0	6.0
<i>cis</i> and <i>trans</i> -di-4-NO ₂ -TPP	(19)	4.2	3.9
Mixed Syntheses of 3-Pyridylphenylporphyrins			
TPP	(18)	6.7	6.5
mono-3-Py-TPP	(8)	4.1	4.1

(a) For abbreviations used in this paper see footnote 10.

2-Acetylpyrrole.

One-half mole of pyrrole (33.5 g) and 0.57 mmoles (62 g) of acetic anhydride were stirred at 0° in a 250 ml round bottom flask. To the mixture of 7.0 g of redistilled boron trifluoride etherate was added in one portion. After one hour 100 ml of water was added. The resulting solution and tar was repeatedly extracted with chloroform. The 2-acetylpyrrole (4.3 g) was purified by repeated crystallization from toluene, mp 90°, lit. 90° (16).

2-(3-Pyridoyl)pyrrole.

N,N-diethylnicotinamide (Aldrich), 73.2 g (0.41 mole) was dissolved in 100 ml of phosphorus oxychloride and stirred for 24 hours under nitrogen. One liter of 1,2-dichloroethane was added and then 27 ml of pyrrole (0.40 mole), dissolved in 50 ml of 1,2-dichloroethane, was added dropwise over a 30 minute period. A thick, black oil formed on the sides of the flask. After 24 hours the liquid layer was cautiously poured into an excess of a saturated sodium carbonate solution. The solution and the tar remaining in the reaction vessel were recombined and the mixture refluxed for 1 hour. The organic layer was flashed to dryness and redissolved in a minimum amount of chloroform. The solution was chromatographed on silica gel (Baker) using chloroform as the eluant. The yield was 24 g (34%). During the chromatography, as the purity of the material increases, it becomes progressively more difficult to elute the ketone from the column with chloroform. It can be eluted with 15% diethyl ether in chloroform, mp 131-132°; nmr: δ 6.35 (m, 1H), 6.90 (m, 1H), 7.25 (m, 1H), 7.40 (dd, 1H), 8.18 (dt, 1H), 8.83 (dd, 1H), 9.17 (d, 1H).

Anal. Calcd. for C₁₀H₈N₂O: C, 69.76; H, 4.68; N, 16.26. Found: C, 69.81; H, 4.69; N, 16.29.

General Procedure for Porphyrin Syntheses from the Carbinols.

The ketone (9.25×10^{-2} moles) was reduced by the method of Silverstein, *et al.* (17) and then added, as a methanol solution (5 ml), to 45 ml of propionic acid. The reaction mixture was refluxed for 105 minutes and then flash evaporated. The residue was neutralized with a minimal amount of ammonium hydroxide and then flashed to dryness after 10 ml of absolute ethanol had been added. The reaction mixtures in the *p*-Cl-TPP and TPP syntheses were chromatographed firstly on silica gel (Baker) using chloroform as the eluant, secondly on alumina (Fisher) using benzene and then thrirdly on silica gel (ICN) using 1:1 chloroform-benzene as the eluant. The T-3-PyP and mono-3-PyTPP reaction mixtures were chromatographed as has been previously described (8). The 4-NO₂-TPP reaction mixture was chromatographed on silica gel and alumina column in chloroform. The porphyrins were separated by chromatography on silica plates using toluene as the eluant.

Acknowledgement.

This investigation was supported in part by the National Instituted of

Health (Grant GM 27663-02) and by the Research Corporation.

REFERENCES AND NOTES

- (1) P. Rothmund, *J. Am. Chem. Soc.*, **57**, 2010 (1935); P. Rothmund, *ibid.*, **61**, 2912 (1939); P. Rothmund and A. R. Menotti, *ibid.*, **63**, 267 (1941); P. Rothmund and A. R. Menotti, *ibid.*, **70**, 1808 (1948).
- (2) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, and L. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).
- (3) R. H. Ball, G. D. Dorough and M. Calvin, *J. Am. Chem. Soc.*, **68**, 2278 (1946).
- (4) G. M. Badger, R. A. Jones, and R. L. Laslett, *Aust. J. Chem.*, **17**, 1028 (1964).
- (5) A. D. Adler, F. R. Longo, and W. Shergalis, *J. Am. Chem. Soc.*, **86**, 3145 (1964).
- (6) A. D. Adler, L. Sklar, F. R. Longo, J. D. Finarelli, and M. G. Finarelli, *J. Heterocyclic Chem.*, **5**, 669 (1968).
- (7) J. B. Kim, A. D. Adler, and F. R. Longo, in "The Porphyrins", Vol. I, part A, D. Dolphin, Ed., Academic Press, 1978, pp. 85-100, and references therein.
- (8) R. G. Little, J. A. Anton, P. A. Loach and J. A. Ibers, *J. Heterocyclic Chem.*, **12**, 343 (1975).
- (9) R. G. Little, *J. Heterocyclic Chem.*, **18**, 129 (1981).
- (10) Abbreviations used in this paper: TPP, 5,10,15,20-tetraphenylporphyrin; T-3-PyP, 5,10,15,20-tetra(3-pyridyl)porphyrin; *p*-Cl-TPP, 5,10,15,20-tetra(*p*-chlorophenyl)porphyrin; TMP, 5,10,15,20-tetramethylporphyrin; mono-4-NO₂-TPP, 5-(*p*-nitrophenyl)-10,15,20-triphenylporphyrin; *cis*-di-4-NO₂-TPP, 5,10-(*p*-nitrophenyl)-15,20-diphenylporphyrin; mono-3-PyTPP, 5-(3-pyridyl)-10,15,20-triphenylporphyrin.
- (11) A. J. Castro, G. Tertzakian, B. T. Nakata and D. A. Brose, *Tetrahedron*, **23**, 4499 (1967).
- (12) M. Strell, A. Zocher and E. Kopp, *Chem. Ber.*, **90**, 1798 (1957).
- (13) L. R. Morgan, Jr. and R. Schunior, *J. Org. Chem.*, **27**, 3696 (1962).
- (14) The chromophore is not a dipyrromethene since a propionic acid solution of the carbinol obtained from 2-benzoyl-3,5-dimethyl-4-ethylpyrrole is also bright red and exhibits a single absorption maxima at 492 nm.
- (15) J. White and G. McGillivray, *J. Org. Chem.*, **42**, 4248 (1977).
- (16) A. de Jong, *Rec. Trav. Chim.*, **48**, 1029 (1929).
- (17) R. M. Silverstein, E. E. Ryskiewicz and S. W. Chaiken, *J. Am. Chem. Soc.*, **76**, 4485 (1954).
- (18) A. Treibs and N. Haberle, *Ann. Chem.*, **718**, 183 (1968).
- (19) E. Tsuchida, *J. Macromol. Chem.*, **A13**, 545 (1979).