Tetrahedron Letters No. 22, pp 2203 - 2206, 1972. Pergamon Press. Printed in Great Britain.

PYRROMETHANE (DIPYRRYLMETHANE) AND TRIPYRRANE SYNTHESIS

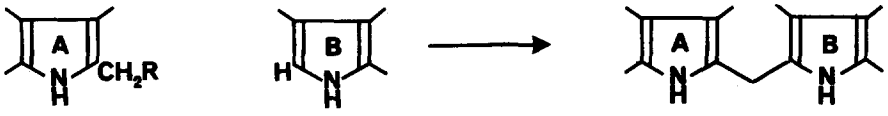
A.M.d'A. Rocha Gonsalves, G.W. Kenner,* and K.M. Smith

Robert Robinson Laboratories, University of Liverpool,

P.O. Box 147, Liverpool, L69 3BX

(Received in UK 29 March 1972; accepted for publication 24 April 1972)

Pyrromethanes (3) are invaluable intermediates in both synthetic[1] and biosynthetic[2] studies of porphyrins. The most popular preparative route[3] to unsymmetrically substituted pyrromethanes is the condensation of a 2-bromomethyl(or acetoxymethyl[4])pyrrole (1) with a 2-unsubstituted pyrrole (2):



(1) (2) (3)

(a) R = Br; (b) R = OAc

The reaction is usually carried out in acetic acid at 140° in the presence of sodium acetate, and furnishes yields of pyrromethanes (3) in the region of 50% after careful chromatography of the crude products. This procedure has been improved[5] in the case of acetoxymethylpyrroles (1b) by performing the condensation with the 2-unsubstituted pyrroles (2) in acetic acid at 90°, thereby achieving yields between 60 and 70%.

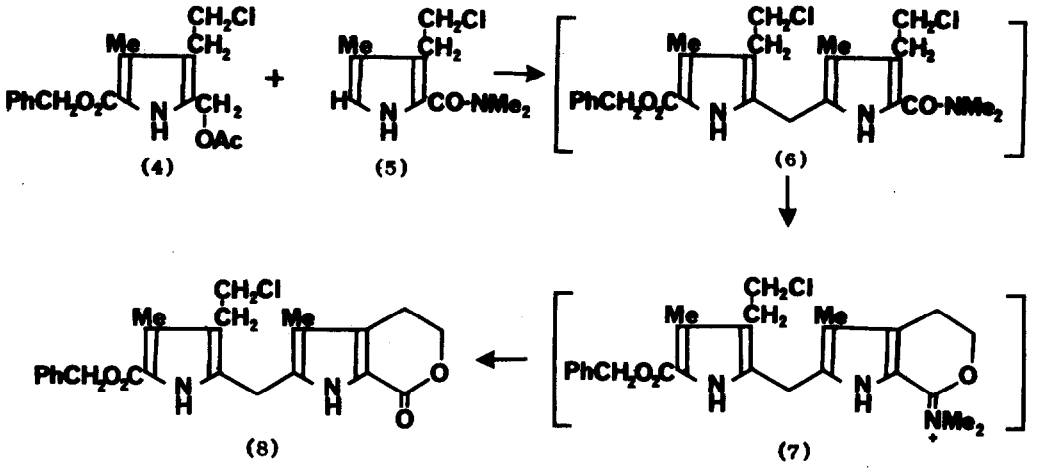
In connection with our studies[6] on the total synthesis of protoporphyrin-IX and its deuteriated derivatives, we required the pyrromethane (6) and attempted its preparation by heating the appropriate pyrroles (4)† and (5)† in acetic acid. The only product isolated from these reactions was the pyrromethane lactone (8)†, m.p. 178-181°. Convinced that this material (8) had arisen from the required pyrromethane (6) through intramolecular attack of the nucleophilic oxygen atom upon the side-chain to give initially (7), we sought milder conditions for the preparation of the pyrromethane (6). As a result, we have uncovered what we consider to be an important technical

---

* Address correspondence to this author.

† New compound which gave a satisfactory elemental analysis.

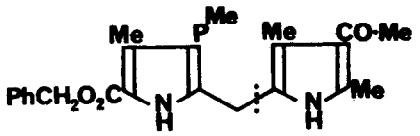
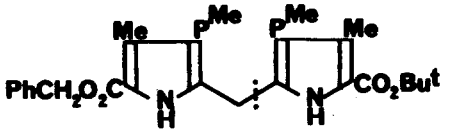
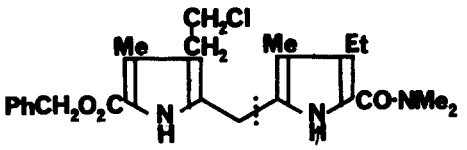
development in pyrromethane synthesis. Treatment of equimolar proportions of the 2-acetoxymethylpyrrole (4) and the 2-unsubstituted pyrrole (5) with a catalytic quantity (<0.1 equiv.) of toluene p-sulphonic acid hydrate in methanol at 35–40° (monitored by t.l.c.) gave 85% of the required pyrromethane (6)†, which was conveniently isolated



without chromatography, by dilution of the reaction mixture with water and collection of the crystalline product. This procedure has been found to be general (see Table for a representative selection of pyrromethanes). In a typical experiment, a suspension of benzyl 2-acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-5-carboxylate (373 mg.) and 3-acetyl-2,4-dimethylpyrrole (137 mg.) in methanol (5 ml.) was treated with toluene p-sulphonic acid hydrate (10 mg.) and heated under nitrogen at 35° during 4 hours. The solution was diluted with water (1 ml.) and the pyrromethane (9) isolated by filtration (410 mg.; 91%) and then recrystallised from methylene chloride / n-hexane (m.p. 136–137° (Lit.[5] 135–136°). N.m.r. spectrum in $CDCl_3$ τ 2.65 (5H,s) $C_6\underline{H}_5$; 4.75 (2H,s) $C_6H_5\underline{CH}_2$; 6.20 (2H,s) $\underline{CH}_2$; 6.38 (3H,s) $O\underline{CH}_3$; ca. 7.4 (4H,m) $\underline{CH}_2\underline{CH}_2$; 7.60 (6H,s) 2 β-$\underline{CH}_3$; 7.74 (6H,s) $CO\underline{CH}_3$ and α-$\underline{CH}_3$).

No pyrromethane was produced when the 2-acetoxymethyl- and 2-unsubstituted pyrroles were heated in methanol in the absence of the toluene p-sulphonic acid and neither was there any evidence of the production of symmetrical pyrromethanes in the presence of the acid catalyst. The methanol and toluene p-sulphonic acid conditions appear to be exceptionally mild, both from the thermal and chemical standpoint. This

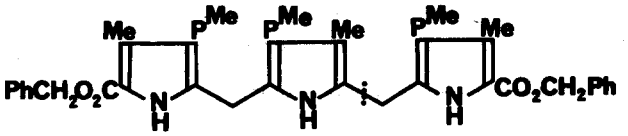
is shown by the facile isolation of (6) and by the fact that t-butyl ester protecting groups survive the procedure (see Table).

Pyrromethane	Yield	Lit. Yield	Ref.
 (9)	91%	70%	5
	85%	47.5%	6a
	90%	† m.p. 158-159°	-

⋮ indicates the point of carbon-carbon bond formation. P^{Me} = $CH_2CH_2CO_2Me$

TABLE

The mildness of the procedure outlined above encouraged us to attempt the synthesis of the tripyrrane (10). These compounds have been of interest in the construction of open-chain polypyrrolic substances for porphyrin synthesis and are of



(10)

great potential interest in current biosynthetic investigations;[2] they are particularly unstable in acidic media and have heretofore been accessible in only moderate yield[5,7]

from non-acidic condensations. When the appropriate 5-unsubstituted pyrromethane and 2-acetoxymethylpyrrole were treated with toluene p-sulphonic acid in methanol, the required tripyrrane (10),† m.p. 97-99° was isolated in 35% yield (1st. crop only; t.l.c. showed the presence of further quantities of the tripyrrane in the mother liquors). (N.m.r. spectrum in $CDCl_3$ τ -0.59, -0.28 (2 x 1H,s) NH_a and NH_c; 1.25 (1H,s) NH_b; 2.76, 2.90 (2 x 5H,m) 2 x C_6H_5; 5.38, 5.42 (2 x 2H,s) 2 x $C_6H_5CH_2$; 6.39, 6.48 (2 x 2H,s) 2 x CH_2; 6.41, 6.43 (3H,s and 6H,s) 3 x OCH_3; 7.1-7.7 (12H,m) 3 x CH_2CH_2; 7.75, 7.81, 7.98 (3 x 3H,s) 3 x β-CH_3.)

ACKNOWLEDGMENTS

We thank the Calouste Gulbenkian Foundation for financial support and the University of Lourenço Marques, Moçambique, for financially supported leave of absence (to A.M.d'A.R.G.).

REFERENCES

1. K.M. Smith, Quart. Rev., 1971, 25, 31.
2. J. Pluscec and L. Bogorad, Biochemistry, 1970, 9, 4736; B. Frydman, S. Reil, A. Valasinas, R.B. Frydman, and H. Rapoport, J. Amer. Chem. Soc., 1971, 93, 2738; A.R. Battersby, I.U.P.A.C. Symposium, Boston, July 1971 (to be published in Pure Appl. Chem.).
3. E.J. Tarlton, S.F. MacDonald, and E. Baltazzi, J. Amer. Chem. Soc., 1960, 82, 4389.
4. 2-Acetoxymethylpyrroles (1b) have been shown to be intermediates in the reaction using the corresponding 2-halomethylpyrroles (e.g. 1a): R. Fletcher, Research Fellowship Report, Liverpool, 1967.
5. P.S. Clezy and A.J. Liepa, Aust. J. Chem., 1970, 23, 2443.
6. (a) R.P. Carr, A.H. Jackson, G.W. Kenner, and G.S. Sach, J. Chem. Soc., C, 1971, 487; (b) A.M.d'A.Rocha Gonsalves, G.W. Kenner, and K.M. Smith, Chem. Comm., 1971, 1304.
7. A. Hayes, G.W. Kenner, and N.R. Williams, J. Chem. Soc., 1958, 3779; A.H. Jackson, G.W. Kenner, and D. Warburton, J. Chem. Soc., 1965, 1328.