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SYNTHESIS OF 6'-AMINOMETHYLTRIPYRRANES OF BIOSYNTHETIC INTEREST

Aldonia Valasinas, Estrella S. Levy and Benjamin Frydman*
Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires
Junin 956, Buenos Aires, Argentina.

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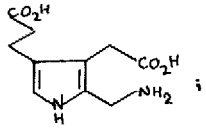
6'-Aminomethyltripyrranes (pyrrylmethyldipyrrylmethanes) are intermediates of great interest for the biosynthetic studies of porphyrins[1]. The tripyrranes derived from the formal self-condensation of porphobilinogen 1 (and isoporphobilinogen 2) have been repeatedly proposed as intermediates in the biosynthesis of both uroporphyrinogen III and uroporphyrinogen I[2].



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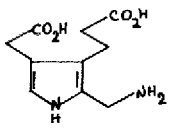

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We have recently[3,1] reported the interaction of some of them with the enzymatic system that polymerizes porphobilinogen to uroporphyrinogens. The obtained results indicated that the specific enzymatic incorporation of tripyrranes into uroporphyrinogens may give the final answer to the mechanism of uroporphyrinogen III biosynthesis[1]. Hence a versatile and simple synthetic method of the aforementioned tripyrranes will be outlined.

Tripyrranes are rather exotic compounds and only a handful of them have been prepared. Simple tripyrranes stabilized by electron-withdrawing substituents have been prepared by condensation of; 1) 2-bromomethylpyrroles with the lithium salt of dipyrrylmethane α-carboxylic acids[4]; 2) a 2-chloromethylpyrrole or a 2-acetoxymethylpyrrole with a 2-unsubstituted dipyrrylmethane[5]; and 3) a 2-acetoxymethylpyrrole with a 2-unsubstituted dipyrrylmethane in the presence of a catalytic amount of p-toluensulphonic acid[6]. Procedures 1) and 2) were found to be unreliable due to secondary rearrangement reactions[4,5], and were discarded[7] for the synthesis of tripyrrane 5. Instead, the prior synthesis of a tripyrrene (stabilized at the (a) bridge) was introduced, which was then transformed into a tripyrrane by reduction[7,8]. We found that procedure 3) also failed to give the desired tripyrranes 5, 7 and 9.

It was however, possible to build up complex linear pyrrylmethane derivatives (SCHEME I) provided certain precautions were taken.

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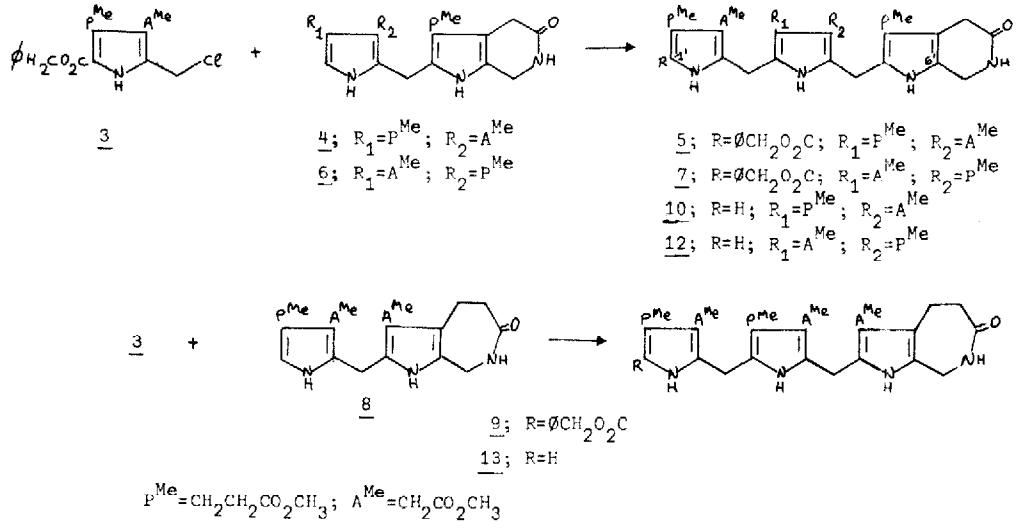
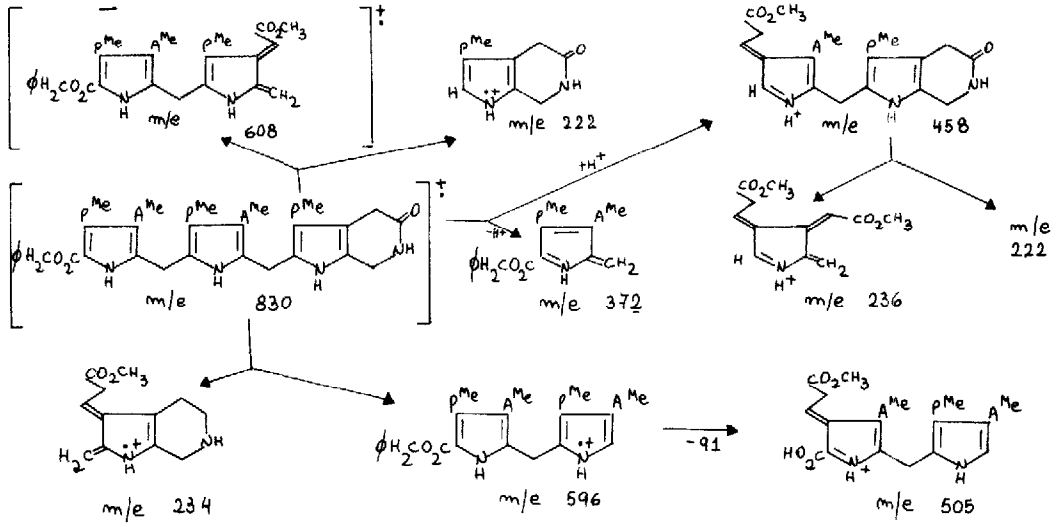
* Address correspondence to this author.



SCHEME I

In a typical experiment a solution of benzyl 2-chloromethyl-3-(∝-methoxycarbonylmethyl)-4-(β-methoxycarbonylethyl) pyrrole-5-carboxylate 3 (216 mg)[9] and dipyrrylmethane lactam 4[10] (216 mg) in 20 ml of dry pyridine was placed in a glass vessel, the solution was thoroughly deareated, the vessel was then closed under vacuum (0,1 Torr), and heated at 100° during 64 hours. After evaporation of the solvent, tlc analysis on silica-gel coated plates (using 4% methanol in chloroform), indicated that a single tripyrrane was formed and that unreacted dipyrrylmethane 4 was still present. They were separated by chromathography on a column (20cm x 2 cm) packed with tlc silica-gel, by using the above mentioned solvent and by applying a slight pressure.

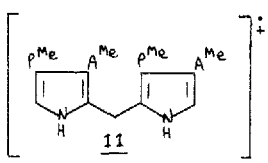


SCHEME II

Tripyrrane 5 (104 mg; 23%) was thus obtained; mp 217-220° (from methanol, capillar tube sealed under vacuum); ir (KBr): 3350 cm^{-1} (NH); 1680 cm^{-1}(amide CO); 1720 cm^{-1} (ring ester CO); 1742 cm^{-1} (side chain ester CO); uv max (ethanol), 285 nm (ε 20,000); (nmr; pyridine-d_5; δ=o, TMS); δ 2.7 (m, 12H, $-CH_2CH_2-$); 3.5 (m, 2H, CH_2CO); 3.6 (b, 15H, OCH_3); 4.05 (s, 4H, CH_2COO); 4.12 (s, 4H, $-CH_2-$); 5.0 (b, 2H, CH_2NH); 5.5 (s, 2H, $CH_2\emptyset$); 7.3 (b, 5H, C_6H_5); ms, (m/e;direct inlet, 210°) , main reference peaks: 830 (M^+, 3%), 695 ($M-C_6H_5CH_2-CO_2$; 13%); 608 (17%); 505 (64%); 372 (24%); 458 (28%); 236 (60%); 222 (100%).(SCHEME II).

By condensation of 3 and 6[10] the tripyrrane 7 was obtained; mp 203-205° (from methanol); ir (KBr): 3450 cm^{-1} (NH); 1745 cm^{-1} (side chain CO); 1730 cm^{-1} (ring ester CO); 1680 cm^{-1} (amide CO); nmr (pyridine-d_5): δ 2.7 (m, 12H, CH_2CH_2); 3.5 (m, 2H, CH_2CO); 3.6 (b, 15H, OCH_3); 4.0 (b, 2H, $-CH_2-$); 4.1 (b, 2H, $-CH_2-$); 4.4 (b, 4H, CH_2COO); 4.7 (m, 2H, CH_2NH); 5.25 (s, 2H, $CH_2\emptyset$); 7.3 (b, 5H, C_6H_5); ms (m/e), 830 (M^+, 3%), 695 (15%), 608 (15%), 505 (70%), 372 (30%), 458 (38%), 236 (20%), 222 (100%). By condensation of 3 and dipyrrylmethane lactam 8[9], the tripyrrane 9 was obtained; mp 226-228° (from methanol, 24%), ir (KBr): 3400 cm^{-1}; 1750 cm^{-1}; 1725 cm^{-1}; 1690 cm^{-1}; uv max (ethanol), 283 nm (ε 24,100); nmr (pyridine -d_5); δ 2.8, 2.7 (b, m, 12H, CH_2CH_2CO, CH_2CH_2), 3.5 (b, 15H, OCH_3); 4.05, 4.17 (b, 4H, $-CH_2-$); 4.25, 4.30 (b, 6H, CH_2COO); 4.7 (b, 2H, CH_2NH); 5.25 (s, 2H, $CH_2\emptyset$); 7.3 (b, 2H, C_6H_5); ms (m/e), 830 (M^+, 6%), 695 (12%), 608 (13%), 505 (50%), 372 (30%), 458 (35%), 236 (60%), 222 (100%).

The benzyloxycarbonyl group of the three tripyrranes was eliminated by hydrogenolysis followed by thermal decarboxylation. In a typical hydrogenolysis experiment, 104 mg of 5 dissolved in 10 ml of glacial acetic acid, was reduced with hydrogen over an equal weight of 10% Pd on charcoal at 50 psi during 2 hours. The residue obtained after filtering the catalyst and evaporating the solvent, was decarboxylated by heating "in vacuo" (0.05 Torr) at 220° during one minute. Only tripyrrane 10 was obtained as judged by tlc analysis. After a purification on a silica-gel column as described above, it was isolated in 33% yield; mp 223-225°, ir (KBr) 3350 cm^{-1} (NH); 1675 cm^{-1} (amide CO), 1725 cm^{-1} (side chain CO), 1750 cm^{-1}; nmr (pyridine-d_5): δ 2.7 (m, 12H, CH_2CH_2); 3.4 (b, 2H, CH_2CO); 3.55 (b, 15H, OCH_3); 3.7 (s, 4H, CH_2COO); 4.0 (b, 4H, $-CH_2-$); 4.8 (m, 2, CH_2NH); 7.0 (b, 1H, C_1,-H); ms (m/e): 696 (M^+, 3%), 474 (M^+-222; 25%), 462 (11, 70%); 222 (100%). The analogous dimethyl-tetraethyl ester has been described[7].



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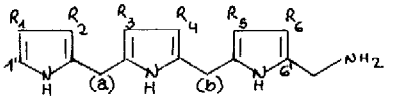
The tripyrrane lactam 12 was obtained from 7 by a similar procedure; (mp 140-142°, 34%); ir (KBr), 3450 cm^{-1}, 1740cm^{-1} 1680 cm^{-1}; nmr (pyridine-d_5): δ 2.7 (m, 12H, CH_2CH_2); 3.45 (b, 2H, CH_2CO); 3.6 (b, 15H, OCH_3); 3.7 (s, 4H, CH_2COO); 4.1 (b, 4H, $-CH_2-$), 4.8 (m, 2, CH_2NH); 7.0 (b, 0.9H, C_1,-H); ms (m/e): 696 (M^+, 5%); 474 (25%), 462 (80%), 222 (100%). Hydrogenolysis and decarboxylation of 9 afforded tripyrrane 13; mp 110-112° (methanol, 36%), ir (KBr), 3350 cm^{-1}, 1720 cm^{-1}, 1680 cm^{-1}, nmr (pyridine-d_5); δ 2.9 (b, m, 12H, CH_2CH_2CO, CH_2CH_2); 3.4 (b, 6H, CH_2COO); 3.6 (b, 15H, OCH_3); 4.0 (b, 4H, $-CH_2-$); 4.25 (m, 2H, CH_2NH); 6.5 (b, 0.8H, C_1,-H) ms (m/e), 696 (M^+, 4%), 474 (40%), 462 (70%), 222 (100%).

Decarboxylation attempts using trifluoroacetic acid resulted in extensive decomposition of either 10, 12, or 13.

The tripyrrane lactams were saponified by using the procedure introduced for the analogous dipyrrylmethane lactams[10, 9]. The lactams 10, 12, and 13 (25 mg) were slowly

dissolved under a stream of nitrogen in a 2N KOD solution (0.5 ml) and the disappearance of the lactam methylene signals was followed by nmr. After 72 hours the saponification of the lactam ring and the ester groups was completed; 14 had nmr (KOD, δ =0 for DSS); δ 2.8 (m, 8H, $-CH_2CH_2-$), 3.7 (b, 6H, $-CH_2COO$), 3.85 (b, 2H, $-CH_2NH_2$), 4.1 (b, 4H, $-CH_2-$), 6.8 (b, 0.8H, C_1,-H) 15 had nmr; δ 2.8 (m, 8H, $-CH_2CH_2-$), 3.6 (b, 6H, $-CH_2COO$), 3.85 (b, 2H,$-CH_2NH_2$), 4.05 (s, 2H, $-CH_2-$), 4.10 (s, 2H, $-CH_2-$), 6.8 (b, 1H, C_1,-H); 16 had nmr: 2.8 (m, 8H, $-CH_2CH_2-$); 3.6 (b, 6H, $-CH_2COO$), 4.0 (s, 4H, $-CH_2-$), 4.3 (s, 2H, CH_2NH_2), 6.9 (b, 0.8H, C_1,-H).



14; $R_1=R_3=R_5=CH_2CH_2CO_2H$; $R_2=R_4=R_6=CH_2CO_2H$
15; $R_1=R_4=R_5=CH_2CH_2CO_2H$; $R_2=R_4=R_6=CH_2CO_2H$
16; $R_1=R_3=R_6=CH_2CH_2CO_2H$; $R_2=R_4=R_5=CH_2CO_2H$

As can be seen the nmr spectra of the three aminomethyltripyrranes differed among them. The very slow exchange of the C_1,-H with deuterium is in contrast with the very fast exchange of the α-free hydrogen of the analogous 2-aminomethyldipyrrylmethanes[9, 10]; and explains the lower porphyrin yields obtained by dimerization of the 6'-aminomethyltripyrranes as compared with the 2-aminomethyldipyrrylmethanes[3]. The 6'-aminomethyltripyrranes were very unstable substances and were directly used in solution at pH 7-8 for enzymatic and chemical studies.

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