Tetrahedron Letters,Vol.26,No.12,pp 1561-1564,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

ADDITION OF DICHLOROCARBENE TO APORPHINOIDS: A NEW ROUTE TO HOMOAPORPHINES

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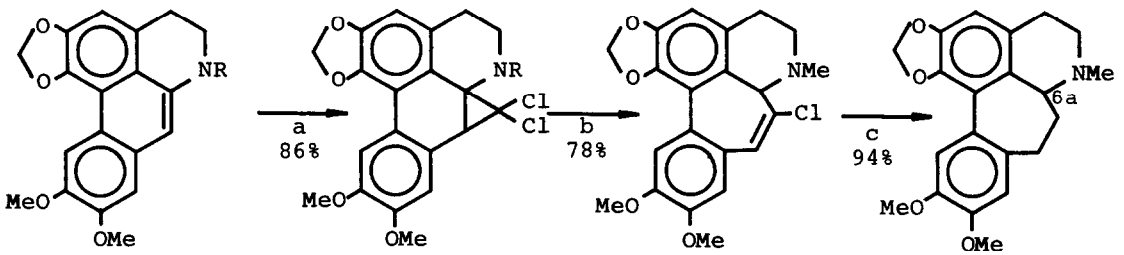
Abstract: An easy and efficient method for the synthesis of homoaporphines is described. It is based on the ring C homologation of aporphines *via* dichlorocarbene adducts.

In continuation of our studies on the reaction of dichlorocarbene with nitrogen compounds[1], we can now report an easy and efficient method for the synthesis of homoaporphines, a small group of bases in which interest has been renewed[2]. It is based on the ring C homologation of aporphines, the largest group of isoquinoline alkaloids. Using this method the new homoaporphines 4, 8 and 13[3] were obtained and are described below.

The reaction of dichlorocarbene with dehydroaporphines has been reported to yield 7-formyl derivatives[4]. However, we have found that when the N-carbethoxydehydroaporphine 1[5] was reacted with Cl_2C: under Phase Transfer conditions, the adduct 2 was obtained in 86% yield. Its reduction with LAH followed by catalytic hydrogenation gave homodicentrine 4[6] (63% overall yield from 1).

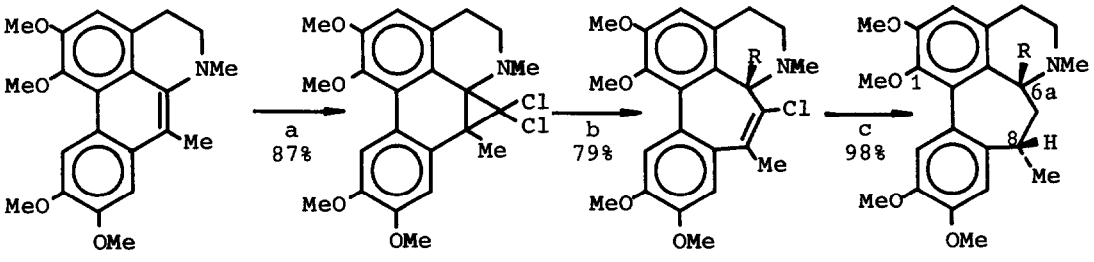


1: R = COOEt 2: R = COOEt 3 4

a) $HCCl_3$, 50% NaOH, TBAC; b) LAH/THF; c) H_2, 10% Pd-C, NaOAc, EtOH

7-Methyldehydroaporphines were found to react with Cl_2C: to give the corresponding adducts. Thus, treatement of 7-methyldehydroglaucine 5 with Cl_2C: readily afforded the unstable adduct 6, which was inmediately subjected to LAH (or LAD) reduction followed by catalytic hydrogenation to give a single diastereomer of 8-methylhomoglaucine 8 (PMR and CMR). The stereochemistry

of 8 was deduced by measurement of the nuclear Overhauser effects (noe) and selective ^{1}H-^{1}H decoupling experiments on 8a and 8b. The multiplicity and coupling constants observed for H-6a, H-7α, H-7β and H-8 were consistent with a *cis* relationship between H-6a and H-8[7]. This assignment is also supported by the observation of a noe between the methyl group at C-8 and the methoxy group at C-1 (Fig. I).



5 6 7a: R = H 8a: R = H

7b: R = D 8b: R = D

a) $HCCl_3$, 50% NaOH, TBAC; b) LAH/THF or LAD/THF; c) H_2, 10% Pd-C, NaOAc, EtOH

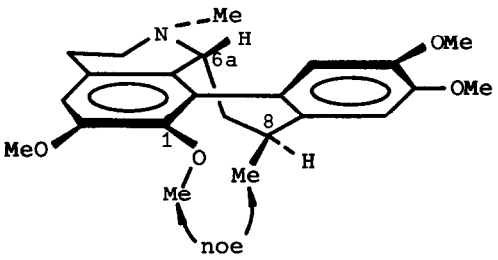
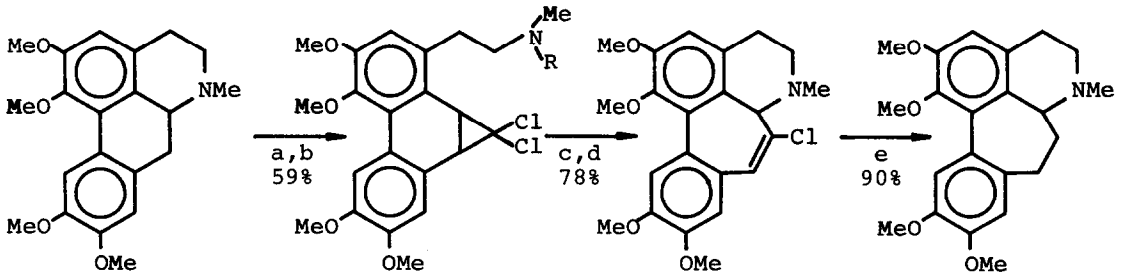


Fig. I

The main drawback of the above synthesis of a simple homoaporphine 4 is the preparation of the initial N-carbethoxy derivative 1, which is a common intermediate in the total synthesis of aporphines and can also be obtained from aporphines[8]. This problem may be resolved in an elegant way by the simple preparation of phenanthrene derivatives with their nitrogen protected with a suitable group, which should be stable towards dichlorocarbene and easily removed without the required dichlorocyclopropane being affected. This was achieved by treatement of glaucine 9 with trifluoracetic anhydride followed by Cl_2C: addition yielding the phenanthrene adduct 10, which was easily N-deprotected (Na_2CO_3, MeOH, rt) to 11. Cyclization-homologation of 11 (toluene, reflux) followed by catalytic hydrogenation (H_2, 10% Pd-C, NaOAc, EtOH) afforded the desired homoglaucine[9] 13 (43% overall yield from 9). This method is thus a very simple path for the synthesis of homoaporphines.



9 10: R = $COCF_3$ 11: R = H 12 13

a) $(CF_3CO)_2O$, Py; b) $HCCl_3$, 50% NaOH, TBAC; c) Na_2CO_3, MeOH, rt.; d) Toluene, reflux; e) H_2, 10% Pd-C, NaOAc, EtOH

ACKNOWLEDGEMENTS: We thank the Comisiõn Asesora (Spain) for its financial support.

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6. 4.- PMR (250MHz, $DCCl_3$),δ: 7.05 (s,1H,Ar), 6.79 (s,1H,Ar), 6.59 (s,1H,Ar), 6.01 (d,1H,J=1.4Hz,O-CH_2-O), 5.85 (d,1H,J=1.4Hz,O-CH_2-O), 3.92, 3.89 (s,6H,2xOMe), 3.36 (dd,1H,J=11.3 and 6.9Hz,H-6a), 3.25-2.93 (m,2H,-CH_2-), 2.77 (dd,1H,J=11.9 and 5.3Hz,-CH_2-), 2.61-2.10 (m,5H,-CH_2-), and 2.37 (s,3H,N-Me) ppm.

CMR (62.83MHz, $DCCl_3$),δ: 148.53, 147.14, 145.97, 142.16, 132.52, 128.17, 126.83, 124.60, 120.74, 112.91, 111.76, 107.37, 100.47, 58.34, 56.16, 55.91, 44.86, 41.71, 35.53, 30.32, and 25.81 ppm.

MS, m/e (%): 353 (M^+,45), 352 (26), 338 (13), 323 (61), 322 (100), 310 (24), 308 (27), 306 (11), 294 (8), 280 (10), 216 (27), and 190 (37).

Its methiodide has mp = 257-9°C (acetone).

7. 8a.-PMR (250MHz, $DCCl_3$),δ: 7.11 (s,1H,Ar), 6.71 (s,1H,Ar), 6.65 (s,1H,Ar), 3.94, 3.89, 3.86 (s,9H,3xOMe), 3.44 (s,3H,1-OMe), 3.35 (dd,1H,J=11.78 and 5.85Hz,H-6a), 3.17 (dt,1H,J=11.64 and 4.15Hz,H-5), 3.08-2.90 (m,2H, H-5 and H-8), 2.83-2.73 (m,1H,H-4), 2.69-2.56 (m,2H,H-4 and H-7β), 2.40 (s,3H,N-Me), 1.87 (t,1H,J=12.56Hz,H-7α), and 0.83 (d,3H,J=7.5Hz, 8-Me) ppm.

CMR (62.83MHz, $DCCl_3$),δ: 151.36 (s), 147.75 (s), 146.60 (s), 143.65 (s), 136.57 (s), 132.77 (s), 128.66 (s), 128.19 (s), 125.78 (s), 115.14 (d), 111.90 (d), 111.00 (d), 59.46 (q), 58.01 (d), 55.74 (q), 55.55 (q), 55.50 (q), 45.19 (t), 41.77 (t), 41.74 (q), 36.73 (d), 25.73 (t), and 22.24 (q) ppm.

MS, m/e (%): 383 (M^+,22), 382 (12), 368 (24), 352 (100), 340 (12), 336 (8), and 246 (22).

Its methiodide has mp = 196-8°C (ethyl acetate).

8b.-PMR (250MHz, $DCCl_3$),δ: 7.11 (s,1H,Ar), 6.71 (s,1H,Ar), 6.65 (s,1H,Ar), 3.94, 3.89, 3.86 (s,9H,3xOMe), 3.44 (s,3H,1-OMe), 3.16 (dt,1H,J=11.5 and 4.5Hz,H-5), 3.05-2.93 (m,2H,H-5 and H-8), 2.82-2.72 (m,1H,H-4), 2.65 (m,1H,H-4), 2.58 (dd,1H,J=12.95 and 9.0Hz,H-7β), 2.38 (s,3H,N-Me), 1.87 (d,1H,J=12.95Hz,H-7α), and 0.82 (d,3H,J=7.5Hz,8-Me) ppm.

MS, m/e (%): 384 (M^+,31), 369 (25), 353 (100), 341 (11), 337 (7), and 246 (22).

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9. 13.-PMR (250MHz, $DCCl_3$),δ: 7.10 (s,1H,Ar), 6.77 (s,1H,Ar), 6.68 (s,1H,Ar), 3.94, 3.90, 3.87, 3.42 (s,12H,4xOMe), 3.32-2.96 (m,3H,H-6a and $-CH_2-$), 2.84-2.74 (m,1H,$-CH_2-$), 2.68-2.02 (m,5H,$-CH_2-$), and 2.39 (s,3H,N-Me) ppm.

CMR (62.83MHz, $DCCl_3$),δ: 151.57, 148.28, 146.94, 144.13, 132.46, 131.87, 128.56, 127.00, 126.86, 113.90, 111.20, 110.81, 60.17, 58.32, 55.92, 55.76, 55.71, 45.00, 41.61, 34.90, 29.97, and 25.45 ppm.

MS, m/e (%): 369 (M^+,28), 368 (13), 354 (18), 338 (100), 326 (5), 322 (10), and 232 (9).

Its methiodide has mp = 234-6°C (acetone).

(Received in UK 25 January 1985)