# SYNTHESIS OF 8H-DIBENZO[a,g]QUINOLIZIN-8-ONES FROM HOMOPHTHALIC ANHYDRIDES AND 1-CHLOROISOQUINOLINES OR ISOQUINOLINE N-OXIDES. A NEW SYNTHESIS OF CASEADINE

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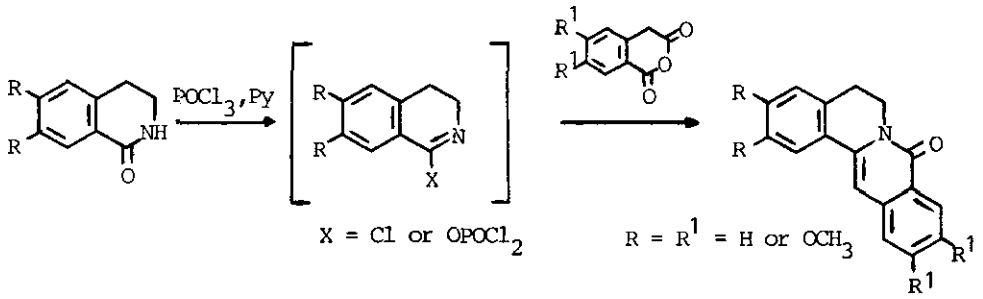
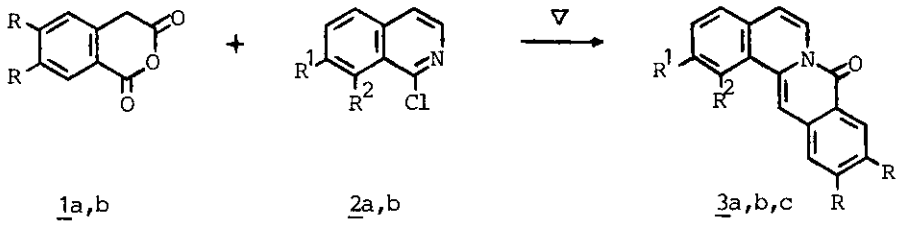
Abstract - The homophthalic anhydrides 1a,b react with the 1-chloroisoquinolines 2a,b to give the 8H-dibenzo[a,g]quinolizin-8-ones 3a,b,c in high yields. The same products 3a,c are obtained from the isoquinoline N-oxides 6a,b and 1a,b in the presence of acetic anhydride. 3c is converted into the tetrahydroprotoberberine alkaloid (±)-caseadine in two steps.

Recently we[1] have shown that the reaction of homophthalic anhydrides with imidates or imidoyl chlorides used as individual compounds or unstable intermediates is a new method for the synthesis of 5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-ones and related isoquinolinones. For example, treatment of 3,4-dihydro-1(2H)-isoquinolinones (3,4-dihydroisocarbostyrils) with phosphoryl chloride in pyridine led to the formation of unstable cyclic intermediates with a possible structure shown below. These intermediates, without isolation, were treated with homophthalic anhydrides to give 5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-ones in high yields.



It is known that 1-chloroisoquinolines corresponding in structure to the imidoyl chlorides shown above are stable compounds and can be easily obtained either from isoquinoline N-oxides[2a] or from isocarbostyrils[3] by treatment with phosphoryl chloride. Suitably substituted isocarbostyrils can be efficiently prepared using different synthetic procedures[3,4]. Moreover it is known that the reaction of α-chloro-substituted nitrogen heteroaromatics with active methylene compounds leads to the introduction of carbon substituents into the heterocyclic nuclei[5,6]. On the other hand, it is shown that homophthalic anhydride is also capable of reacting as an active methylene compound[7].

We investigated the reaction of the homophthalic anhydrides 1a,b with 1-chloroisoquinolines 2a,b under reflux in an inert solvent. From 1a,b and 2a were obtained the 8H-dibenzo[a,g]quinolizin-8-ones 3a[8,9] and 3b in 83 and 80% yields, respectively.



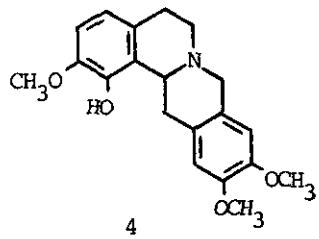
1a,b 2a,b 3a,b,c

a : R = H a : $R^1 = R^2 = H$ a : $R = R^1 = R^2 = H$

b : $R = OCH_3$ b : $R^1 = OCH_3$, $R^2 = OCH_2C_6H_5$ b : $R = OCH_3$, $R^1 = R^2 = H$

c : $R = R^1 = OCH_3$, $R^2 = OCH_2C_6H_5$

Using this approach for the synthesis of 8H-dibenzo[a,g]quinolizin-8-ones we decided to transform a suitably substituted compound of the type 3, namely 3c, into a tetrahydroprotoberberine alkaloid (±)-caseadine (4). The levorotatory isomer of 4 has been isolated from Corydalis caseana A. Gray and several authors performed the synthesis of racemic 4 using Mannich condensation of suitably substituted benzylisoquinolines[10].



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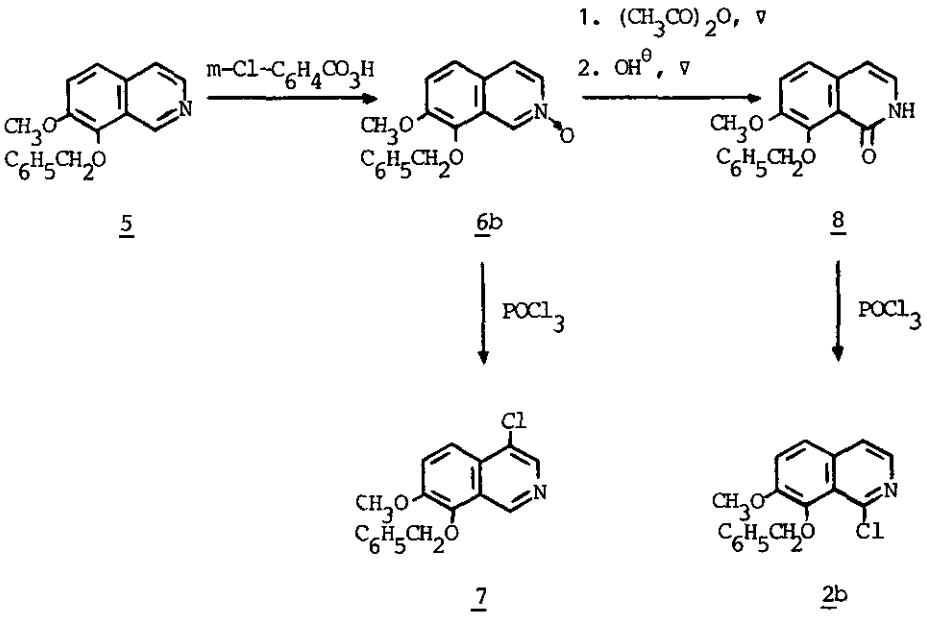
For the synthesis of (±)-caseadine (4) it was necessary to prepare the 1-chloroisoquinoline 2b having a protected phenolic function as a starting compound. For this reason the easily accessible, according to the method of Jackson and Steward, isoquinoline 5[11] was treated with m-chloroperbenzoic acid to give the N-oxide 6b in 91% yield. On treatment of 6b with phosphoryl chloride, the 4-chloroisoquinoline 7 was obtained in 51% yield. In order to prepare the desired 2b from 6b, the isocarbostyril 8 was prepared from 6b in 24% yield according to the known procedure[2b]. Treatment of 8 with phosphoryl chloride led to formation of the 1-chloroisoquinoline 2b in 81% yield.

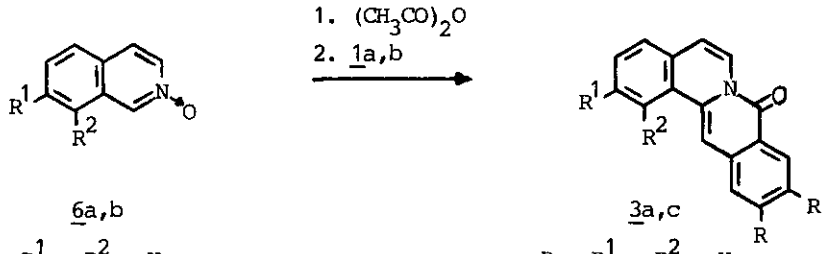



5 6b 8 7 2b

From the reaction of 2b with the homophthalic anhydride 1b under the conditions already described for the synthesis of 3a,b, the 8H-dibenzo[a,g]quinolizin-8-one 3c was obtained in 59% yield.

As it is known, Hamana and coworkers have found that quinoline N-oxide readily reacts with active methylene compounds in the presence of acetic anhydride to give 2-substituted quinolines, the reaction being accompanied by deoxygenation of the N-oxide function[12a]. The same authors have studied the reaction of different aromatic N-oxides with active methylene compounds in the presence of acylating agents and have shown that it is a useful method for α-alkylation of the heteroaromatic ring[12b,c].

On these grounds it seemed reasonable to examine the reaction of isoquinoline N-oxides with homophthalic anhydrides as active methylene compounds in the presence of acetic anhydride. Thus, by treatment of the isoquinoline N-oxide (6a) with the homophthalic anhydride 1a in the presence of acetic anhydride, the product identical with the already described 3a was obtained in 55% yield. Under the same conditions from the N-oxide 6b and 1b a product identical with the already described 3c was obtained in 53% yield.




6a,b

a : $R^1 = R^2 = H$

b : $R^1 = OCH_3$, $R^2 = OCH_2C_6H_5$

3a,c

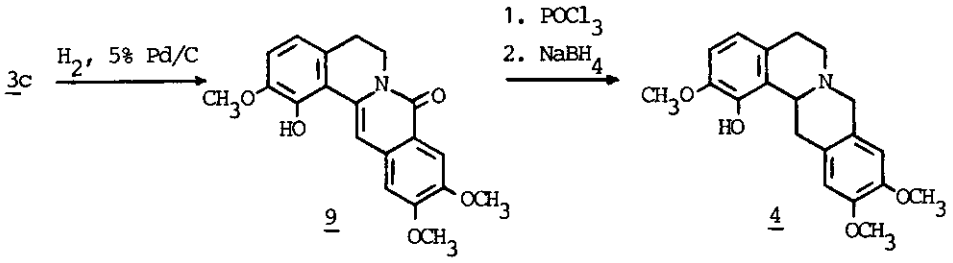
a : $R = R^1 = R^2 = H$

c : $R = R^1 = OCH_3$, $R^2 = OCH_2C_6H_5$

The relatively lower yields of 3a,c may be due to some side reactions as it is known that homophthalic anhydrides undergo acylation, dimerisation or autocondensation under the influence of acylating agents and/or bases[6,13].

In comparison with the known methods for the preparation of 8H-dibenzo[a,g]quinolizin-8-ones as the cyclization using Reissert compounds[8] and the Pomeranz-Fritsch cyclization of 3-arylisocarbostyrils[14], the presently described procedures starting from homophthalic anhydrides and 1-chloroisoquinolines or isoquinoline N-oxides are convergent syntheses.

The 8H-dibenzo[a,g]quinolizin-8-one 3c was converted into (±)-caseadine in two steps. By catalytical hydrogenation of 3c in the presence of 5% Pd/C, the 5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-one 9 was obtained in 90% yield. The latter was transformed analogously to a known approach[15] into the product identical with an authentic sample (±)-caseadine (4)[10] in 76% yield.




Experimental

All melting points are not corrected. The IR spectra were recorded on a SPECORD 71-IR instrument using 1% chloroform solutions. The $^1$H-NMR spectra were taken on a TESLA BS-467 (60MHz) or BS-487-C (80MHz) or BRUKER SPECTROSPIN (250MHz) spectrometers using TMS as internal standard.

Synthesis of the starting compounds:

7-Methoxy-8-benzyloxyisoquinoline N-oxide (6b). To 2.650 g (10 mmol) of 7-methoxy-8-benzyloxyisoquinoline (5)[11] in 100 ml of chloroform was added 4.936 g (20 mmol) of 70% m-chloroperbenzoic acid with stirring at room temperature. Stirring was continued for 4 h and the resulting clear solution after standing overnight was chromatographed through a basic alumina ("Reanal") column with chloroform. After evaporation of the solvent under reduced pressure, the resulting oil was recrystallized from dry benzene/dry ether to give 2.575 g (91%) of 6b, mp 100-102°C. Found: C, 72.45; H, 5.31. Calc. for $C_{17}H_{15}NO_3$ (281.30): C, 72.58; H, 5.37%. IR $cm^{-1}$: 1555, 1610, 1635. $^1$H-NMR ($CDCl_3$, 80MHz) $\delta$: 3.95 (s, 3H, $OCH_3$); 5.14 (s, 2H, $OCH_2$); 7.2-7.6 (m, 8H, arom-H); 7.89 (d, J = 6Hz, 1H, 3-H); 8.89 (s, 1H, 1-H).

4-Chloro-7-methoxy-8-benzyloxyisoquinoline (7). To a cooled solution of 0.562 g (2 mmol) of 6b in 15 ml of dry chloroform was added 1.50 ml of phosphoryl chloride and the resultant mixture was refluxed for 5 h. After cooling, the reaction mixture was evaporated under reduced pressure and crushed ice was added to the residue. The mixture was neutralized with aqueous sodium carbonate and extracted with chloroform. The combined chloroform extracts were dried over sodium sulphate, the solvent was removed and the crude product was chromatographed on silica gel 60 Merck with n-hexane:ether 7:3 to give 0.307 g (51.2%) of 7, mp 77-79°C (ether/n-hexane). Found: C, 68.23; H, 4.76. Calc. for $C_{17}H_{14}ClNO_2$ (299.75): C, 68.11; H, 4.70%. IR $cm^{-1}$: 1560, 1580. $^1$H-NMR (80MHz) $\delta$: 3.96 (s, 3H, $OCH_3$); 5.23 (s, 2H, $OCH_2$); 7.1-7.6 (m, 8H, arom-H); 9.25 (s, 1H, 1-H).

7-Methoxy-8-benzyloxy-1(2H)-isoquinolinone (8). A mixture of 0.562 g (2 mmol) of 6b and 5 ml of acetic anhydride was refluxed for 5 h. After removing the reagent under reduced pressure, 10 ml of 10% aqueous sodium hydroxide was added, the mixture was heated on a steam bath for 1 h, cooled and extracted with chloroform. The combined extracts were washed with water , dried over sodium sulphate, the solvent removed and the crude product was chromatographed on silica gel 60 Merck with ether to give 0.137 g (24.3%) of 8, mp 173-175°C (benzene/n-hexane). Found: C, 72.85; H, 5.43. Calc. for $C_{17}H_{15}NO_3$ (281.30): C, 72.58; H, 5.37%. IR $cm^{-1}$: 1655 (C=O), 3400 (NH). $^1$H-NMR ($CDCl_3$, 60MHz) $\delta$: 3.73 (s, 3H, $OCH_3$); 5.00 (s, 2H, $OCH_2$); 6.21(d, J=7Hz,1H,4-H); 6.79 (d, J=7Hz, 1H, 3-H); 7.0-7.8 (m, 7H, arom-H); 11.91 (broad s, 1H, NH).

1-Chloro-7-methoxy-8-benzyloxyisoquinoline (2b). A mixture of 0.281 g (1 mmol) of 8 and 5 ml of phosphoryl chloride was refluxed for 0.5 h. After cooling the reagent was removed under reduced pressure and crushed ice was added to the residue. The mixture was neutralized with aqueous sodium carbonate, extracted with chloroform and the combined extracts were dried over sodium sulfate. The residue from the extract was chromatographed on silica gel 60 Merck with ether: n-hexane 1:2 to give 0.243 g (81%) of 2b, mp 61-63°C (n-hexane/ether). Found: C, 68.21; H 4.80. Calc. for $C_{17}H_{14}ClNO_2$ (299.75): C, 68.11; H, 4.70%. IR $cm^{-1}$: 1520, 1540, 1590. $^1$H-NMR ($CDCl_3$, 60MHz) $\delta$: 3.84 (s, 3H, $OCH_3$); 5.01 (s, 2H, $OCH_2$); 7.1-7.7 (m, 8H, arom-H); 7.98 (d, J=6Hz, 1H, 3-H).

Synthesis of the 8H-dibenzo[a,g]quinolizin-8-ones 3a,b,c from the homophthalic anhydrides 1a,b and the 1-chloroisoquinolines 2a,b (Method A) or the isoquinoline N-oxides 6a,b (Method B):

General procedure for method A: The homophthalic anhydride 1a,b (2 mmol) was added in small portions for 10 min to a solution of 1-chloroisoquinoline 2a,b (2.2 mmol) in dry chlorobenzene (1 ml) at 130°C. The reaction mixture was then heated under reflux for 1 h and then cooled. The solvent was removed under reduced pressure and the residue recrystallized from a suitable solvent.

General procedure for method B: To a solution of isoquinoline N-oxide 6a,b (2.2 mmol) in dry chloroform (2 ml), acetic anhydride (2.2 mmol) was added at room temperature. The solution was stirred for 15 min, homophthalic anhydride 1a,b (2 mmol) was added. Stirring was continued at room temperature for 1 h and the mixture was alloved to stand overnight. After removing the solvents under reduced pressure, the residue was recrystallized from a suitable solvent.

The results of the general procedures for methods A and B are summarized in TABLE 1.

TABLE 1

| Product | Yield[%] by method A | Yield[%] by method B | mp [°C][a/] (solvent) | IR ($CHCl_3$) $\nu_{C=O}$[$cm^{-1}$] | $^1$H-NMR ($CDCl_3$, 80MHz) $\delta$: |
|---|---|---|---|---|---|
| 3a [b/] | 83.4 | 55.1 | 146-148 [c/] ($CH_3OH$) | 1655 | 6.49 (d, J=8Hz, 1H, 5-H); 7.0-7.6 (m, 9H, arom-H + 13-H); 7.9 (broad s, 1H, 9-H); 8.43 (d, J=8Hz, 1H, 6-H). |
| 3b [d/] | 80.3 | - | 197-199 ($CH_3OH$-$CHCl_3$) | 1650 | 3.98 (s, 6H, $2OCH_3$); 6.60 (d, J=8Hz, 1H, 5-H); 6.81 + 7.18 + 7.70 (3s, 3H, arom-H + 13-H); 7.3-7.6 (m, 3H, arom-H); 7.9 (broad s, 1H, 9-H); 8.76 (d, J=8Hz, 1H, 6-H). |

| | | | | | |
|---|---|---|---|---|---|
| 3c [e] | 58.8 | 53.2 | 184-185 ($CH_3OH$-$CHCl_3$) | 1645 | 3.87 + 3.95 + 4.01 (3s, each 3H, $3OCH_3$); 5.02 (s, 2H, $OCH_2$); 6.41 + 7.10 + 7.83 + 8.52 (4s, 5H, arom-H + 13-H); 6.56 (d, J=8Hz, 1H, 5-H); 7.2-7.7(m, 5H, $C_6H_5$); 8.50 (d, J=8Hz, 1H, 6-H). |

a/ Mixture mp of products obtained according to the methods A and B not depressed.
b/ Found: C, 83.44; H, 4.73. Calc. for $C_{17}H_{11}NO$ (245.27): C, 83.24; H, 4.52%.
c/ Lit.[8] mp 143-145°C ($CH_3OH$).
d/ Found: C, 74.61; H, 5.14. Calc. for $C_{19}H_{15}NO_3$ (305.32): C, 74.74; H, 4.95%.
e/ Found: C, 73.37; H, 5.25. Calc. for $C_{27}H_{23}NO_5$ (441.46): C, 73.45; H, 5.25%.

Transformation of 3c into (±)-caseadine (4):

1-Hydroxy-2,10,11-trimethoxy-5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-one (9). A solution of 0.884 g (2 mmol) of 3c in 50 ml of chloroform was catalytically hydrogenated in the presence of 5% Pd/C at ordinary pressure and temperature to give 0.614 g (90%) of 9, mp 261-263°C (chloroform/methanol). Found: C, 68.11; H, 5.15. Calc. for $C_{20}H_{19}NO_5$ (353.36): C, 67.98; H, 5.42%. IR $cm^{-1}$: 1645 (C=O), 3500 (OH). $^1$H-NMR ($CDCl_3$, 60MHz) $\delta$: 2.78 (t, J=6Hz, 2H, 5-H); 3.83 (s, 3H, $OCH_3$); 3.92(s, 6H, $2OCH_3$); 4.27 (t, J=6Hz, 2H, 6-H); 6.63 (s, 1H, OH); 6.69 + 6.70 + 6.87 + 7.63 + 7.75 (5s, 5H, arom-H + 13-H).

(±)-Caseadine (4). A mixture of 0.353 g (1 mmol) of 9 in 12 ml of dry chloroform with 12 ml of phosphoryl chloride was refluxed for 0.5 h, cooled and the reaction mixture evaporated under reduced pressure to give a product, which was dissolved in 30 ml of dry methanol. To the cooled methanolic solution 0.456 g (12 mmol) of sodium borohydride was added in portions with stirring. The reaction mixture was stirred then at room temperature for 0.5 h, the solvent was distilled off, 10 ml of water was added and the crude product was extracted with chloroform. The combined chloroform extracts were dried over sodium sulphate and the solvent removed under reduced pressure. The residue was chromatographed on silica gel 60 Merck to give 0.258 g (75.6%) of 4, mp 90-92°C (ether/hexane). Mixed mp with an authentic sample of (±)-caseadine[10] was not depressed. Found: C, 70.42; H, 7.02. Calc. for $C_{20}H_{23}NO_4$ (341.39): C, 70.36; H, 6.79%. IR $cm^{-1}$: 2755, 2785, 2815 (Bohl-

mann bands), 3545 (OH). $^1$H-NMR ($C_6D_6$, 250MHz) δ : 3.20 + 3.38 + 3.49 (3s, each 3H, 3O$CH_3$), 4.25 (dd, J=11.9 and 3.3Hz, 1H, 13a-H); 6.44 (d, J=8.3Hz, 1H, 3-H); 6.43 + 6.54 (2s, each 1H, 9-H and 12-H); 6.62 (d, J=8.3Hz, 1H, 4-H).

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