One-Pot Synthesis of 5,6-Dihydro-8*H*-dibenzo[*a*,*g*]quinolizine-8-ones and Related Isoquinolines; A New Synthesis of Xylopinine

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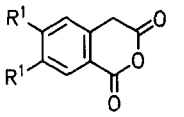
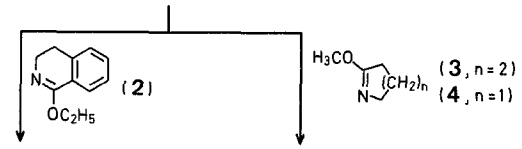
The reaction of homophthalic anhydrides with Schiff bases or cyclic imines was recently shown to afford the corresponding 3,4-dihydro-1(2*H*)-isoquinolinones, berbin-8-ones[1,2,3], and hexadehydro-yohimbane-21-ones[4] in a single stage. This approach was also applied in the preparation of protoberberine[5,6] and benzophenanthridine[7] alkaloids. We now report the results from the reaction of homophthalic anhydrides with some derivatives of lactams. It is well known that lactim ethers[8,9] and lactam complexes with acylating agents, most often with phosphoryl chloride[10-13], play an important role in the synthesis of heterocycles.

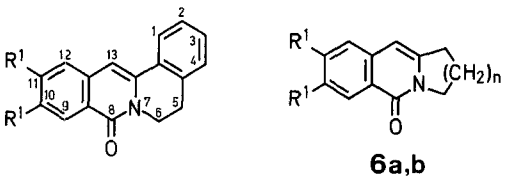
Refluxing the homophthalic anhydrides **1a, b** (1,3-dioxo-3,4-dihydro-1*H*-2-benzopyrans) with the lactim ethers **2**[14], **3**[15], or **4**[16] in an inert solvent leads to formation of the 5,6-dihydro-8*H*-dibenzo[*a*,*g*]quinolizine-8-ones i.e. 13,13a-didehydroberbine-8-ones **(5a, b)**, the 1,2,3,4-tetrahydro-6*H*-benzo[*b*]quinolizine-6-ones **(6a, b)**, or the 1,2-dihydro-3*H*,5*H*-pyrrolo[1,2-*b*]isoquinoline-5-ones **(7a, b)** in yields of 40 to 57%.



1a R^1 = H
b R^1 = OCH_3

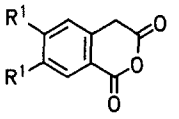


(2) **(3, n = 2)** **(4, n = 1)**

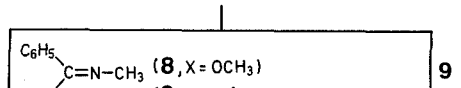


5a,b **6a,b** **7a,b**

The known[17] 2-methyl-3-phenyl-1(2*H*)-isoquinolinone **(10a)** was obtained from the reaction of **1a** with **8**[18] or **9**[19]. The change from the imidate **8** to the imidoyl chloride **9** markedly improves the yields. The hitherto undescribed **10b** was prepared analogously from **1b** and **9**.



1a,b



(8, X = OCH_3) **(9, X = Cl)** **9**

10a **10b**

Imidoyl chlorides corresponding in structure to the lactim ethers **2-4** are formed as intermediates in the reaction between lactams and some acylating agents[8] and are known to be unstable. For this reason **1** was made to react with the following lactams activated with phosphoryl chloride in

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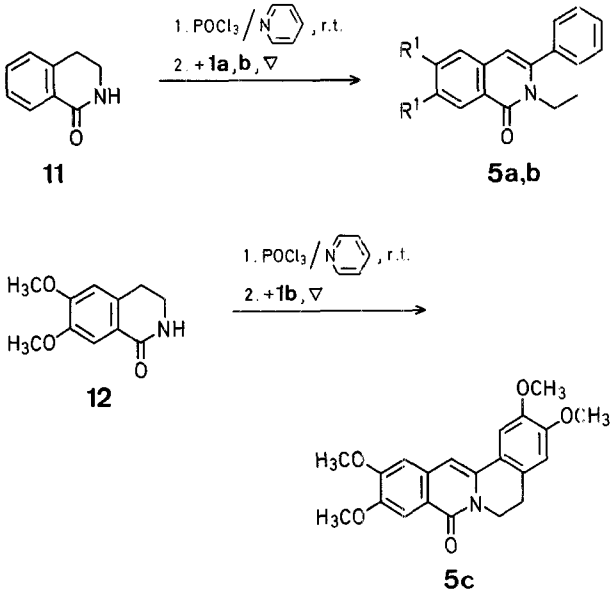
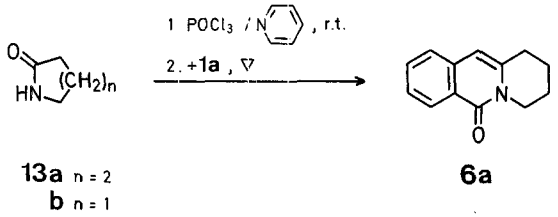
pyridine[13]: 3,4-dihydro-1(2*H*)-isoquinolinone (**11**)[20], 6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinone (corydaldine; **12**)[21], piperidine-2-one (**13a**), and pyrrolidine-2-one (**13b**).





Treatment of **11** in pyridine with phosphoryl chloride at room temperature followed by heating in the presence of **1a, b** afforded **5a, b** in 85% yields. Under the same conditions **5c** was obtained in 87% yield from **12** and **1b**, while from piperidine-2-one (**13a**) or pyrrolidine-2-one (**13b**) and **1a** was isolated **6a** in 30% yield in the first case; the corresponding **7a** was not detected in the second case. Since it is known that pyrrolidine-2-one undergoes self-condensation in the presence of phosphoryl chloride[10] it can be assumed that under the discussed reaction conditions this undesired reaction takes place.

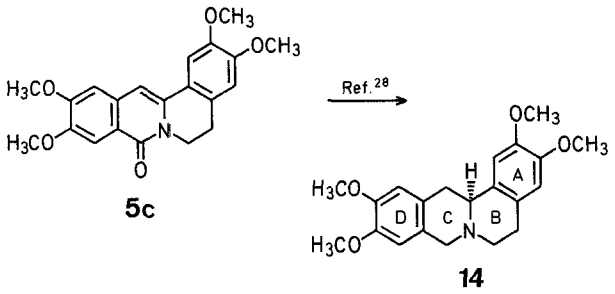
The presently developed procedure for the synthesis of didehydroberbin-8-ones from homophthalic anhydrides and dihydro-1(2*H*)-isoquinolinone derivatives proceeds in a single stage in contrast to the other known synthetic approaches[6,22-26] and is easier to carry out than the photochemical syntheses[27-30]. Some 13,13a-didehydroberbin-8-ones are natural products[31].

Table. Reactions of Homophthalic Anhydrides **1a, b** with Imidates **2, 3, 4,** or **8** or Imidoyl Chloride **9**, or Activated Lactams **11, 12, 13a**

Product	Yield [%] by Procedure A	B	m.p. [°C] (solvent)	Molecular formula[a]	I.R. ($CHCl_3$) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS/80 MHz) δ [ppm]
5a[b]	45 (C_6H_5Cl)	85	99.5–101.5° (*n*-C_6H_{14})[c] [102–102.5° (*n*-C_6H_{14}/ether)][27]	$C_{17}H_{13}NO$ (247.2)	1652	2.97 (t, *J* = 6.3 Hz, 2H, H-5); 4.37 (t, *J* = 6.3 Hz, 2H, H-6); 6.95 (s, 1H, H-13); 7.0–7.9 (m, 7H_{arom}); 8.43 (apparent d, 1H, H-9)
5b[b]	40 (C_6H_5Cl)	85	182–184° (C_2H_5OH/H_2O)[c]	$C_{19}H_{17}NO_3$ (307.3)	1650	3.00 (t, *J* = 6.3 Hz, 2H, H-5); 4.00 (s, 6H, 2OCH_3); 4.38 (t, *J* = 6.3 Hz, 2H, H-6); 6.6–8.0 (m, 6H_{arom} + H-13)
5c[b]	—	87	196.5–198° (CH_3OH) [196.5–198° (CH_3OH)][29]	$C_{21}H_{21}NO_5$ (367.1)	1649	2.98 (t, *J* = 6.2 Hz, 2H, H-5); 3.98 (s, 3H, OCH_3); 4.03 (s, 9H, 3OCH_3); 4.40 (t, *J* = 6.2 Hz, 2H, H-6); 6.73 + 6.80 + 6.90 + 7.23, 7.78 (5s, 4H_{arom} + H-13)
6a[b]	52 (C_6H_5Cl)	30	102–104° (*n*-C_6H_{14}/ether)[c]	$C_{13}H_{13}NO$ (199.2)	1655	1.6–2.2 (m, 4H, H-2, H-3); 2.78 (t, *J* = 6.4 Hz, 2H, H-2); 4.10 (t, *J* = 6.4 Hz, 2H, H-4); 6.20 (s, 1H, H-11); 7.1–7.8 (m, 3H_{arom}); 8.38 (apparent d, 1H, H-7)
6b[d]	55 (C_6H_5Cl)	—	159–161° (C_6H_6/*n*-C_6H_{14})	$C_{15}H_{17}NO_3$ (259.2)	1650	1.6–2.2 (m, 4H, H-2, H-3); 2.83 (t, *J* = 6.4 Hz, 2H, H-2); 3.98 + 4.00 (2s, 6H, 2OCH_3); 4.21 (t, *J* = 6.4 Hz, 2H, H-4); 6.20 (s, 1H, H-11); 6.75 (s, 1H, H-10); 7.75 (s, 1H, H-7)
7a[b]	51 ($C_6H_5CH_3$)	—	95–97° (*n*-C_6H_{14})	$C_{12}H_{11}NO$ (185.2)	1660	1.8–2.4 (m, 2H, H-2); 3.03 (t, *J* = 7.4 Hz, 2H, H-1); 4.15 (t, *J* = 7.4 Hz, 2H, H-3); 6.30 (s, 1H, H-10); 7.0–7.7 (m, 3H_{arom}); 8.38 (apparent d, 1H, H-6)
7b[d]	57 ($C_6H_5CH_3$)	—	206–208° (2-butanone)	$C_{14}H_{15}NO_3$ (245.2)	1662	2.0–2.5 (m, 2H, H-2); 3.10 (t, *J* = 7.3 Hz, 2H, H-1); 3.98 + 4.00 (2s, 6H, 2OCH_3); 4.18 (t, *J* = 7.3 Hz, 2H, H-3); 6.28 (s, 1H, H-10); 6.78 (s, 1H, H-9); 7.73 (s, 1H, H-6)
10a[b]	82 (C_6H_5Cl)[e] 25 (C_6H_5Cl)[f]	—	68.5–70.5° (*n*-C_6H_{14})[c] [70–71° (C_2H_5OH)][17]	$C_{16}H_{13}NO$ (235.2)	1650	3.24 (s, 3H, NCH_3); 6.15 (s, 1H, H-4); 7.0–7.6 (m, 8H_{arom}); 8.23 (apparent d, 1H, H-8)
10b[d]	78 (C_6H_5Cl)[e]	—	229–231° (C_6H_6)	$C_{18}H_{17}NO_3$ (295.3)	1650	3.48 (s, 3H, NCH_3); 4.00 + 4.05 (2s, 6H, 2OCH_3); 6.39 (s, 1H, H-4); 6.85 (s, 1H, H-5); 7.3–7.6 (m, 6H_{arom}); 7.85 (s, 1H, H-8)

[a] The microanalytical data showed the following maximal deviations from the theoretical values: C, +0.31, H, ±0.24.
[b] Purified by column chromatography.
[c] Mixture m.p. of products from procedure A and B not depressed.
[d] Purified by recrystallization.
[e] From imidoyl chloride **9**.
[f] From imidate **8**.

The procedure can also serve for the preparation of protoberberine alkaloids as illustrated by the conversion of **5c** into (±)-xylopinine **(14)** by a known method[28]. Suitably substituted homophthalic anhydrides[5,6] can be employed for building the ring D of the alkaloid molecule with substituents at the desired positions.



5c **14**

The melting points were determined on a Kofler instrument and are uncorrected. The I.R. spectra were recorded on a Specord 71-IR instrument using 1% chloroform solutions. The ^{1}H-N.M.R. spectra were taken on a Tesla BS-487-C (80 MHz) apparatus with TMS as internal standard.

Reaction of Homophthalic Anhydrides 1a, b with Imidates or Imidoyl Chlorides; General Procedure A:

The homophthalic anhydride **1a, b** (2 mmol) is added portionwise during 10 min to a solution of imidate **2, 3, 4,** or **8** or imidoyl chloride **9** (2.2 mmol) in dry toluene or dry chlorobenzene (1 ml) at 110 °C or 130 °C, respectively. The reaction mixture is then heated under reflux for 1 h, cooled, diluted with chloroform (100 ml), washed with 10% aqueous sodium hydroxide (3 × 20 ml), dried with sodium sulphate, and the solvents distilled off. The solid residue is recrystallized from a suitable solvent or subjected to column chromatography on silica gel 60 Merck (substance:sorbent 1:100; *n*-hexane/diethyl ether or ethyl acetate in different proportions as eluents).

Reaction of the Homophthalic Anhydrides 1a, b with Activated Lactams; General Procedure B:

A solution of phosphoryl chloride (2.2 mmol) in dry chlorobenzene (1 ml) is added during 5 min to a stirred solution of the corresponding lactam (2.2 mmol) and dry pyridine (2.2 mmol) in dry chlorobenzene (1 ml) at room temperature. The suspension is stirred for another 15 min, homophthalic anhydride (2 mmol) added, stirring continued for 15 min, and the reaction mixture heated under reflux for 1 h. The reaction mixture is cooled, diluted with chloroform (100 ml), washed with 10% aqueous sodium hydroxide (3 × 20 ml), dried with sodium sulphate, and the solvents removed. The residue is purified by column chromatography as described in Procedure A.

(±)-Xylopinine (14) from 5c:

The crude product obtained by treatment of **5c** (0.184 g, 0.5 mmol) according to Ref.[28] is purified by column chromatography and recrystallization from diethyl ether/*n*-hexane to give **14**; yield: 0.148 g (83%); m.p. 146–148 °C; Ref.[32], m.p. 146–148 °C.

$C_{21}H_{25}NO_4$	calc.	C 70.96	H 7.09
(355.4)	found	71.26	7.23

I.R. ($CHCl_3$): ν = 2810, 2790, 2750 cm^{-1} (Bohlmann bands).

^{1}H-N.M.R. ($CDCl_3$/TMS/100 MHz): δ = 2.4–4.2 (m, 9H, $4CH_2$ + H-13a); 3.82 + 3.88 (2s, 12H, $4OCH_3$); 6.58 + 6.64 + 6.70 + 6.76 ppm (4s, $4H_{arom}$).

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