Synthesis of β-Lactams via Cycloaddition of Hydrazones with Phenoxyketene

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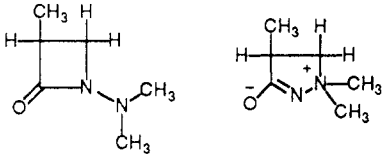
Phenoxyketene is capable of annelating the disubstituted hydrazones to afford stereoselectively cis-monocyclic β-lactams with a 1-amino functionality. The ease of cycloaddition is governed by substituents on the azomethine carbon as well as on the hydrazone nitrogen. The 4-disubstituted β-lactams (**4a–c** and **6a–b**) were prepared through the reaction of *N,N*-diphenylhydrazones and *N*-methyl-*N*-phenylhydrazones of ketones with phenoxyacetyl chloride/Et_3N in dichloromethane. A similar reaction using aldehyde and ketone hydrazones, derived from *N,N*-dimethylhydrazine, produced 4-monosubstituted (**8a–d**) as well as 4-disubstituted (**8e–l**) β-lactams in good yields.

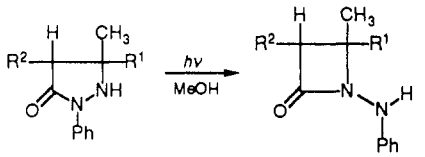
In recent years several monocyclic β-lactams discovered in nature[1,2] have been shown to possess high activity against Gram-negative organisms. In view of this, a suitably substituted monocyclic β-lactam ring might perhaps be the minimum requirement for biological activity.[3] Recently, preparation of various types of heteroatom-activated β-lactams have also been reported.[4,5] In continuation of our work on the synthesis of monocyclic β-lactams[6] as potential antibiotics, we report in this paper the synthesis of such compounds from hydrazones.

The imine–ketene cycloaddition is well established and a versatile route to racemic β-lactams.[7] Over the years, various kinds of imine synthons have been used to prepare novel β-lactams.[8] Previously,[9] we demonstrated an elegant use of glycine for preparing α-amino cis-β-lactams. In order to prepare 1-amino β-lactams, we sought to explore the use of hydrazones as the imine components.

Sokolova and co-workers[10] reported the preparation of several 1-(dimethylamino)azetidin-2-ones from 1,1-dimethylhydrazine and α,β-unsaturated acids, but these compounds were later shown by them[11] to be "inner salts", 1,1-dimethylpyrazolidinium 3-oxides.



Ege,[12] during her studies on photochemistry of heterocyclic compounds, found that 1-aminoazetidin-2-ones can be prepared by ring contraction of unsubstituted and substituted 2-phenylpyrazolidin-3-ones.



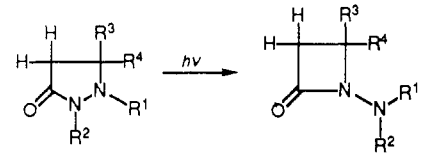
a: $R^1 = R^2 = H$

b: $R^1 = H$; $R^2 = CH_3$

c: $R^1 = CH_3$; $R^2 = HC(CH_3)X$

where X = OH, NH_2, NHCOMe

Johnson[13] extended the work to other pyrazolidin-3-ones which on photolysis yield the corresponding azetidin-2-ones.



R^1	R^2	R^3	R^4
H	H	CH_3	CH_3
H	$COCH_3$	$-(CH_2)_5-$	
$COCH_3$	H	$-(CH_2)_2S(CH_2)_2-$	

Pifferi et al.[14] also prepared such compounds by condensing 1-(carbobenzyloxy)-1-benzylhydrazine with 2-propyl-2-(bromomethyl)valeryl chloride followed by hydrogenolysis in ethanol. Some of these compounds were shown to possess antiinflammatory activity.

Recently, Shanker and co-workers[15] published the synthesis of 1-aminoazetidin-2-ones from phenylhydrazones using chloroacetyl chloride/Et_3N. But the conclusions drawn in the absence of any NMR spectral data seems to be ambiguous. IR absorption reported at 1710 cm^{-1} is also quite deviated from the expected value for the β-lactam carbonyl absorption.

Results and Discussion

We have observed that the aldehyde/ketone phenylhydrazones **1** do not undergo cycloaddition with phen-

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(14) (a) Pifferi, G.; Consonni, P.; Testa, E. *Gazz. Chim. Ital.* **1967**, *97*, 1719. (b) Pifferi, G.; Testa, E. British Patent 1 192 952, May 28, 1970; *Chem. Abstr.* **1970**, *73*, 55961*b*.

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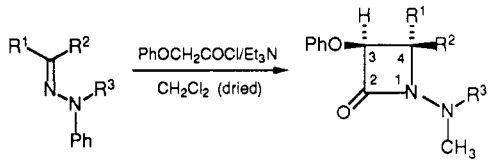
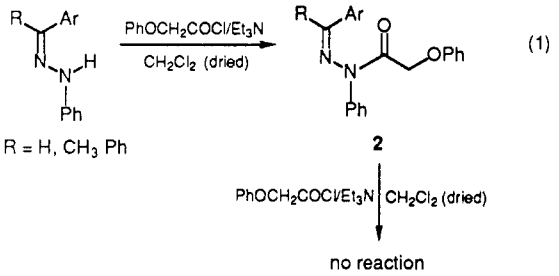
Table I



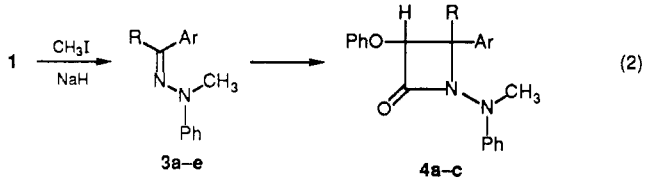
3, 4	R^1	R^2	R^3	IR ($\nu_{C=O}$), cm^{-1}	^1H NMR (C_3-H)	NOE (% increase in C_3-H signal intensity)
a	CH_3	Ph	CH_3	1765	5.17	20.1
b	Ph	Ph	CH_3	1760	5.67	–
c	$-(CH_2)_5-$		CH_3	1760	4.74	–
d	H	Ph	CH_3	–	–	–
e	H	C(H)=CHPh	CH_3	–	–	–
5, 6						
a	CH_3	C_2H_5	Ph	1765	4.90	17.3
b	$-(CH_2)_5-$		Ph	1765	4.87	–
c	H	C(H)=CHPh	Ph	–	–	–

oxyketene to yield any β-lactam, and instead the free NH group gets acylated to give the compounds **2** showing an IR absorption band at 1685–1695 cm^{-1}. The NMR spectra also show a sharp 2 H singlet at δ 5.4–5.5 for CH_2 protons. These acyclated hydrazones fail to react with an additional mole of phenoxyacetyl chloride in the presence of triethylamine to give β-lactam compounds (eq 1). The starting material is recovered unchanged.



(1)

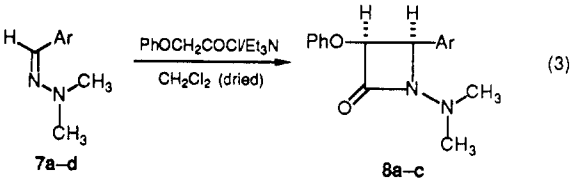
In the light of above observations, we chose to alkylate the phenylhydrazones and then try the cycloaddition reaction. The hydrazones **1** were methylated with methyl iodide in the presence of a strong base to procure the *N*-methyl-*N*-phenylhydrazones **3a–e** in good yields. All these hydrazones were subjected to the reaction of phenoxyacetyl chloride in the presence of Et_3N (eq 2). Among



(2)

these, only the ketone hydrazones **3a–c** underwent cycloaddition smoothly to yield the corresponding 1-aminoazetidin-2-ones **4a–c** (Table I). Similar results were observed when hydrazones **5a–c**, derived from *N,N*-diphenylhydrazine hydrochloride, were subjected to β-lactam formation (Table I).

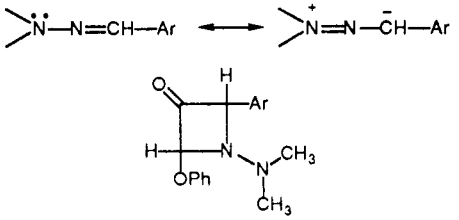
Among the various hydrazones, the *N,N*-dimethylhydrazones (DMHs) are unique in their synthetic applications as amply demonstrated by Corey and Enders.[16] In view of this, we thought of using them for β-lactam formation. Various DMHs (**7a–k**) were prepared quantitatively from a variety of aldehydes/ketones by refluxing them in easily procurable *N,N*-dimethylhydrazine. In this case the formation of β-lactams from both aldehyde and ketone hydrazones is of special interest. The aldehyde hydrazones **7a–d** when subjected to annelation with phenoxyacetyl chloride, in the presence of Et_3N, in dry CH_2Cl_2, gave the corresponding β-lactams **8a–d** (eq 3) as white



(3)

solids which were purified by recrystallization or by column chromatography. The cycloaddition reaction in all these cases was stereoselective and produced only the cis isomers of the β-lactams showing J = 5.0 Hz for C_3 and C_4 hydrogens.[17] IR, as expected, showed the β-lactam carbonyl absorption at 1760–1770 cm^{-1} (Table II).

It is also worth noting that DMHs of aldehydes did not undergo C-acylation.[18] In view of the enamine nature of these hydrazones, the formation of the alternative cyclobutanone structure can also be visualized. However, ^1H NMR data clearly support the β-lactam structure for these products; the C_3 and C_4 protons, as expected, showed a pair of doublets with a coupling constant (J = 5.0 Hz) corresponding to their cis orientation. Moreover neither proton is exchangeable with D_2O in presence of a base. This also rules out the possibility of a cyclobutanone structure in which these hydrogens are more acidic.



Further, the ketone hydrazones **7e–k** also reacted smoothly producing the corresponding β-lactams **8e–l**. The

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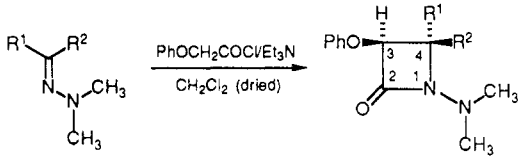
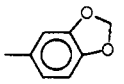
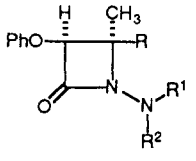
Table II



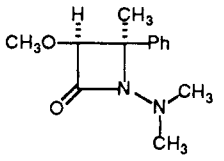
7 8

7, 8	R^1	R^2	IR ($\nu_{C=O}$), cm^{-1}	^1H NMR, δ		J_{3-4}, Hz	NOE (% increase in C_3-H signal intensity)
				C_3-H	C_4-H		
a	H	Ph	1770	5.30	5.13	5.0	-
b	H		1760	5.30	5.03	5.0	-
c	H		1760	5.35	5.33	5.0	-
d	H	C(H)=CHPh	1770	5.25	4.85	5.0	-
e	CH_3	CH_3	1755	4.70	-	-	-
f	CH_3	C_2H_5	1760	4.73	-	-	16.3
g	CH_3	$CH(CH_3)_2$	1760	4.67	-	-	15.0
h		$-(CH_2)_5-$	1760	4.67	-	-	-
i	CH_3	Ph	1745	4.90	-	-	25.2
j	Ph	Ph	1745	5.63	-	-	-
k	Ph	C(O)Ph	1765	6.03	-	-	-
l	C(O)Ph	Ph	1770	5.70	-	-	-

NMR spectra of these compounds showed resonances in the expected positions. The C_3-H appeared as a sharp singlet, confirming the formation of a single isomer of a β-lactam. However, it was difficult to assign the stereoorientation of the groups at C_3 and C_4 in these compounds. For this reason we prepared the corresponding 3-methoxy β-lactam **9** from acetophenone hydrazone using methoxyketene. The NMR signal for the methoxy protons in this compound appeared at higher field (δ = 3.13) than usual. This upfield shift clearly indicated the cis relationship of C_3-methoxy group with C_4-phenyl group.[19] In this configuration the methoxy protons lie in the shielding cone of the benzene nucleus. This also rules out the possibility of the alternative cyclobutanone structures in which methoxy and phenyl groups would not be on adjacent carbons. The molecular models clearly indicate that in such cyclobutanone structures the methoxy group cannot experience the ring current effect of phenyl group. Based on this observation, as well on the constant value for C_3-H signal ($\delta \approx 4.7$) in β-lactams with a CH_3 group at the C_4 position (see Table II), we have assigned *Z* stereochemistry to these compounds prepared from ketone hydrazones. This stereochemical assignment has been further confirmed by NOE experiments. An enhancement (15–25%) in the intensity of the C_3-H signal was observed on irradiating the C_4-CH_3 protons in compounds **4a**, **6a**, **8f**, **8g**, and **8i**. This confirmed the cis orientation of the C_3-H and C_4-CH_3 groups in these compounds.

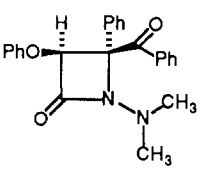


4a, 6a, 8f, g, i

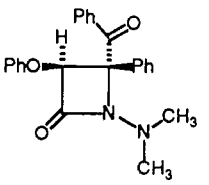


9

Benzil on treatment with excess of dimethylhydrazine yielded only the monohydrazone **7k**, which on annelation produced a mixture of isomeric β-lactams **8k** and **8l**. These could be easily separated by fractional recrystallization using ethanol (Table II).



8k
(C_3-H δ = 6.03)



8l
(C_3-H δ = 5.70)

The configuration for **8k** and **8l** has been tentatively assigned on the basis of ^1H NMR spectra; the C_3-H appearing high field due to the shielding of the phenyl ring of the C_4-benzoyl group in **8l**.

Experimental Section

Phenylhydrazones were prepared by literature procedures.[20] ^1H NMR spectra were recorded at 60 and 90 MHz on Varian EM 360 L and EM 390 spectrometers in $CDCl_3$ solutions containing TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. NOE measurements were recorded on a JEOL FX 90 Q FT-NMR spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalysis for all new compounds were in satisfactory agreement with the calculated values (C, ±0.3; H, ±0.3; N, ±0.4%).

***N*-Methyl-*N*-phenylhydrazones (3a–e).** NaH (4.00 g), washed in *n*-hexane, was added to the phenylhydrazone (10 mmol) in dry THF (40 mL) at low temperature. After the mixture was stirred for 15 min, methyl iodide (15 mmol) was added dropwise with continued stirring. After 3 h of stirring the reaction mixture was refluxed for 2 h. THF was removed under reduced pressure. The contents were diluted with water (15 mL), extracted with ether, and dried (Na_2SO_4). On evaporating the solvent, *N*-methyl-*N*-phenylhydrazones were obtained in almost quantitative yields as yellow solids, except **3c**. **3a**: mp 97–98 °C; ^1H NMR

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($CDCl_3$) δ 7.13–8.13 (m, 10 H, Ar), 3.27 (s, 3 H, NCH_3), 2.37 (s, 3 H, CH_3). **3b**: mp 68–69 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.67 (m, 15 H, Ar), 2.90 (s, 3 H, NCH_3). **3c**: thick oil; ^1H NMR ($CDCl_3$) δ 6.73–7.30 (m, 5 H, Ar), 3.00 (s, 3 H, NCH_3), 2.43, 1.83 (br, 4 H + 6 H, cyclohexane). **3d**: ^1H NMR ($CDCl_3$) δ 7.03–7.90 (m, 11 H, Ar and CH), 3.53 (s, 3 H, NCH_3).

Preparation of Hydrazones. *N,N*-Diphenylhydrazones and *N,N*-dimethylhydrazones were prepared by literature procedures.[21,22]

***N,N*-Diphenylhydrazones 5a and 5b.** The mixture of the ketone (10 mmol), *N,N*-diphenylhydrazine hydrochloride (10 mmol), and NaOH (20 mmol) in ethanol (50 mL) was refluxed for 18 h. Ethanol was removed under reduced pressure. The reaction mixture was diluted with water (20 mL), extracted with ether (2 × 25 mL), and dried over Na_2SO_4. On evaporating the ether, hydrazones were obtained as liquids which were purified by passing through a silica gel column using petroleum ether and CH_2Cl_2 (2:1) as eluent. **5a**: ^1H NMR ($CDCl_3$) δ 7.03–7.73 (m, 10 H, Ar), 2.50 (q, 2 H, CH_2), 1.77 (s, 3 H, CH_3), 1.20 (t, 3 H, CH_2CH_3). **5b**: ^1H NMR ($CDCl_3$) δ 7.00–7.50 (m, 10 H, Ar), 2.43, 1.67 (br, 4 H + 6 H, cyclohexane).

***N,N*-Diphenylhydrazone 5c.** *N,N*-Diphenylhydrazine hydrochloride (5 mmol) was stirred with triethylamine (10 mmol) in dried dichloromethane (40 mL) for 20 min. The reaction mixture was washed with aqueous $NaHCO_3$ and water. After evaporating the dichloromethane, the liberated hydrazine liquid was taken in ethanol (25 mL). To this was added cinnamaldehyde (5 mmol), and the reaction mixture was refluxed for 8 h. Ethanol was removed under reduced pressure to afford **5c** as a pale yellow liquid.

***N,N*-Dimethylhydrazones 7a, b, h, i, k. General Procedure (See Table II).** *N,N*-Dimethylhydrazine (15 mmol, ethanol solution) was added dropwise to the stirring solution of aldehyde/ketone (10 mmol) and ethanol (50 mL) at 10 °C. After being stirred for half an hour at room temperature, the reaction mixture was refluxed for 18–20 h, and thereafter ethanol was removed under reduced pressure. The reaction mixture was diluted with water (20 mL), extracted with ether (2 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to afford *N,N*-dimethylhydrazones as liquids in good yields (70–80%) except in **7h** where only 30% yield was obtained.

In runs **7b** and **7i**, the reaction mixture was refluxed for 3 h. The reaction mixture in **7b** solidified on cooling, and after workup the hydrazone was recovered as a yellow solid, mp 54–55 °C. **7a**: ^1H NMR ($CDCl_3$) δ 7.13–7.63 (m, 6 H, Ar and CH), 2.90 (s, 6 H, $N(CH_3)_2$). **7b**: ^1H NMR ($CDCl_3$) δ 6.77–7.30 (m, 4 H, Ar and CH), 6.13 (s, 2 H, OCH_2), 2.93 (s, 6 H, $N(CH_3)_2$). **7h**: ^1H NMR ($CDCl_3$) δ 2.50 (s, 6 H, $N(CH_3)_2$), 2.40, 1.73 (br, 4 H + 6 H cyclohexane). **7i**: ^1H NMR ($CDCl_3$) δ 7.40–8.13 (m, 5 H, Ar), 2.53, 2.63 (s each, 2 × 3 H, $N(CH_3)_2$), 2.27 (s, 3 H, CH_3). **7k**: ^1H NMR ($CDCl_3$) δ 7.03–8.03 (m, 10 H, Ar), 2.60, 2.83 (s each, 2 × 3 H, $N(CH_3)_2$).

***N,N*-Dimethylhydrazones 7c–g and 7j. General Procedure (See Table II).** To the ice-cold aldehyde/ketone (10 mmol), was added dropwise *N,N*-dimethylhydrazine (15 mmol). After being allowed to warm slowly to room temperature, the reaction mixture was refluxed for 20–24 h until its color changed to pale yellow. After cooling, a few pellets of KOH were added to the reaction mixture to induce the separation of the organic layer. The organic layer was extracted with ether, washed with water, and dried (Na_2SO_4). After removing the solvent, hydrazones were collected as liquids.

The reaction mixture was refluxed for 6 h and 1 h for **7d** and **7c**, respectively. **7c**: ^1H NMR ($CDCl_3$) δ 7.00–7.97 (m, 5 H, Ar and CH), 2.83 (s, 6 H, $N(CH_3)_2$). **7e**: ^1H NMR ($CDCl_3$) δ 2.43, 2.47 (s each, 2 × 3 H, $C(CH_3)_2$), 1.97, 2.01 (s each, 2 × 3 H, $N(CH_3)_2$). **7f**: ^1H NMR ($CDCl_3$) δ 2.53 (s, 6 H, $N(CH_3)_2$), 2.27 (q, 2 H, CH_2), 2.03 (s, 3 H, CH_3), 1.07 (t, 3 H, CH_2CH_3). **7j**: ^1H NMR ($CDCl_3$) δ 7.37–8.00 (m, 10 H, Ar), 2.57 (s, 6 H, $N(CH_3)_2$).

Reaction of Disubstituted Hydrazones with Phenoxyketene (4a–c, 6a–b, 8a–l). General Procedure (See Table I and II). Phenoxyacetyl chloride (10 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a well-stirred solution of appropriate hydrazone (10 mmol) and triethylamine (12 mmol) in dry CH_2Cl_2 (100 mL) at 10 °C. The contents were stirred for 6 h and kept overnight. The mixture was washed with saturated $NaHCO_3$ solution (30 mL) followed by water (3 × 50 mL). The organic layer was dried over $CaCl_2$, and the solvent was removed in vacuo. Recrystallization from ethanol afforded the 1-aminoazetidin-2-ones as solids in good yields. Compound **4c**, however, did not solidify. **4a**: mp 106 °C; IR 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87–7.67 (m, 15 H, Ar), 5.17 (s, 1 H, C_3-H), 3.27 (s, 3 H, NCH_3), 2.02 (s, 3 H, CH_3). **4b**: mp 150–151 °C; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83–7.43 (m, 20 H, Ar), 5.67 (s, 1 H, C_3-H), 3.13 (s, 3 H, NCH_3). **4c**: thick oil; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87–7.37 (m, 10 H, Ar), 4.74 (s, 1 H, C_3-H), 3.27 (s, 3 H, NCH_3), 1.30–1.93 (br, 10 H, cyclohexane). **6a**: mp 117–119 °C; IR 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07–7.50 (m, 15 H, Ar), 4.90 (s, 1 H, C_3-H), 1.83 (q, 2 H, CH_2), 1.50 (s, 3 H, CH_3), 0.87 (t, 3 H, CH_2CH_3). **6b**: mp 116–117 °C; IR 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.57 (m, 15 H, Ar), 4.87 (s, 1 H, C_3-H), 1.50–1.93 (br, 10 H, cyclohexane). **8a**: mp 120–121 °C; IR 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70–7.60 (m, 10 H, Ar), 5.30 (d, 1 H, C_3-H), 5.13 (d, 1 H, C_4-H), 2.74 (s, 6 H, $N(CH_3)_2$). **8b**: mp 128–130 °C; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83–7.40 (m, 8 H, Ar), 6.03 (s, 2 H, OCH_2), 5.23 (d, 1 H, C_3-H), 5.03 (d, 1 H, C_4-H), 2.74 (s, 6 H, $N(CH_3)_2$). **8c**: mp 103–104 °C; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.77–7.83 (m, 9 H, Ar), 5.77 (d, 1 H, C_3-H), 5.33 (d, 1 H, C_4-H), 2.73 (s, 6 H, $N(CH_3)_2$). **8d**: mp 128–129 °C; IR 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.47 (m, 10 H, Ar), 6.90 (d, 1 H, =CHPh, J = 18 Hz), 6.57 (dd, 1 H, CH=CH, J = 10 and 18 Hz), 5.27 (d, 1 H, C_3-H, J = 5.0 Hz), 4.83 (dd, 1 H, C_4-H, J = 5.0 and 10 Hz), 2.83 (s, 6 H, $N(CH_3)_2$). **8e**: mp 84–86 °C; IR 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–7.50 (m, 5 H, Ar), 4.70 (s, 1 H, C_3-H), 2.90 (s, 6 H, $N(CH_3)_2$), 1.33, 1.52 (s each, 2 × 3 H, $(CH_3)_2$). **8f**: mp 38–40 °C; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–7.50 (m, 5 H, Ar), 4.73 (s, 1 H, C_3-H), 2.97 (s, 6 H, $N(CH_3)_2$), 1.80 (q, 2 H, CH_2), 1.50 (s, 3 H, CH_3), 1.07 (t, 3 H, CH_2CH_3). **8g**: mp 86–88 °C; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93–7.43 (m, 5 H, Ar), 4.67 (s, 1 H, C_3-H), 2.93 (s, 6 H, $N(CH_3)_2$), 2.20 (m, 1 H, CH<), 1.40 (s, 3 H, CH_3), 1.00, 1.03 (d each, 2 × 3 H, isopropyl). **8h**: mp 72–73 °C; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97–7.40 (m, 5 H, Ar), 4.67 (s, 1 H, C_3-H), 2.87 (s, 6 H, $N(CH_3)_2$), 1.27–2.00 (m, 10 H, cyclohexane). **8i**: mp 128–130 °C; IR 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70–7.67 (m, 10 H, Ar), 4.90 (s, 1 H, C_3-H), 2.97 (s, 6 H, $N(CH_3)_2$), 2.00 (s, 3 H, CH_3). **8j**: mp 120–121 °C; IR 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93–7.93 (m, 15 H, Ar), 5.63 (s, 1 H, C_3-H), 2.93 (s, 6 H, $N(CH_3)_2$). **8k**: mp 160–161 °C; IR 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97–7.97 (m, 15 H, Ar), 6.03 (s, 1 H, C_3-H), 2.90 (s, 6 H, $N(CH_3)_2$). **8l**: mp 95–96 °C; IR 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13–8.13 (m, 15 H, Ar), 5.70 (s, 1 H, C_3-H), 3.03 (s, 6 H, $N(CH_3)_2$).

3-Methoxy-1-(*N,N*-dimethylamino)azetidin-2-one (9). Phosphorous oxychloride (1.54 g, 10 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a well-stirred solution of acetophenone-hydrazone **7i** (1.62 g, 10 mmol), methoxy acetic acid (900 mg, 10 mmol), and triethylamine (2.02 g, 20 mmol) in dry CH_2Cl_2 (100 mL) at 10 °C. The mixture was stirred overnight followed by refluxing for 4 h. After washing with $NaHCO_3$ solution and water, the CH_2Cl_2 layer was dried ($CaCl_2$) and evaporated to a residue, which was fractionated by neutral alumina column chromatography. Elution with CH_2Cl_2 afforded the β-lactam **9** as a white solid: mp 83–84 °C; IR 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.53 (m, 5 H, Ar), 4.04 (s, 1 H, C_3-H), 3.13 (s, 3 H, OCH_3), 2.83 (s, 6 H, $N(CH_3)_2$), 1.78 (s, 3 H, CH_3).

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Registry No. 1 (R = Me, Ar = Ph), 583-11-9; 1 (R = Ar = Ph), 574-61-8; 1 (R,Ar = CH_{25}), 946-82-7; 1 (R = H, Ar = Pp), 588-64-7; 1 (R = H, Ar = PhCH=CH), 1216-15-5; **3a**, 3741-87-5; **3b**, 1665-83-4; **3c**, 5311-87-5; **3d**, 2989-45-9; (±)-**4a**, 125331-20-6; (±)-**4b**, 125331-21-7; (±)-**4c**, 125331-22-8; **5a**, 78692-78-1; **5b**, 19691-06-6; **5c**, 23718-87-8; (±)-**6a**, 125331-23-9; (±)-**6b**, 125331-24-0; **7a**, 1075-70-3; **7b**, 14371-16-5; **7c**, 5051-47-8; **7d**, 13466-39-2; **7e**, 13483-31-3; **7f**, 5758-05-4; **7g**, 28236-87-5; **7h**, 10424-93-8; **7i**, 13466-32-5; **7j**, 24398-55-8; **4k**, 65296-04-0; (±)-**8a**, 125331-25-1; (±)-**8b**, 125331-26-2; (±)-**8c**, 125331-27-3; (±)-**8d**, 125331-28-4;

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(±)-**8e**, 125331-29-5; (±)-**8f**, 125331-30-8; (±)-**8g**, 125331-31-9; (±)-**8h**, 125331-32-0; (±)-**8i**, 125331-33-1; (±)-**8j**, 125331-34-2; (±)-**8k**, 125331-35-3; (±)-**8l**, 125331-36-4; (±)-**9**, 125331-37-5; $CH_3C(O)CH_2CH_3$, 78-93-3; PhCHO, 100-52-7; *o*-ClC_6H_4CHO, 89-98-5; $CH_3C(O)CH_3$, 67-64-1; $CH_3C(O)CH(CH_3)_2$, 563-80-4; $CH_3C(O)Ph$, 98-86-2; PhC(O)Ph, 119-61-9; PhC(O)C(O)Ph, 134-81-6; cyclohexanone, 108-94-1; *N,N*-diphenylhydrazine hydrochloride, 530-47-2; *N,N*-diphenylhydrazine, 530-50-7; *N,N*-dimethylhydrazine, 57-14-7; cinnamaldehyde, 104-55-2; 1,3-benzodioxole-5-carboxaldehyde, 120-57-0; phenoxyacetyl chloride, 701-99-5; methoxyacetic acid, 625-45-6; phenoxyketene, 107855-45-8.

Intramolecular Pictet–Spengler Reaction of *N*-Alkoxytryptophans and Tryptamines. 2.[1] Synthesis of Corynanthe Alkaloid Derivatives Containing a Tetrahydro-1,2-oxazine as the D Ring

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The *N*-hydroxtryptamines **1–3** were converted into the *N*-alkoxy derivatives **26–29** by successive protection with 2-(trimethylsilyl)ethyl chloroformate providing **19–21**, reaction with functionalized alkylhalides, and deprotection with tetrabutylammonium fluoride. Intramolecular cyclization of **26–29** under acidic or reductive conditions gave the corynanthe analogues **4–6** in good yields.

Introduction

The tetrahydro-β-carboline nucleus is a structural feature present in many indole alkaloids. Common to all these indole bases is a tryptamine unit, which in a convincing variety of alkaloids has been found to have its genesis in tryptophan.[2]

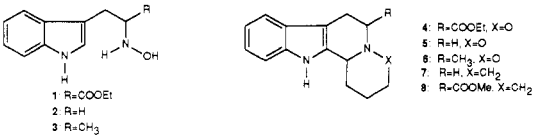
Due to the interesting biological effects such as inhibition of monoamine oxidase (MAO) enzymes,[3] neurotransmitter reuptake,[3] binding to benzodiazepine receptors,[3] carcinogenic properties,[3b] and antiviral activity[4] a wide array of β-carbolines have been prepared starting from various tryptamine and tryptophan derivatives. However, rare are those starting from *N*-hydroxytryptophan[5] (**1**) or *N*-hydroxytryptamine[6] (**2**) to give *N*(2)-hydroxy-1,2,3,4-tetrahydro-β-carboline derivatives. Because of the central significance of *N*-hydroxytryptophan in biotransformation pathways[7] which is substantiated by the detection of *N*-hydroxytryptamine in rabbit and guinea pig liver[8] and the isolation of secondary metabolites containing the *N*-hydroxytryptophan (e.g. astechrome[9]) or the *N*-hydroxytryptamine moiety (e.g. geneserine,[10] eudistomins[4]), we wanted to study the pharmacological impact of the introduction of a N–O bond in the β-carboline alkaloids.

Interesting target structures are **4–6** since these contain the structural feature of the *N*-hydroxy compounds **1–3**. These molecules are direct analogues of the simple corynanthe alkaloids **7**[11,12] and **8**,[12e,13] containing a tetrahydro-1,2-oxazine as the D ring (Chart I).

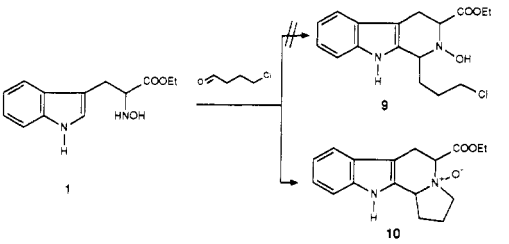
Strategy

The standard methods for the construction of the C ring in the corynanthe alkaloids are the Bischler–Napieralski[3b] and the Pictet–Spengler[3b] reactions or cyclization via pyridinium salts.[3b,14] Recently the conversion of **1** into 1,3-disubstituted *N*(2)-hydroxy-1,2,3,4-tetrahydro-β-carbolines via the Pictet–Spengler reaction has been reported.[5e] Therefore our first approach to compounds **4–6**

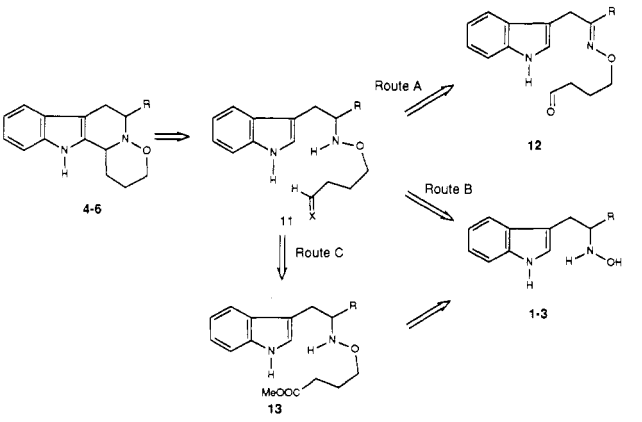
Chart I



Scheme I



Scheme II



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