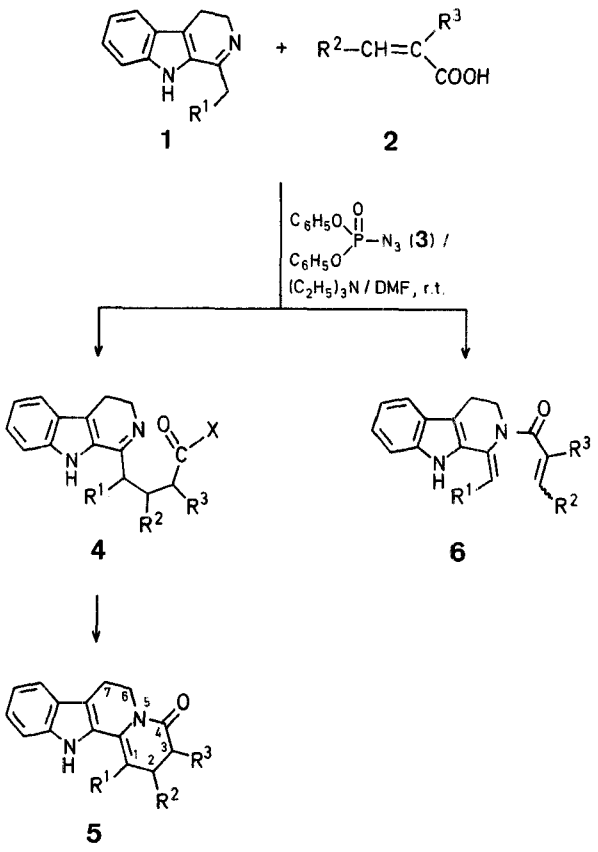

A One-pot Synthesis of 2,6,7,12-Tetrahydroindolo[2,3-*a*]-quinolizin-4 (3*H*)-ones

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In recent years, the title compounds have been proved to be useful intermediates in the synthesis of indole alkaloids such as dihydrocorynantheol[1], flavopereirine[2], and diastereomeric yohimbanes[2]. The earlier method[3] for their synthesis involving the reaction of tryptamine with glutaric anhydride followed by cyclization of the resulting *N*-(2-indol-3-ylethyl)-glutarimide with phosphorus pentoxide in refluxing xylene affords the products in low yield (31%) and is only applicable to symmetrically substituted anhydrides. More recently, two approaches have been reported for their preparation by reacting the readily available imines **1**, as *C,N*-ambident nucleophiles, with α,β-unsaturated esters[1,4] and chlorides[2]. While the first method frequently requires high temperatures and prolonged reaction times which lead to low yields due to the lability of intermediates, the second one necessitates the use of photochemical apparatus in a two-step procedure.

During our studies on the synthesis of vincamine, an excellent cerebral vasodilator drug, we found that the addition of acrylic acid to imine **1** ($R^1 = C_2H_5$) in the presence of diphenyl phosphoroazidate **(3)**[5] and triethylamine in dimethylformamide led regiospecifically to the key precursor 1-ethyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one **(5b)** directly in nearly quantitative yield[6].

We have now investigated the scope of this reaction by variation of the electrophilic component and report here the preparation of a large variety of substituted compounds **5** (Tables 1, 2).

The formation of **5** from **1** can be reasonably assumed as proceeding by an initial Michael addition of **1** to the electrophilic double bond followed by an intramolecular nucleophilic attack of the imino nitrogen at the powerfully activated carbonyl function in **4** (X = N_3). The yields with β- and α,β-substituted acrylic acids are diminished because of a side reaction forming the easily hydrolyzable *N*-acylated intermediates **6**[2], which are unable to cyclize under the conditions used.

The cyclization of intermediates **4u** and **4v** could occur affording a mixture of two diastereomers, however only one of the stereoisomers is selectively produced, in which two substituents at positions 2 and 3 are oriented *trans* to each other.

The use of diphenyl phosphor azidate **(3)** offers several advantages over other condensing agents such as dicyclohexylcarbodiimide, benzotriazolyl-*N*-oxytris[dimethylamino]-phosphonium hexafluorophosphate[7], 3,3'-(chlorodiphosphinlidene)-bis[2-oxo-1,3-oxazolidine][8], and chlorodiphenylphosphine oxide[9], leading to **5** in higher yields and easily separable from contaminating by-products.

This method may be limited to the title compounds derived from α-, α,β-, and β-substituted acrylic acids since, when this annulation was attempted with β,β-disubstituted acrylic acids such as β,β-dimethylacrylic acid and β-phenylcinnamic acid, a myriad of products were detected by T.L.C. Despite this drawback, the ease of reaction as well as the availability of imines **1** and α,β-unsaturated acids **2** make this approach attractive for the preparation of the title compounds.

All acrylic acids except **2**(R^2 = H, R^3 = 4-O_2N—C_6H_4), diphenyl phosphoroazidate **(3)**, triethylamine, and dimethylformamide were commercially available materials and were purified by standard procedures before use. The acids **2**(R^2 = H, R^3 = 4-O_2N—C_6H_4)[10] and imines **1** (R^1 = H[11], C_2H_5[12], C_6H_5[13]) were prepared according to reported methods.

1-Ethyl-3-methyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (5s); Typical Procedure:

A solution of 1-propyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (**1**, R^1 = C_2H_5; 2.12 g, 10 mmol), methacrylic acid (**2**, R^2 = H, R^3 = CH_3; 0.95 g, 11 mmol) and triethylamine (1.11 g, 11 mmol) in dry dimethylformamide (20 ml) is cooled in an ice-bath under a nitrogen atmosphere. When the internal temperature has dropped below 5 °C,

Table 1. 2,6,7,12-Tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-ones **5a–v** prepared

5	R^1	R^2	R^3	Reaction time (h)	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c] or Lit. m.p. [°C]
a	H	H	H	0.5	95	234–236° (ethanol)	237–238°[3]
b	C_2H_5	H	H	1	91	233–235° (benzene)	235°[6]
c	C_6H_5	H	H	1	88	114–116° (pentane)	$C_{21}H_{18}N_2O$ (314.4)
d	H	CH_3	H	3.5	78	185–187° (diisopropyl ether)	$C_{16}H_{16}N_2O$ (252.3)
e	H	C_6H_5	H	6	65	185–190° (dichloromethane/ethyl acetate)	$C_{21}H_{18}N_2O$ (314.4)
f	H	(*E*)-H_3C—CH=CH—	H	5.5	73	159–161° (ether)	$C_{18}H_{18}N_2O$ (278.4)
g	H	4-H_3CO—C_6H_4	H	8	61	215 (dec) (dichloromethane/ethyl acetate)	$C_{22}H_{20}N_2O_2$ (344.4)
h	H	H	CH_3	1	87	157–159° (diisopropyl ether)	$C_{16}H_{16}N_2O$ (252.3)
i	H	H	C_6H_5	1.5	85	200–201° (ethyl acetate)	$C_{21}H_{18}N_2O$ (314.4)
j	H	H	H_3C—CO—NH	4	88	> 300° (ethyl acetate/methanol)	$C_{17}H_{17}N_3O_2$ (295.3)
k	H	H	C_2H_5	1	91	179–181° (ether)	$C_{17}H_{18}N_2O$ (266.35)
l	H	H	4-O_2N—C_6H_4	2	83	234–236° (ether)	$C_{21}H_{17}N_3O_3$ (359.4)
m	C_2H_5	CH_3	H	8	79	206–207° (dichloromethane/ethyl acetate)	$C_{18}H_{20}N_2O$ (280.4)
n	C_2H_5	C_6H_5	H	8.5	53	118–120° (ethyl acetate)	$C_{23}H_{22}N_2O$ (342.4)
o	C_2H_5	H	C_6H_5	2.5	79	181–183° (ethanol)	$C_{23}H_{22}N_2O$ (342.4)
p	C_2H_5	H	4-O_2N—C_6H_4	3	77	226–228° (ethanol)	$C_{23}H_{21}N_3O_3$ (387.4)
q	C_2H_5	H	H_3C—CO—NH	2.5	78	128–130° (ethyl acetate/methanol)	$C_{19}H_{21}N_3O_2$ (323.4)
r	C_2H_5	H	C_2H_5	3	82	226–228° (ether)	$C_{19}H_{22}N_2O$ (294.4)
s	C_2H_5	H	CH_3	2	87	178–179° (ether)	$C_{18}H_{20}N_2O$ (280.4)
t	H	CH_3	CH_3	12	54[d]	182 (dec) (ether)	$C_{17}H_{18}N_2O$ (266.35)
u	H	C_6H_5	H_3C—CO—NH	12	54[d]	290–292° (ethyl acetate/methanol)	$C_{23}H_{21}N_3O_2$ (371.4)
					8[e]	287–290° (ethyl acetate/methanol)	
v	C_2H_5	C_6H_5	H_3C—CO—NH	12.5	39[d]	238–240° (ethyl acetate/methanol)	$C_{25}H_{25}N_3O_2$ (399.5)
					19[e]	227–228° (ethyl acetate/methanol)	

[a] Yield of isolated product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.25, N ±0.18.
[d] *trans*-Isomer.
[e] *cis*-Isomer.

Table 2. Spectral Data of Compounds **5a–v**

5	I.R. ($CHCl_3$)[a] ν [cm^{-1}]	^{1}H-N.M.R. (solvent/TMS)[b] δ [ppm]
a	3475, 1665, 1650	$CDCl_3$: 2.40–2.80 (m, 4H, 2-H + 3-H); 2.95 (t, 2H, 7-H, J = 6 Hz); 4.15 (t, 2H, 6-H, J = 6 Hz); 5.53 (t, 1H, 1-H, J = 4.5 Hz); 8.10 (br. s, 1H, NH)
b	3500, 1665, 1645	$CDCl_3$: 1.26 (t, 3H, CH_2—CH_3, J = 7 Hz); 2.86 (t, 2H, 7-H, J = 6 Hz); 4.06 (t, 2H, 6-H, J = 6 Hz); 8.23 (br. s, 1H, NH)
c	3450, 1650, 1645	$CDCl_3$: 2.93 (t, 2H, 7-H, J = 6 Hz); 4.23 (t, 2H, 6-H, J = 6 Hz)
d	3470, 1660, 1645	DMSO-d_6: 1.15 (d, 3H, CH_3, J = 7 Hz); 3.74 (ddd, 1H, 6-H, J = 12.3, 6.7, 6.5 Hz); 4.20 (dt, 1H, 6-H, J = 12.3, 5.2 Hz); 5.70 (d, 1H, 1-H, J = 3.3 Hz); 11.30 (br. s, 1H, NH)[c]
e	3470, 1665, 1650	DMSO-d_6: 3.80–4.20 (m, 3H, 2-H + 6-H); 6.00 (d, 1H, 1-H, J = 4.5 Hz); 11.26 (br. s, 1H, NH)
f	3470, 1660, 1650	$CDCl_3$: 1.73 (d, 3H, CH_3, J = 5 Hz); 2.66 (m, 2H, 7-H); 2.97 (t, 2H, 3-H, J = 6.5 Hz); 5.40–5.61 (m, 3H, 1-H + CH=CH); 8.10 (br. s, 1H, NH)
g	3460, 1660, 1645	DMSO-d_6: 3.86 (s, 3H, OCH_3); 4.02 (m, 3H, 2-H + 6-H); 11.26 (br. s, 1H, NH)
h	3465, 1665, 1655	$CDCl_3$: 1.37 (d, 3H, CH_3, J = 6.5 Hz); 3.00 (t, 2H, 7-H, J = 6.9 Hz); 3.76 (dt, 1H, 6-H, J = 12.0, 6.8 Hz); 4.53 (dt, 1H, 6-H, J = 12.0, 5.4 Hz); 5.53 (t, 1H, 1-H, J = 5.4 Hz); 8.07 (br. s, 1H, NH)[c]
i	3470, 1670, 1655	$CDCl_3$: 2.95 (t, 2H, 7-H, J = 6 Hz); 3.85 (t, 1H, 3-H, J = 7 Hz); 4.18 (t, 2H, 6-H, J = 6 Hz); 5.50 (t, 1H, 1-H, J = 4.5 Hz); 8.48 (br. s, 1H, NH)
j	3350, 3220, 1658, 1635[d]	DMSO-d_6: 1.94 (s, 3H, CH_3); 4.49 (dt, 1H, 3-H, J = 13, 8.5 Hz); 5.85 (dd, 1H, 1-H, J = 6, 4 Hz); 8.13 (d, 1H, NH—CO, J = 8.5 Hz); 11.26 (br. s, 1H, NH)
k	3440, 1645	$CDCl_3$: 0.98 (t, 3H, CH_3, J = 7.0 Hz); 2.89 (dd, 2H, 7-H, J = 6.0 Hz); 4.20 (dt, 1H, 6-H, J = 12.0, 5.0 Hz); 4.32 (dt, 1H, 6-H, J = 12.0, 6.0 Hz); 5.52 (t, 1H, 1-H, J = 5.1 Hz); 8.52 (br. s, 1H, NH)[c]
l	3500, 1660, 1520, 1340	DMSO-d_6: 2.95 (t, 2H, 7-H, J = 5 Hz); 5.96 (t, 1H, 1-H, J = 5 Hz); 8.25 (d, $2H_{arom}$, J = 9 Hz)
m	3500, 1645	DMSO-d_6: 1.03 (d, 3H, 2-CH_3, J = 7.0 Hz); 1.17 (t, 3H, CH_2—CH_3, J = 7.0 Hz); 4.83 (ddd, 1H, 6-H, J = 11.7, 4.7, 4.3 Hz); 10.40 (br. s, 1H, NH)
n	3460, 1660, 1645	DMSO-d_6: 1.18 (t, 3H, CH_2—CH_3, J = 7.0 Hz); 3.73 (dd, 1H, 2-H, J = 6.7, 2.3 Hz); 4.87 (ddd, 1H, 6-H, J = 13.3, 4.8, 3.0 Hz); 10.50 (br. s, 1H, NH)
o	3495, 1650, 1600	$CDCl_3$: 1.10 (t, 3H, CH_3, J = 7 Hz); 2.50 (q, 2H, CH_2—CH_3, J = 7 Hz); 2.96 (t, 2H, 7-H, J = 7 Hz); 4.13 (dt, 1H, 6-H, J = 12, 6 Hz); 4.21 (dt, 1H, 6-H, J = 12, 6 Hz); 8.20 (br. s, 1H, NH)
p	3500, 1660, 1520, 1350	DMSO-d_6: 1.06 (t, 3H, CH_3, J = 7 Hz); 2.59 (q, 2H, CH_2—CH_3, J = 7 Hz); 2.90 (t, 2H, 7-H, J = 5.5 Hz)
q	3350, 1660, 1635[d]	DMSO-d_6: 1.15 (t, 3H, CH_3—CH_2, J = 7.0 Hz); 1.93 (s, 3H, CO—CH_3); 4.38 (dt, 1H, 3-H, J = 10.0, 7.7 Hz); 4.64 (dt, 1H, 6-H, J = 12.2, 4.8 Hz); 8.10 (d, 1H, NH—CO) J = 7.7 Hz); 10.42 (br. s, 1H, NH)
r	3500, 1645	$CDCl_3$: 1.05 (t, 3H, 3-CH_2—CH_3, J = 7.0 Hz); 1.36 (t, 3H, 1-CH_2—CH_3, J = 7.0 Hz); 2.62 (q, 2H, 1-CH_2—CH_3, J = 7.0 Hz); 2.92 (t, 2H, 7-H, J = 7.0 Hz); 4.11 (m, 2H, 6-H); 8.10 (br. s, 1H, NH)
s	3500, 1645	$CDCl_3$: 1.28 (d, 3H, 3-CH_3, J = 6 Hz); 1.34 (t, 3H, CH_2—CH_3, J = 7 Hz); 2.60 (q, 2H, CH_2—CH_3, J = 7 Hz); 2.90 (dd, 2H, 7-H, J = 6 Hz); 3.72 (dt, 1H, 6-H, J = 12, 6 Hz); 4.40 (dt, 1H, 6-H, J = 12, 5 Hz); 8.06 (br. s, 1 H, NH)
t	3470, 1660, 1650	DMSO-d_6: 1.15 (d, 6H, 2-CH_3 + 3-CH_3) J = 6.1 Hz); 2.31 (m, 2H, 2-H + 3-H); 2.86 (t, 2H, 7-H, J = 6.5 Hz); 3.67 (dt, 1H, 6-H, J = 12.5, 5.5 Hz); 4.23 (dt, 1H, 6-H, J = 12.5, 6.2 Hz); 5.70 (d, 1H, 1-H, J = 5.5 Hz); 11.25 (br. s, 1H, NH)[c,e]
u	3380, 3220 1675, 1660	DMSO-d_6: 1.75 (s, 3H, CH_3); 3.96 (dd, 1H, 2-H, J = 13.5, 2.8 Hz); 4.66 (dd, 1H, 3-H, J = 13.5, 9.6 Hz); 5.84 (d, 1H, 1-H, J = 2.8 Hz); 8.14 (d, 1H, NH—CO, J = 9.6 Hz); 10.28 (br. s, 1H, NH)[c,e] DMSO-d_6: 1.91 (s, 3H, CH_3); 4.10 (t, 1H, 2-H, J = 7.1 Hz); 4.70 (m, 1H, 6-H); 4.95 (dd, 1H, 3-H, J = 7.1, 6.8 Hz); 6.14 (d, 1H, 1-H, J = 6.8 Hz); 11.37 (br. s, 1H, NH)[c,f]
v	3500, 3440, 1670	DMSO-d_6: 1.06 (t, 3H, 1-CH_2—CH_3, J = 7.3 Hz); 1.86 (s, 3H, CO—CH_3); 3.67 (d, 1H, 2-H, J = 2.7 Hz); 4.43 (dd, 1H, 3-H, J = 7.8, 2.7 Hz); 4.69 (dt, 1H, 6-H, J = 12.4, 7.8 Hz); 8.45 (d, 1H, NH—CO, J = 7.8 Hz); 10.54 (br. s, 1H, NH)[c,e] 1.15 (t, 3H, CH_2—CH_3, J = 7.3 Hz); 2.00 (s, 3H, CO—CH_3); 3.97 (d, 1H, 2-H, J = 6.8 Hz); 4.81 (t, 1H, 3-H, J = 6.8 Hz); 10.45 (br. s, 1H, NH)[c,f]

[a] Recorded on a Perkin-Elmer 257 spectrophotometer.
[b] ^{1}H-N.M.R. spectra were taken on a Bruker WP 80 (80 MHz) spectrometer unless otherwise stated.
[c] 200 MHz spectra.
[d] In Nujol mull.
[e] *trans*-Isomer.
[f] *cis*-Isomer.

the azide **3** (3.03 g, 11 mmol) is added at a rate so that the temperature does not exceed 10 °C (20 min). After the addition is complete, the dark reaction mixture is allowed to warm to room temperature and stirring is continued for additional 100 min. The solvent is then evaporated in vacuo (< 40 °C) and the brown solid residue is purified by flash chromatography[14] on silica gel S (Merck, 230–400 mesh) using dichloromethane/ethyl acetate (9:1) as eluent. Recrystallization from ether affords pure **5s** as white needles; yield: 2.44 g (87%); m.p. 178–179 °C; R_f = 0.32 (dichloromethane/ethyl acetate, 9:1).

$C_{18}H_{20}N_2O$	calc.	C 77.11	H 7.19	N 9.99
(280.4)	found	77.21	7.18	10.01

U.V. (C_2H_5OH): λ_{max} = 231 (log ε = 4.46), 309 (4.34), 321 nm (4.31).
M.S., *m/e* (rel. int. %) = 280 (70), 265 (100), 251 (41), 223 (15), 167 (24).

For the chromatographic purification of **5j**, **5q** and **5u**, chloroform/ethyl acetate (3:7) is used as eluent.

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