Tetrahedron. Vol. 27, pp. 3465 to 3476. Pergamon Press 1971. Printed in Great Britain

SYNTHESIS OF ANALOGUES OF CRYPTOPLEURINE

S. FOLDEAK*

School of Pharmacy, Portsmouth Polytechnic

(*Received in the UK* 13 *March* 1971; *Accepted for publication* 7 *April* 1971)

Abstract—New analogues of cryptopleurine with different aromatic methoxyl and chloro substituents have been synthesized. Intermediate isomeric 1-hydroxyphenanthro[9.10*b*]quinolizidines have been isolated and characterized. Yields in the Pschorr reaction have been improved by the novel use of sulphite ion. Some of the compounds have been found to have antifungal activity.

PHENANTHROQUINOLIZIDINE alkaloids from *Cryptocarpa pleurosperma* (cryptopleurine,[1] I, $R_1 = R_2 = R_3 = OCH_3$, $R_4 = R_5 = R_6 = R_7 = H$; cryptopleuridine[2] I, $R_1R_2 = OCH_2O$, $R_3 = OCH_3$, $R_4 = R_5 = R_6 = H$, $R_7 = OH$) and the closely related phenanthroindolizidine (II) alkaloids from *Tylophora* species[3] are of interest not only because of problems of structure and stereochemistry but also because of a range of biological activities. Vesicant,[4] mitotic,[5] anti-leukaemic[6] and selective antifungal[7] effects have been reported among others. Synthesis of new anologues of cryptopleurine with different substituents in the aromatic rings was therefore undertaken. The intermediate alcohols ($R_6 = OH$) were isolated and their stereoisomers separated and characterized.

Cryptopleurine has recently been synthesized[8] by a route based on biogenetic considerations, but the present work followed essentially the earlier route of synthesis[9,10] with some modifications by which yields were improved. In particular the synthesis of substituted phenanthrene-9-carboxylic acids by the Pschorr[9] reaction is usually effected from the appropriate 2-amino-α-phenylcinnamic acids by diazotisation followed, without isolation of the diazonium compound, by cyclization by a variety of reagents. Reaction times are long and yields variable[12] between 25 and 80%. This step was therefore investigated and it was found firstly that isolation of the diazonium compounds as the quite stable hydrogen sulphates was advantageous and secondly that the cyclization was very efficiently promoted by sulphite ion giving 80% overall yields of phenanthrene acids. While the work was in progress promotion of the cyclization by potassium iodide was reported.[13] Combination of these two methods was found to give optimum yields. The mechanism whereby these reagents promote cyclization is unknown, but may resemble that proposed[12,14] for hypophosphinic acid, which functions as a reducing agent.

The acids were converted to acid chlorides with oxalyl chloride, esterified, reduced with LAH and treated with phosphorus tribromide to give the corresponding bromomethyl derivatives (III, R = Br). These reacted with ethyl pipecolinate to give the esters (IV, R = Et) which were hydrolyzed to the acids (IV, R = H). In polyphosphoric acid these gave the ketones (V) in about 80% yield. The ketones are

* Present address: Institute of Organic Chemistry, Josef Attila University, Szeged, Hungary.

sensitive to air and light, especially in solution, and care must be taken during their isolation.

The reported[9,10] preparations employed direct reduction of the ketones by the Wolff-Kishner method, which, however, also removes OMe groups.[9] Reduction to the alcohols (VI) was therefore effected by a variety of methods all of which gave mixtures of isomeric alcohols designated A and B, separable by TLC. LAH reduction gave a mixture of 60% A and 40% B generally unsuitable for preparation separation. Catalytic reduction with Adams catalyst gave a mixture with 75% A with 25% B from which pure A was obtained. In contrast the use of Pd-C in acid media gave 30% A and 70% B allowing preparation of pure B. Under these conditions aromatic halogen is removed, so that B isomers of halogenated compounds could not be obtained in this way.

TABLE 1. IR ABSORPTION OF HYDROXY GROUP IN PHENANTHROQUINOLIZIDINES

Compound	Free OH			Bonded OH		
I. R_6 = OH, R_4 = R_5 = R_7 = H	ν_{max} cm^{-1}	ε^a_{max}	$\Delta\nu^a_{\frac{1}{2}}$ cm^{-1}	ν_{max} cm^{-1}	ε^a_{max}	$\Delta\nu^a_{\frac{1}{2}}$ cm^{-1}
A(R_1 = R_2 = R_3 = H)	3600	weak	—	3566	24	64
B(R_1 = R_2 = R_3 = H)	3600	65	16·5	—	—	—
A(R_1 = R_2 = OCH_3 R_3 = H)	—	—	—	3568	23	63
B(R_1 = R_2 = OCH_3 R_3 = H)	3598	72	13·8	—	—	—
A(R_1 = R_2 = H R_3 = Cl_1)	—	—	—	3565	27	68
B(R_1 = R_2 = H R_3 = OCH_3	3602	73	16·5	—	—	—

Spectra were run in a 4 cm cell at concentrations around 0·001 molar. Intensity data are approximate because of the low solubility.

The configurations of the two isomers were determined by consideration of the IR spectra (Table 1) in dilute solution in carbon tetrachloride. All the compounds show strong Bohlmann[15] bands indicating that both isomers have predominantly *trans* ring fusion. The configuration of the OH groups can therefore be determined from the presence or absence of intramolecular H-bonding.[16,17,18,19]

The A isomers show a broad band around 3566 cm^{-1} indicative of intramolecularly bonded OH. Examination of Dreiding models suggests that this is due to H-bonding with the ring nitrogen, possible only with the OH in a pseudoaxial configuration *trans* to the bridgehead hydrogen. The closest approach of the hydroxyl H to the nitrogen in models is about 2·8 Å; at least 0·3 Å greater than that in 1-hydroxyquinolizidines which have been found[19] to show a hydroxyl-nitrogen bonded band at 3526 cm^{-1}. The H-bond in the A isomers would therefore be expected to be weaker and to occur at the observed higher frequency. It also seems reasonable to attribute the small free OH band near 3600 cm^{-1} to a small proportion of non bonded pseudoaxial *trans* ring molecules rather than equilibrium with the pseudoequatorial *cis* ring.

The B isomers show a single sharp OH band around 3600 cm^{-1} with much the same intensity in each case. These are clearly free OH bands, which with the absence

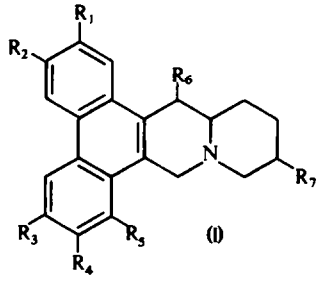
of any detectable bands at lower frequencies indicate a pseudoequatorial configuration *cis* to the bridgehead hydrogen. The absence of detectable H-bonding also indicates the lack of an equilibrium between the two isomers. Stable conformations of dibenzoquinolizidine have been reported.[20]

The stereospecific nature of the reductions agree with previously reported reductions of ketoquinolizidine[19,20,22] and ketoindolizidine but do not follow the postulated[21] "anchor effect" in quinolizidine. It seems likely that the two benzene rings alter the interaction with the catalyst surface. The two isomers are not interconverted under hydrogenation conditions.

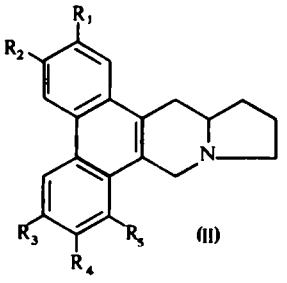
The alcohols were dehydrated with perchloric acid to give the quaternary compounds (VII). These show IR absorption at around 1700 cm^{-1} like the quinolizidine immonium compounds previously described[23,24] and also like them showed a shift to around 1630 cm^{-1} in base indicative of isomerization to an eneamine. The quaternary compounds were reduced with LAH or sodium borohydride to the phenanthroquinolizidines (VIII). Reduction with LAH was slow and caused some loss of aromatic halogen. Reduction with sodium borohydride was fast and completely hydrogenolyzed aromatic halogen. The same phenanthroquinolizidine was obtained from either of the isomeric alcohols or by direct reduction[10] of the corresponding ketone.

TABLE 2. ACTIVITY OF PHENANTHRO[9.10*b*]QUINOLIZIDINES AGAINST *Actinomucor repens*

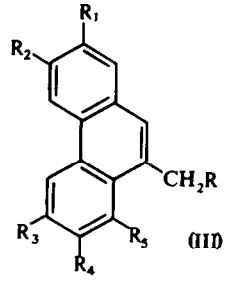
Formula I, R_7 = H						Isomer	Min. inhib. Conc. μg/ml
R_1	R_2	R_3	R_4	R_5	R_6		
H	H	H	H	H	OH	B	20
H	H	H	H	H	OH	A	5
OCH_3	OCH_3	H	H	H	OH	B	5
OCH_3	OCH_3	H	H	H	OH	A	2·5
H	H	OCH_3	H	H	OH	B	5
H	H	OCH_3	H	H	OH	A	5
H	H	OCH_3	OCH_3	H	OH	A + B	10
H	H	H	H	OCH_3	OH	B	∞
H	H	Cl	H	H	OH	A	∞
OCH_3	OCH_3	Cl	H	H	OH	A	0·6
OCH_3	OCH_3	OCH_3	H	H	OH	—	0·16
H	H	H	H	H	H	—	5
OCH_3	OCH_3	H	H	H	H	—	0·05
H	H	OCH_3	H	H	H	—	0·6
H	H	OCH_3	OCH_3	H	H	—	Results awaited
H	H	H	H	OCH_3	H	—	20
OCH_3	OCH_3	OCH_3	H	H	H	—	0·04



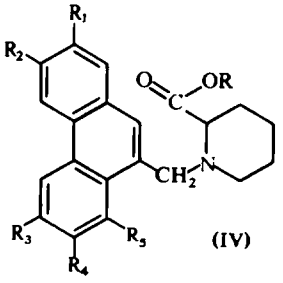
(I)



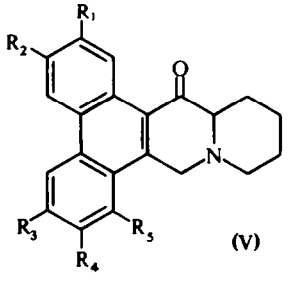
(II)



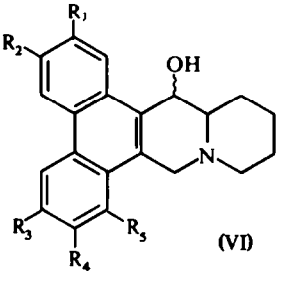
(III)



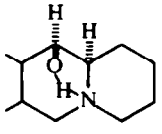
(IV)



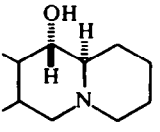
(V)



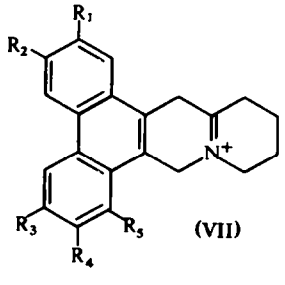
(VI)



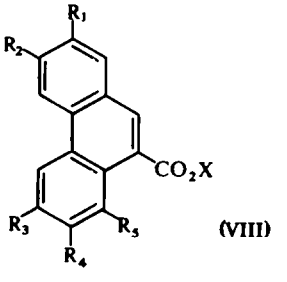
(VIA)



(VIB)



(VII)



(VIII)

EXPERIMENTAL

M.ps are uncorrected. IR spectra were determined on a Perkin–Elmer 257 spectrometer as discs (KCl) or mulls (Nujol), or on a Perkin–Elmer 521 grating spectrometer for solns in CCl_4. The UV spectra were determined on a Unicam SP800.

Substituted phenanthrene-9-carboxylic acids—General procedure. The appropriate α-phenyl-2-amino-cinnamic acid (0·5 mol) was suspended or dissolved in acetone (600 ml), cooled (ice bath) stirred and 5N H_2SO_4 (21 ml) added followed by amyl nitrite (16 ml) in 4 portions over 20 min. The mixture was stirred at 2–5° for 2 hr and then filtered. The solid was washed with cold acetone (20 ml) and dried *in vacuo* at 40°, yields 80–95%. In this way was prepared α-*(4-chlorophenyl)-2-diazoniumcinnamic acid hydrogen sulphate*, yellow plates from H_2O/Me_2CO m.p. 90° ν^{Nujol}_{max} 2265 cm^{-1}. (Found: C, 47·0; H, 3·2; N, 7·4. $C_{15}H_{11}ClN_2SO_6$ requires: C, 47·1; H, 2·9; N, 7·3%). Other diazonium compounds were used without further purification. The diazonium compound (14 g) was suspended in acetone (150 ml), cooled (ice bath), stirred and a soln of KI (6 g) in water (10 ml) added in 3 portions over 5 min, followed by 40% $NaHSO_3$ aq (1 to 2 ml) in water (10 ml). The mixture was stirred at room temp for 50 min and then sufficient (10 to 70 ml) water added to obtain a ppt which was collected, washed with water, dried and crystallized from solvent shown, yields 50–90%. In this way were prepared the compounds in Table 3.

Ethyl phenanthrene-9-carboxylates—General procedure. The acid (0·25 mol) and oxalyl chloride (0·75 mol) in dry $CHCl_3$ (80 ml) were kept at room temp for 30 min and then at reflux for 2 hr. The solvent was removed *in vacuo* and the residual solid kept with EtOH (70 ml) at reflux for 4 hr, filtered hot and set aside to crystallize. The product was recrystallized from solvent shown. In this way were prepared the esters in Table 3.

9-Hydroxymethylphenanthrenes—General procedure. The ester (0·02 mol) was added over 5 min to LAH (1·8 g, 0·048 mol) in THF (100 ml) and the soln stirred for 3 hr at room temp. It was then treated with EtOH and water filtered. The ppt was washed well with THF (and also boiled with $CHCl_3$ in the preparation of the 2,3-dimethoxy derivative). The combined solns were concentrated *in vacuo* and the residue crystallized from the solvents shown. In this way were prepared the compounds in Table 4. 9-Hydroxymethylphenanthrene itself was prepared by Raney nickel catalyzed reduction of phenanthrene-9-aldehyde.[26]

9-Bromomethylphenanthrenes—General procedure. The hydroxymethyl compound (0·02 mol) in dry $CHCl_3$ (70 ml) was cooled (ice bath) stirred and PBr_3 (0·02 mol) in dry $CHCl_3$ (15 ml) added over 5 to 10 min. The mixture was kept at room temp for 40 min and at 40 to 45° for 15 to 20 min. It was then poured onto ice. The $CHCl_3$ layer was separated, washed twice with water, dried (Na_2SO_4) concentrated *in vacuo* and the residue crystallized from the solvent shown. In this way were prepared the compounds in Table 5.

9-(2'-Ethoxycarbonylpiperidino) methylphenanthrenes —General procedure. The bromomethyl compound (0·01 mol) ethyl pipecolate[22] (0·02 mol) and benzene (50 ml) were kept at reflux for 1·5 hr. The warm soln was filtered and the solid washed with benzene. The combined filtrate and washings were concentrated *in vacuo* and the residue crystallized from solvent as shown. In this way were prepared the compounds in Table 6. The two compounds which did not crystallize (but which showed only one spot on TLC) were used in the next stage without further purification.

1-Oxophenanthro[9.10b]quinolizidines—General procedure. The piperidinomethylphenanthrene (0·01 mol), EtOH (50 ml), KOH (4·0 g) and water (6 ml) were kept at reflux for 20 min. The clear soln was diluted with water (25 ml) and AcOH (6 ml) added. The ppt was collected and dried well at 60 to 80°. (The 2,3-dimethoxy and 2,3-dimethoxy-6-chloro derivatives are more conveniently isolated as K salts), yields quantitative. This acid (0·01 mol) and polyphosphoric acid (20 g) were kept under N_2 on an oil bath at 110–120° for 5 to 6 hr and then cooled. The brown viscous soln was poured onto ice water (150 ml) and made alkaline (pH 8 to 9) with 50% NaOH aq taking especial care to keep the temp below 40°. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* at a maximum temp of 35° to give a solid which was crystallized from solvent shown. In this way were prepared the compounds in Table 7. The 6-chloro compound required heating for 20 hr with polyphosphoric acid.

1-Hydroxyphenanthro[9.10b]quinolizidines. Three general methods were used. The ratio of A to B isomers produced was established by TLC on Kieselgel-G nach Stahl (Merck) developing with benzene (20):EtOH(1):MeOH(1) mixture and reading density on a Vitatron.

(A) *Reduction with Adams catalyst.* The ketone (380 mg) in THF (50 ml) and EtOH (20 ml) with Adams catalyst (380 mg) was hydrogenated at room temp and 3 atm pressure for 8 hr. The soln was filtered and concentrated *in vacuo*. The residue was suspended in acetone, in which oily products rapidly solidified, and filtered to give a white solid. A/B ratio about 75:25.

TABLE 3. PHENANTHRENE CARBOXYLATES

R_1	R_2	R_3	R_4	R_5	Ester X = C_2H_5 Formula VIII	Found % C	Found % H	Required % C	Required % H	Ester X = C_2H_5 m.p. °C	Ester X = C_2H_5 Lit. m.p.	Ester X = C_2H_5 Recryst.	Acid X = H Yield %	Acid X = H m.p. °C	Acid X = H Lit. m.p.	Acid X = H Recryst.	Acid X = H Yield %
H	H	H	H	H													
OCH_3	OCH_3	H	H	H						131	124–126[28]	EtOH	90	272	267[29]	HOAc	70
H	H	OCH_3	H	H						53	43–45	$CHCl_3$/EtOH	86	241–242	239[31]	HOAc	88
H	H	OCH_3	OCH_3	H	$C_{19}H_{18}O_4$	72·9	6·2	73·5	5·8	113	—		85	248–249	252[29]	HOAc	48
H	H	H	H	OCH_3	$C_{18}H_{16}O_3$	77·4	5·3	77·1	5·7	62–63	—	EtOH/H_2O	70	216	215[31]	—	88
H	H	Cl	H	H	$C_{17}H_{13}ClO_2$					95	94–95[30]	EtOH	80	297–298	291–292[30]	EtOH	90
OCH_3	OCH_3	Cl	H	H	$C_{19}H_{17}ClO_4$	66·4	4·8	66·2	5·0	148	—	$CHCl_3$/EtOH	80	276–277	268–269[32]	—	Quant.
OCH_3	OCH_3	OCH_3	H	H						135–136	136–137[10]	EtOH	80	217	217–218[10]	HOAc	65

TABLE 4. HYDROXYMETHYLPHENANTHRENES

R_1	R_2	R_3	R_4	R_5	Formula III. R = OH	Formula % C	Formula % H	Required % C	Required % H	m.p. °C	Lit. m.p. °C	Recryst.	Yield %
H	H	H	H	H	$C_{15}H_{12}O$	—	—	–	—	152–153	149[33]	PhH	80
OCH_3	OCH_3	H	H	H	$C_{17}H_{16}O_3$	-	—	—	-	204	194–196[28]	EtOH	92
H	H	OCH_3	H	H	$C_{16}H_{14}O_2$	—	-	—	—	147–148	143–145[28]	EtOH	88
H	H	OCH_3	OCH_3	H	$C_{17}H_{16}O_3$	75·8	6·2	76·1	6·0	158–159	—	EtOH	86
H	H	H	H	OCH_3	$C_{16}H_{14}O_2$	80·3	6·3	80·6	5·9	120–121	—	EtOH	81
H	H	Cl	H	H	$C_{15}H_{11}ClO$	73·8	4·5	74·2	4·6	155	–	EtOH	85
OCH_3	OCH_3	Cl	H	H	$C_{17}H_{15}ClO_3$	67·4	4·7	67·4	4·9	198–199	—	EtOH	90
OCH_3	OCH_3	OCH_3	H	H	$C_{18}H_{18}O_4$	—	—	—	—	186–187	184–187[7]	EtOH	85

TABLE 5. BROMOMETHYLPHENANTHRENES

R_1	R_2	R_3	R_4	R_5	Formula III, R = Br	Found %		Required %		m.p. °C	Lit. m.p. °C	Recryst.	Yield %
						C	H	C	H				
H	H	H	H	H	$C_{15}H_{11}Br$	66·2	4·0	66·4	4·1	122–123	114–115[33]	PhH	80
OCH_3	OCH_3	H	H	H	$C_{17}H_{15}BrO_2$	61·3	4·6	61·6	4·6	159–160	162–163[28]	PhH	80
H	H	OCH_3	H	H	$C_{16}H_{13}BrO$	63·3	4·2	63·8	4·3	125–126	121–122[28]	PhH	80
H	H	OCH_3	OCH_3	H	$C_{17}H_{15}BrO_2$	62·2	4·7	61·6	4·6	174–175	—	PhH	85
H	H	H	H	OCH_3	$C_{16}H_{13}BrO$	63·5	4·4	63·8	4·3	124–126	—	PhH	80
H	H	Cl	H	H	$C_{15}H_{10}BrCl$	58·3	3·2	58·9	3·2	173	—	$CHCl_3$	95
OCH_3	OCH_3	Cl	H	H	$C_{17}H_{14}BrClO_2$	55·7	3·7	55·8	3·9	210	—	PhH	83
OCH_3	OCH_3	OCH_3	H	H	$C_{18}H_{17}BrO_3$	60·0	4·8	59·8	4·7	157	—	PhH	85

TABLE 6. (ETHOXYCARBONYLPIPERIDINO)METHYLPHENANTHRENES

R_1	R_2	R_3	R_4	R_5	Formula IV. R = C_2H_5	Found %			Required %			m.p. °C	Recryst.	Yield %
						C	H	N	C	H	N			
H	H	H	H	H	$C_{23}H_{25}NO$	79·5	6·7	4·1	79·5	7·2	4·0	90	EtOH	90
OCH_3	OCH_3	H	H	H	$C_{25}H_{28}NO_4$	73·3	7·1	3·5	73·7	6·9	3·4	117–117·5	EtOH	95
H	H	OCH_3	H	H	$C_{24}H_{27}NO_3$	—	—	—	—	—	—	Oil	—	90
H	H	OCH_3	OCH_3	H	$C_{25}H_{28}NO_4$	73·2	7·1	3·3	73·7	6·9	3·4	98–99	EtOH	90
H	H	H	H	OCH_3	$C_{24}H_{27}NO_3$	—	—	—	—	—	—	Oil	—	90
H	H	Cl	H	H	$C_{23}H_{24}ClNO_2$	71·9	7·1	3·4	72·3	6·3	3·7	83–84	EtOH	96
OCH_3	OCH_3	Cl	H	H	$C_{25}H_{28}ClNO_4$	67·2	6·4	2·9	67·9	6·4	3·2	191–192	PhH	91
OCH_3	OCH_3	OCH_3	H	H	$C_{26}H_{31}NO_5$	71·1	7·4	3·5	71·4	7·1	3·2	145	EtOH	95

TABLE 7. OXOPHENANTHRO[9.10*b*]QUINOLIZIDINES

R_1	R_2	R_3	R_4	R_5	Formula V	Found %			Required %			m.p. °C	Lit. m.p. °C	Recryst.	ν_{max} cm^{-1}	Yield %
						C	H	N	C	H	N					
H	H	H	H	H	$C_{21}H_{19}NO$	-	—	—	—	—	—	173–174	168–169[6]	CH_2Cl_2–EtOH	1676	6
OCH_3	OCH_3	H	H	H	$C_{23}H_{23}NO_3$	76·1	6·8	3·6	76·4	6·4	3·6	175–176	—	CH_2Cl_2–Me_2CO	1670	80
H	H	OCH_3	H	H	$C_{22}H_{21}NO_2$	79·9	6·4	3·9	79·7	6·4	4·2	142	—	Me_2CO	1670	60
H	H	OCH_3	OCH_3	H	$C_{23}H_{23}NO_3$	76·0	6·6	3·8	76·4	6·4	3·9	212–213	–	Me_2CO	1662	70
H	H	H	H	OCH_3	$C_{22}H_{21}NO_2$	79·0	6·4	3·8	79·7	6·4	4·2	150–152	—	Me_2CO	1660	50
H	H	Cl	H	H	$C_{21}H_{18}ClNO$	75·2	5·5	3·8	75·1	5·4	4·2	112–113	—	CH_2Cl_2–Me_2CO	1675	71
OCH_3	OCH_3	Cl	H	H	$C_{23}H_{22}ClNO_3$	69·2	5·4	3·2	69·8	5·6	3·5	225–226	—	CH_2Cl_2–Me_2CO	1666	69
OCH_3	OCH_3	OCH_3	H	H	$C_{24}H_{25}NO_4$	—	—	—	—	—	–	158–159	155[6]	PhH	1672	76

TABLE 8. HYDROXYPHENANTHRO[9.10*b*]QUINOLIZIDINES

R_1	R_2	R_3	R_4	R_5	Fomula VI	Found %			Required %			Isomer	m.p. °C (decomp.)	Yield %	Recryst.	Method
						C	H	N	C	H	N					
H	H	H	H	H	$C_{21}H_{21}NO$	83·3	7·0	4·4	83·1	7·0	4·6	A	231–233	63	PhH	Cat(A)
H	H	H	H	H	$C_{21}H_{21}NO$	83·4	7·1	4·6	83·1	7·0	4·6	B	208–209	68	PhH–EtOH	Cat(B)
OCH_3	OCH_3	H	H	H	$C_{23}H_{25}NO_3$	75·9	7·1	3·7	76·0	6·9	3·8	A	250–251	45	PhH	LAH(C)
OCH_3	OCH_3	H	H	H	$C_{23}H_{25}NO_3$	76·1	6·8	3·8	76·0	6·9	3·8	B	266–267	60	PhH–EtOH	Cat(B)
H	H	OCH_3	H	H	$C_{22}H_{23}NO_2$	78·8	7·0	4·2	79·2	6·9	4·2	A	208–209	65	PhH	Cat(A)
H	H	OCH_3	H	H	$C_{22}H_{23}NO_2$	78·9	6·8	4·4	79·2	6·9	4·2	B	215–216	80	PhH–EtOH	Cat(B)
H	H	OCH_3	OCH_3	H	$C_{23}H_{25}NO_3$	76·2	6·8	3·7	76·0	6·9	3·8	A	201–203	50	PhH–EtOH	Cat(A)
H	H	OCH_3	OCH_3	H	$C_{23}H_{25}NO_3$	76·1	6·9	3·6	76·0	6·9	3·8	B	227–228	50	PhH	Cat(B)
H	H	H	H	OCH_3	$C_{22}H_{23}NO_2$	79·2	6·9	4·2	79·2	6·9	4·2	B	253–255	60	$CHCl_3$–PhH	Cat(B)
H	H	Cl	H	H	$C_{21}H_{20}ClNO$	74·2	6·2	4·3	74·6	6·0	4·1	A + B	238–242	65	PhH	LAH(C)
OCH_3	OCH_3	Cl	H	H	$C_{23}H_{24}ClNO_3$	69·7	6·3	3·2	69·4	6·1	3·5	A + B	233–235	60	PhH–petrol	LAH(C)
OCH_3	OCH_3	OCH_3	H	H	$C_{24}H_{27}NO_4$	72·8	6·8	3·2	73·2	6·9	3·5	A	236–237	40	Me_2CO	Cat(A)
OCH_3	OCH_3	OCH_3	H	H	$C_{24}H_{27}NO_4$	72·7	6·9	3·7	73·2	6·9	3·5	B	208–209	50	Me_2CO	Cat(B)

TABLE 9. PHENANTHRO[9.10*b*]QUINOLIZIDINES

R_1	R_2	R_3	R_4	R_5	ν_{max} immonium cm^{-1}	Fomula % I. $R_6 = R_7 = H$	Found %			Required %			m.p. °C	Lit. m.p.	Yield %	Recrystl.
							C	H	N	C	H	N				
H	H	H	H	H	1705								174–175	168–170[6]	74	Me_2CO
OCH_3	OCH_3	H	H	H	1710	$C_{23}H_{25}NO_2$	79·2	7·3	4·0	79·5	7·3	4·0	188–189	—	88	PhH–EtOH
H	H	OCH_3	H	H	1704	$C_{22}H_{23}NO$	83·3	7·2	4·5	83·2	7·3	4·4	161	—	82	PhH–EtOH
H	H	OCH_3	OCH_3	H	1708	$C_{23}H_{25}NO_2$	79·0	6·9	4·2	79·5	7·3	4·0	165–166	—	76	PhH–petrol
H	H	H	H	OCH_3	1712	$C_{22}H_{23}NO$	83·5	7·1	4·3	83·2	7·3	4·4	170	–	69	Me_2CO
OCH_3	OCH_3	OCH_3	H	H	1700								197–198	199–201[7]	56	Me_2CO

(B) *Reduction with palladium catalyst.* The ketone (380 mg) in THF (50 ml), EtOH (50 ml), water (5 ml) and 0·5N HCl (4 ml) with 10% Pd–C (380 mg) was hydrogenated at room temp and 1 atm for 16 hr. The soln was filtered, concentrated *in vacuo* to one third of its volume and water (50 ml) and 2N NaOH (2 ml) added. The mixture was extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and concentrated to give a residue which was treated with acetone as above. A/B ratio about 22:78.

(C) *Reduction with complex hydride.* The ketone (380 mg) was added to LAH (200 mg) suspended in THF (30 ml) and the mixture was stirred at room temp for 40 to 50 min. It was then cooled (ice bath), treated cautiously with EtOH and then water, filtered and washed with THF. The combined filtrate and washings were concentrated *in vacuo* and the residue treated with acetone as above. A/B ratio about 60:40.

In these ways were prepared the compounds shown in Table 8. Pure isomers were separated by repeated recrystallization from solvents shown. All compounds decomposed at the temps given for m.p.

Phenanthro[9.10b]*quinolizidine.* Phenanthro[9.10*b*]quinolizidin-1-ol, A isomer (100 mg), AcOH (20 ml) and 60% perchloric acid (0·3 ml) were kept at 135° (bath) for 3 hr. The ppt was then collected and washed with EtOH. White solid m.p. 325° (dec). This compound (105 mg) and LAH (100 mg) in THF (5 ml) were kept at room temp for 8 hr. The mixture was treated as in method C above and the resultant solid crystallized from acetone to give the *phenanthroquinolizidine* m.p. 174–175° (60 mg). The m.p. was not depressed by product similarly obtained from the B isomer, or by product obtained by reduction of the immonium salt with borohydride ethanol at room temp for 50 min. The m.p. was also not depressed by material prepared as previously described.[9]

In this way were obtained also the compounds shown in Table 9. Reduction of halogenated compounds with borohydride gave the corresponding dehalogenated derivatives, identified by mixed m.p. and elemental analysis. Reduction of halogenated compounds with LAH gave mixtures.

Acknowledgements—I thank the President and Governors of Portsmouth Polytechnic for a Research Fellowship during which this work was carried out, and Professor K. Kovacs for the opportunity to work with alkaloids. I am indebted to Mr. A. Wood of the Tropical Products Institute for determination of the high resolution IR spectra, and to Dr. L. Ferenczy of the Josef Atila University of Szeged for determination of the antifungal activity. I am grateful to Dr. E. Crundwell for help and advice, and for his assistance in preparing the manuscript.

REFERENCES

[1] E. Gellert and N. V. Riggs, *Austral. J. Chem.* **1**, 113 (1954);
E. Gellert, *Ibid.* **9**, 489 (1956);
H. Hoffman, *Austral. J. Expt. Biol. Med. Sci.* **30**, 541 (1952);
N. K. Hart, S. R. Johns and J. A. Lamberton, *Austral. J. Chem.* **21**, 2579 (1968)
[2] S. R. Johns, J. A. Lamberton, A. A. Sioumis and R. I. Willing, *Ibid.* **23**, 353 (1970)
[3] T. R. Govindachari, *The Alkaloids* (Ed. R. H. Manske) Vol. 9. p. 517. Academic Press, New York (1967)
[4] I. S. de la Lauda, *Austral. J. Expt. Biol. Med. Sci.* **26**, 181 (1948)
[5] C. Barnard, *Austral. J. Sci.* **12**, 30 (1949)
K. W. Cleland, *Ibid.* **12**, 144 (1950)
[6] E. Gellert and R. Rudzats, *J. Medic. Chem.* **7**, 361 (1964)
[7] L. Ferenczy *et al.*, *Lecture abstract of the First International Congress of Plant Pathology.* London, 14–16. July (1968)
[8] T. M. Paton, P. L. Pauson and T. S. Stevens, *J. Chem. Soc.* 1309 (1969)
[9] P. Marchini and B. Belleau, *Canad. J. Chem.* **36**, 581 (1958)
[10] C. K. Bradsher and H. Berger, *J. Am. Chem. Soc.* **79**, 3287 (1957)
[11] I. Leake, *Chem. Rev.* **56**, 27 (1956)
[12] DeLos F. Detar, *The Pschorr Synthesis* in Organic Reactions IX. p. 409. Wiley, New York (1957)
[13] B. Chauncy and E. Gellert, *Austral. J. Chem.* **22**, 993 (1969)
[14] N. Kornblum, G. D. Cooper and J. E. Taylor, *J. Am. Chem. Soc.* **72**, 3013 (1950)
[15] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958)
[16] H. S. Aaron, Ch. P. Rader and G. E. Wicks, *J. Org. Chem.* **31**, 3502 (1966)
[17] H. S. Aaron, *Chem. & Ind.* 1338 (1965)

[18] Ch. P. Rader, R. L. Young and H. S. Aaron, *J. Org. Chem.* **30**, 1536 (1965)
H. S. Aaron, C. Parker Ferguson and Ch. P. Rader, *J. Am. Chem. Soc.* **89**, 1431 (1967)
[19] A. S. Aaron, G. E. Wicks, Ch. P. Rader, *J. Org. Chem.* **29**, 2248 (1964)
A. S. Aaron and C. P. Ferguson, *Tetrahedron Letters*, 6191 (1968)
[20] T. Takemoto, Y. Kondo, *Pharm. Soc. Japan* **83**, 162 (1963)
[21] Ch. P. Rader, G. E. Wicks, R. L. Young, H. S. Aaron, *J. Org. Chem.* **29**, 2252 (1964)
[22] H. Mohrle, Chr. Karl and U. Scheidegger, *Tetrahedron* **24**, 6813 (1968)
[23] N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.* **76**, 2781 (1954)
[24] N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *Ibid.* **77**, 439 (1955)
[25] T. R. Govindachari, M. V. Laksmikanthan, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958)
T. R. Govindachari, I. S. Ragada, N. Viswanathan, *J. Chem. Soc.* 1357 (1962)
[26] A. Rieche, H. Gross and E. Hofl, *Chem. Ber.* **93**, 88 (1960)
[27] W. A. Reckov and D. S. Tarbel, *J. Am. Chem. Soc.* **74**, 4960 (1952)
[28] C. K. Bradsher and R. B. Desai, *Rec. Trav. Chim.* **83**(6), 593 (1954)
[29] J. W. Cook, J. D. London and R. K. Razdan, *J. Chem. Soc.* 4234 (1954)
[30] P. Nylen, *Chem. Ber.* **53B**, 158 (1920)
[31] R. Pschorr, O. Wolfes and W. Buchow, *Dtsch. Chem. Ges.* **33**, 176 (1900)
[32] E. L. May, *J. Am. Chem. Soc.* **69**, 717 (1947)
[33] E. Mosettig and J. Van de Camp, *Ibid.* **55**, 2995 (1933)