Tetrahedron Vol. 45, No. 3, pp. 757 to 762, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

A CONVENIENT APPROACH TO THE SYNTHESIS OF PRENYL-, FURO- AND PYRANO-QUINOLINE ALKALOIDS OF THE RUTACEAE

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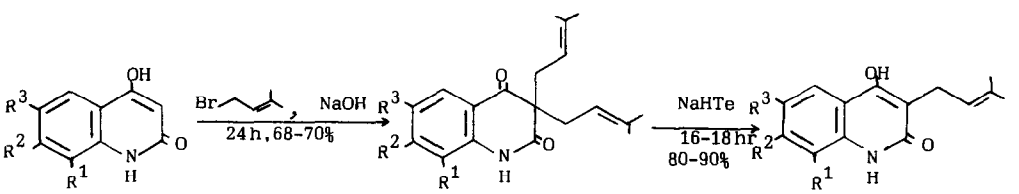
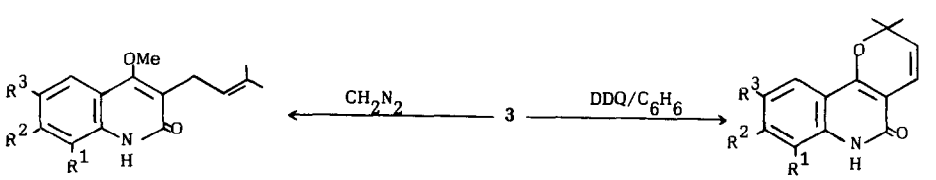
(*Received in UK* 19 *October* 1988)

Abstract : A convenient method for the synthesis of 4-hydroxy-3-prenyl-2-quinolones, which have been recognised as precursors to prenyl-, furo- and pyranoquinoline alkaloids of the Rutaceae is described. The methodology involves C,C-diprenylation of 2,4-dihydroxyquinoline followed by partial deallylation using sodium hydrogen telluride reagent.

The plant family Rutaceae is known[1] to be prolific in the production of alkaloids bearing 3-prenyl-2-quinolone, furo(2,3-b)-, pyrano(2,3-b)- and pyrano(3,2-c)-quinoline systems. Typical examples of these alkaloids are atanine(**4a**), dictamnine(**6**), khaplofoline(**9**) and flindersine(**5a**). The biogenesis of these alkaloids have been established[2] as proceeding through 4-hydroxyquinolin-2(1*H*)one(**1a**)which, in turn, is derived from anthranilic acid and acetic acid. The pivotal step in the biosynthetic route is the C-prenylation of **1a** to give 4-hydroxy-3-(3-methylbut-2-enyl) quinolin-2(1*H*)one(**3a**). Several reports have appeared in the literature[3] wherein an attempt has been made to glean a biomimetic synthesis of **3a** by appending a prenyl group onto the C_3-position of **1a**. But the yield realised of **3a** in those attempts is not quite appreciable and is often attended by the formation of C,C-, C,O- and O-prenylated products.

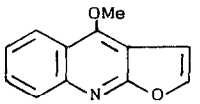


1 **2** **3**



4 **5**

a: $R^1=R^2=R^3=H$; b: $R^1=OMe$, $R^2=R^3=H$; c: $R^2=OMe$, $R^1=R^3=H$; d: $R^3=OMe$, $R^1=R^2=H$



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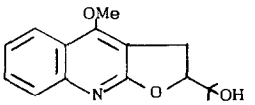

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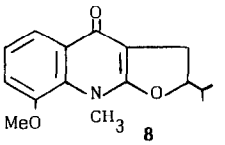

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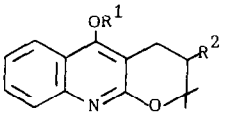
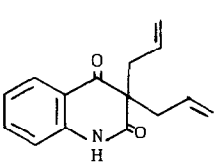


9 : $R^1=R^2=H$

10 : R^1=Me, R^2=OH

Now we wish to report a simple tactic for a neat derivation of **3** from **1** and as a corollary the accomplishment of an elegant approach to the synthesis of the titled alkaloids. Addition of three molar excess of prenyl bromide to a well stirred solution of **1a** in aqueous sodium hydroxide (5%) kept at 50°C, followed by further stirring for 20-24 hr at the same temperature gave the diprenylated quinolone **2a** in an yield of 68-70% (90-92% based on unrecovered **1a**). Interestingly, when **2a** was treated with sodium hydrogen telluride in boiling ethanol it neatly underwent partial deallylation, as observed earlier[4], to give an almost quantitative yield of the known 4-hydroxy-3prenyl-2-quinolone(**3a**)[5]. Extension of the technique to **1b**, **1c** and **1d** gave a similar series of compounds. The diprenylquinolones(**2**) are insoluble in aqueous alkali and are characterised by infra-red spectra containing bands attributable to the carbonyl (1680-1690 cm^{-1}) as well as the amide carbonyl (1650-1665 cm^{-1}). The hydroxyquinolones (**3**) are easily identified by their ready solubility in aqueous sodium hydroxide and by the reddish brown colouration they gave with neutral ferric chloride solution. Their infra-red spectra showed, in the carbonyl region, only a band at 1640 cm^{-1} attributable to the amide carbonyl. The correctness of the structures assigned for the products were attested by their ^{1}H.-N.M.R. spectra as well as by their ready conversion with diazomethane to give the corresponding 4-methoxy-3-prenyl-2-quinolones(**4**). Further proof was adduced by dehydrocyclisation, using DDQ in boiling benzene, of **3a**, **3b**, and **3d** to the known pyrano(3,2-c)quinolone alkaloids flindersine(**5a**)[5] 8-methoxyflindersine(**5b**)[5] and haplamine(**5d**)[7] respectively. Apart from **4** and **5**, the alkaloid systems **6** to **10** have been successfully derived by way of **4** as exemplifed by the synthesis of dictamnine(**6**)[8], khaplofoline(**9**)[9], platydesmine(**7**)[10] and geibalansine(**10**)[10] from **4a** and lunacrine(**8**)[11] from **4b**. Thus the simple high yield conversion **1**→**3**, in two steps represents a productive potentially useful approach to the titled alkaloid systems.

The unique action of sodium hydrogen telluride in stripping **2** of one of its allyl groups is of considerable mechanistic interest. The reagent has been recognised[12] to operate through different mechanistic modes, depending on the functionality with which it chemically reacts. It involves the reagent as a nucleophilic or as a reducing agent. In the deallylation reaction the involvement of the reagent with the side-chain vinyl is evident, as the compound **12**, with saturated side chain, remains intact even after prolonged treatment with it. It may be reasonably assumed, as outlined below, that the deallylation reaction encountered with **2a** is triggered by an electron transfer to the vinyl bond in one of the allyl groups followed



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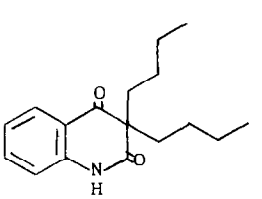
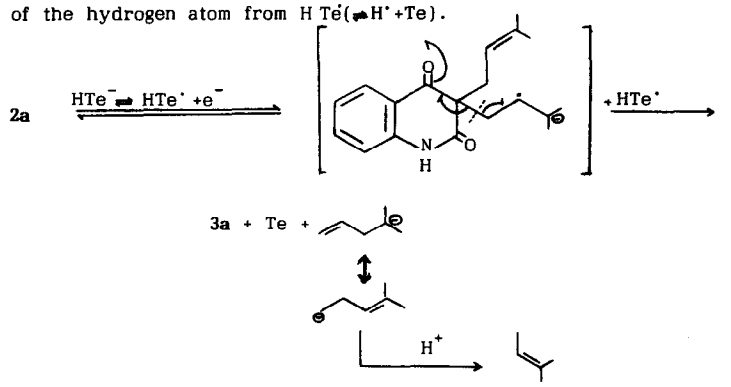


12

by extrusion of the allyl group as resonance-stabilised anion with a simultaneous capture, at the oxygen terminal, of the hydrogen atom from H Te(⇌H⁺+Te).



The other mechanistic pathways[12] involving a hydride (H^-) transfer or a hydrogen atom ($H^\cdot$) transfer similar to the electron transfer may be envisaged for the reaction. They are excluded as there are no marked reduction in rate due to steric hindrance. For eg. **2a** and **11** underwent deallylation reaction almost to the same extent. Moreover the side chain double bond lacks positive polar character, required for a hydride addition.

EXPERIMENTAL

Melting points, were determined on a Boetius micro-heating table and are uncorrected. The ^{1}H-NMR spectra were recorded on a Hitachi R-600 spectrometer using TMS as an internal standard. The I.R. spectra were recorded on a Perkin Elmer model 597 spectrophotometer.

General procedure:

Preparation of 2,4-diydroxyquinolines(**1**): The 4-hydroxyquinolines(**1**) were prepared by heating excess aniline with diethyl malonate and cyclising the resulting dianilide with polyphosphoric acid (instead of $AlCl_3$ used by Zeigler[13]). The dianilides prepared (from aniline,o-,m- and p-anisidines respectively) were : **13a** (Yield:98.4%, m.p 226-227°(EtOH), IR(KBr)ϑ_{max} 3250, 1650cm^{-1}) **13b** (Yield : 95.5%, m.p.158 -160°(C_6H_6-Petrol), IR(KBr)ϑ_{max}: 3250,1640 cm^{-1}) **13c** (Yield : 90%, m.p > 300°(EtOH), IR(KBr)ϑ_{max}: 3250, 1635 cm^{-1}) **13d** (Yield : 98.7%, m.p. 238 -240°(C_6H_6-EtOH), IR(KBr)ϑ_{max}: 3200, 1640 cm^{-1})

The solid dianilide **13** (0,1m) with 5-7 times its weight of polyphosphoric acid was heated on an oil bath at 120-140°, After 5-6 hr the reaction mixture was cooled, poured into 500g of crushed ice, left overnight and filtered to furnsish **1**. **1a**[14] (Yield : 99%, m.p.>300° (EtOH), IR(KBr)ϑ_{max}: 3400-2900, 1640 cm^{-1}) **1b**[15] (Yield : 80% m.p. 245 -248°)EtOH), IR(KBr) ϑ_{max}: 3300-2900, 1640 cm^{-1}) **1c** (Yield : 75%, m.p>300°(EtOH), IR(KBr)ϑ_{max}3400,1640 cm^{-1}) **1d**[3c] (Yield : 85%, m.p. 298°-300°(EtOH), IR(KBr)ϑ_{max} : 3350-2900, 1640 cm^{-1})

Preparation of **2**: To a well stirred solution of **1a**(0.05 m) in sodium hydroxide (7.5 g in 150 ml water) at 50°was added drop-wise prenyl bromide (18.2 ml,0.15 m) and stirred further at the same temperature for 20-24 hr, after which the reaction mixture was made alkaline with sodium hydroxide solution. The reaction mixture was then extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulphate, filtered and evaporated to give a residue which was chromatographed over a short column of neutral alumina with petrol:ethyl-acetate to give the diprenyl compound **2**.

The Physical and spectral data of **2** are indicated in Table - I.

Conversion of **2** to **3**[4]: To a solution of sodium hydrogen telluride, formed *in situ* from tellurium powder (1.3 g) and sodium borohydride (0.95 g) in absolute ethanol, and brought to pH 7.5 by addition of deoxygenated acetic acid at -20°C was added **2** (0.005 m) and refluxed for 16-18 hr. The solution was cooled and filtered, and the filtrate evaporated. The residue obtained was

Table I : Compounds **2,3,4** and 5 prepared

Compound	m.p(°C)	Yield (%)	IR(KBr)ν_{max} cm^{-1}	Elemental Analysis Molecular Formula	Observed C%,H%,N% (Calculated C%,H%,N%)	^{1}H-NMR δ ppm
2a	123-125 (petrol) lit[3d] 126	70	2995,1690,1660	$C_{19}H_{23}O_2N$ (297.40)	76.32,7.51,4.63 (76.74,7.8,4.71)	* 1.65,1.5(2s,6H each,=C(CH_3)$_2$);2.8(d,J=6Hz,4H,-CH_2-); 4.95(t,J=6Hz,2H,-CH=);6.6-7.4(m,3H,C_6,C_7,C_8H),7.6(d, J=9Hz,1H,C_5H);10.75(s,1H,NH).
2b	118-119 (petrol) lit[3b] 118-119	68	2990,1685,1655	$C_{20}H_{25}NO_3$ (327.43)	73.17,7.49,4.21 (73.37,7.70,4.28)	* 1.6-1.7(2s,6H each,=C(CH_3)$_2$);2.8(d,J=6Hz,4H,-CH_2-); 4(s,3H,-OCH_3);5(t,J=6Hz,2H,-CH=);7.1-7.4(m,2H,C_5,C_7H); 7.6(d,J=9Hz,1H,C_5H);8.25(s,1H,NH).
2c	132 (C_6H_6-petrol)	68	2985,1685,1655	$C_{20}H_{25}NO_3$ (327.43)	73.20,7.81,4.20 (73.37,7.70,4.28)	* 1.62,1.7(2s,6H each,=C(CH_3)$_2$);2.8(d,J=6Hz,4H,-CH_2-); 4(s,3H,-OCH_3);5(t,J=6Hz,2H,-CH=);6.5-6.8(m,2H,C_6,C_8H); 7.9(d,J=10Hz,1H,C_5H);10.1(s,1H,NH).
2d	134-135 (petrol) lit[3c] 134-135	70	2995,1685,1660	$C_{20}H_{25}NO_3$ (327.43)	73.47,7.38,4.58 (73,37,7.70,4.28)	* 1.4,1.5(2s,6H each,=C(CH_3)$_2$);2.55(d,J=6Hz,4H,-CH_2-); 3.75(s,3H,OCH_3);4.85(t,J=6Hz,2H,-CH=)6.95-7.5(m,3H, arom);10.7(s,1H,NH).
3a	182-183 (C_6H_6-EtOH) lit[5]180-182	90	3200,2900,1640	$C_{14}H_{15}NO_3$ (229.28)	73.24,6.31,6.25 (73.34,6.59,6.11)	* 1.55,1.7(2s,6H,=C(CH_3)$_2$);3.3(d,J=6Hz,2H,-CH_2-); 5.2 (t,J=6Hz,1H,-CH=);6.9-7.4(m,3H,C_6,C_7,C_8H);7.9(d,J=9Hz, 1H,C_5H);8.2(s,1H,NH).
3b	226-228 C_6H_6-EtOH) lit[5] 224-228	92	3100,2995,1640	$C_{15}H_{17}NO_3$ (259.31)	64.72,6.45,5.31 (69.48,6.61,5.4)	* 1.6,1.7(2s,3H each,=C(CH_3)$_2$);3.25(d,J=6Hz,2H,-CH_2-); 3.8(s,3H,-OCH_3),5.2(t,J=6H_z,1H,-CH=);6.9-7.25(m,2H, C_6,C_7H);7.45(d,J=9Hz,C_5H);8.2(s,1H,NH).
3c	238-240 (C_6H_6-EtOH)	50	3100,2900,1640	$C_{15}H_{17}NO_3$ (259.31)	69.75,6.54,5.33 (69.48,6.61,5.4)	@ 1.62,1,7(2s,3H each,=C(CH_3)$_2$);3.2(d,J=6Hz,2H,-CH_2-); 3.8(s,3H,-OCH_3);5.1(t,J=6Hz,1H,-CH=),6.8-7.45(m,3H, arom);8.3(s,1H,NH).

Table 1 Contd.

3d	159-160 (C_2H_5OH) lit[3c] 158-160	89	3100,2995,1640	$C_{15}H_{17}NO_3$ (259.31)	69.37,6.51,5.39 (69.48,6.61,5.4)	* 1.62,1.7(2s,3H each,=C(CH_3)$_2$);3.2(d,J=6Hz,2H,-CH_2-); 3.8(s,3H,-OCH_3);5.2(t,J=6Hz,1H,-CH=);6.85-7.5(m,3H, arom);8.7(s,1H,NH).
4a	132-134 (C_6H_6-petrol) lit[5] 132-134	90	2990,1650	$C_{15}H_{17}NO_3$ (243.31)	74.42,7.12,5.53 (74.05,7.04,5.76)	* 1.75,1.85(2s,3H each,=C(CH_3)$_2$);5.32(t,J=6Hz,-CH=); 3.4(d,J=6Hz,2H,-CH_2-);3.9(s,3H,-OCH_3);6.9-7.6(m,3H,C_6, C_7,C_8H);7.7(d,J=9Hz,1H,C_5H);13(s,1H,NH).
4b	119-121 (C_6H_6) lit[5,6] 119-121	85	2995,1650	$C_{16}H_{19}NO_3$ (273.33)	69.99,7.12,5.07 (70.31,7.01,5.12)	* 1.65,1.8(2s,3H each,=C(CH_3)$_2$);3.5(d,J=6Hz,2H,-CH_2-); 3.85,3.95(2s,3H each,2xOCH_3),5.2(t,J=6Hz,1H,-CH=); 7-7.25(m,2H,C_6,C_7H);7.45(d,J=9Hz,1H,C_5H);12.7(brs, 1H,NH).
4c	117-120 (C_6H_6-petrol)	80	2990,1655	$C_{16}H_{19}NO_3$ (273,33)	70.62,7.08,5.21 (70.31,7.01,5.12)	* 1.65,1.75(2s,3H each,=C(CH_3)$_2$);3.42(d,J=6Hz,2H,-CH_2-); 3.82,3.9(2s, 3H each,2xOCH_3);5.2(t,J=6Hz,1H,-CH=);6.83-7.47(m,3H,arom);11.3(s,1H,NH).
4d	152-153 (C_6H_6- Ethyl acetate)	80	2995,1645	$C_{16}H_{19}NO_3$ (273.33)	70.8,6.99,5.05 (70.31,7.01,5.12)	* 1.63,1.75(2s,3H each,=C(CH_3)$_2$);3.5(d,J=6Hz,2H,-CH_2-); 3.8,3.9(2s,3H each,2xOCH_3);5.2(t,J=6Hz,1H,-CH=);6.7--7.5(m,arom,4H);12.5(brs,1H,NH).
5a	196-197 (MeOH) lit[5] 196-197	68	3090,1655,	$C_{14}H_{13}NO_2$ (227.27)	73.69,5.71,6.13 (73.99,5.77,6.16)	* 1.45(s,6H,C(CH_3)$_2$);5.25(d,J=6Hz,1H,-CH=);6.7(d,J=6Hz, 1H,Ar-CH=);6.9-7.5(m,6H,arom),11.5(s,1H,NH).
5b	178 (C_6H_6) lit[5] 178	72	2995,1660	$C_{15}H_{16}NO_3$ (258.3)	69.73,6.14,5.31 (69.75,6.24,5.42)	* 1.4(s,6H,C(CH_3)$_2$);3.9(s,3H,OCH_3);5.5(d,1H,-CH=);6.7 (d,J=6Hz,1H,Ar-CH=);6.8-7.5(m,5H,arom);9.3(s,1H,NH).
5d	187-190 (C_6H_6-EtOH) lit[7](187-190)	80	2990,1655	$C_{15}H_{16}NO_3$ (258.3)	69.71,6.15,5.38 (69.75,6.24,5.42)	* 1.4(s,6H,C(CH_3)$_2$),3.85(s,3H,OCH_3),5.45(d,1H,J=6Hz, -CH=);6.7(d,J=6Hz,1H,Ar-CH=);6.85-7.4(m,5H,arom); 10.7(s,1H,NH).

Solvent : *$CDCl_3$ @$DMSOd_6$

dissolved in water and extracted with chloroform (to remove traces of starting material if any). The aqueous layer was then acidified with acetic acid, when **3** precipitated out. It was filtered, washed with water, dried and recrystallised.

Table I shows the physical and spectral data of **3**.

Conversion of **3** to **4** : To a well stirred solution of **3** (0.001 m) in ethanol at 0°C was added, a dry ethereal solution of diazomethane (prepared from 5 g of nitrosomethyl urea) and stirred at the same temperature for an hour. The ether was evaporated and residue recrystallised from benzene : ethylacetate to give **4**.

The physical and spectral data of **4** are shown in Table I.

Conversion of **3** to **5**: A mixture of **3** (0.001 m) and DDQ (0.001 m) in benzene (50 ml) was refluxed for 12 hr. The reaction mixture was filtered, evaporated, to give a residue which was dissolved in chloroform and washed with sodium bicarbonate and water. Evaporation of the extract furnished **5**.

The physical and spectral data of **5** are indicated in Table I.

ACKNOWLEDGEMENTS

We acknowledge the CSIR (New Delhi) for the award of a research associateship to one of us (NS). We thank Mr.M. Palaniswamy for the ^{1}H-NMR and IR spectra.

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