New Synthesis of (±)-Meroquinene Aldehyde and its Epimer from (±)-Norcamphor

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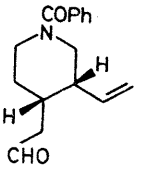
Summary A new route converting (±)-norcamphor into ±-meroquinene aldehyde (**1**), a key intermediate in the synthesis of the cinchona alkaloids, and its epimer, (±)-epimeroquinene aldehyde (**2**), has been developed.

RECENTLY a new stereospecific route leading to the emetine alkaloids in a racemic form has been developed using (±)-norcamphor; this method seems to be potentially useful for chiral syntheses of alkaloids from the chiral norcamphor.[1] Extension of this method allowed a new synthesis of (±)-meroquinene aldehyde[2] (**1**), a key intermediate in the synthesis of the cinchona alkaloids,[3] and its epimer, (±)-epimeroquinene aldehyde (**2**), through a stereospecific reaction sequence.

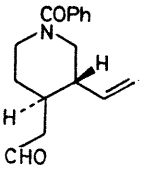
Treatment of the bicyclic lactone (**3**),[4] obtained in 88% yield by Baeyer–Villiger oxidation of norcamphor, with allyl bromide in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPT) in the presence of lithium di-isopropylamide (LDA)[5] led to a stereospecific alkylation to give (**4**),† b.p. 152—154 °C (15 Torr), in 55·5% yield, which, on heating with benzylamine at 180 °C, followed by oxidation with Jones' reagent, yielded the oxo amide (**6**), m.p. 72—74 °C, in 68% overall yield *via* (**5**), m.p. 110—112 °C. Regiospecific dithioalkylation[6] of (**6**) by trimethylene dithiotosylate *via* a pyrrolidine enamine intermediate gave the dithian (**7**), m.p. 146—148 °C, which on cleavage with KOH in Bu^{t}OH[7] afforded the open chain compound (**8**), m.p. 134—135 °C, in 48% overall yield. Since various attempts to reduce the amide group of (**8**) have failed, (**8**) was converted into the glutarimide (**9**) in 85% yield by heating at 180 °C.

Compound (**9**) possessed the requisite configuration for the quinine precursor (**1**) and was reduced to the corresponding piperidine (**10**). However, an unexpected epimerization took place under the conditions employed giving the unwanted *trans*-compound (**11**) in addition to the desired *cis*-isomer (**10**). Reduction of (**9**) with $LiAlH_4$ in THF at 0 °C to room temperature, followed by separation by silica gel chromatography afforded (**10**) and (**11**) in a ratio of 54:46 in 82% total yield.

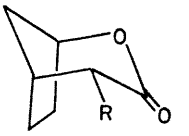
Debenzylation of (**10**) with benzyloxycarbonyl chloride[8] gave the carbamate (**12**) which was hydrolysed with methyl iodide in aqueous MeCN[9] to give the aldehyde (**13**) in 65% overall yield. Compound (**13**) was converted into the acetal (**14**) which was treated with a catalytic amount of OsO_4 in the presence of $NaIO_4$[10] to yield the aldehyde (**15**), which on reduction with $NaBH_4$ afforded the primary alcohol (**16**) in 83% overall yield. Treatment of (**16**) with *o*-nitrophenyl selenocyanate and Bu$^n_3$P provided the selenide (**17**); reaction of (**17**) with 30% H_2O_2[11] gave the meroquinene derivative (**18**), oil, δ 4·80—5·40 (m, 5H, CH=CH_2, –HCOCH$_2$CH$_2$O, and CH_2Ph) and 5·55—6·23 (m,



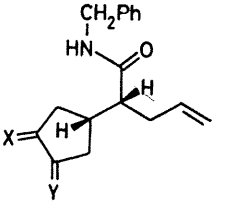
(1)



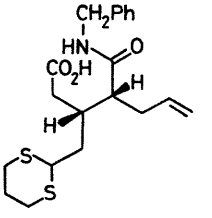
(2)



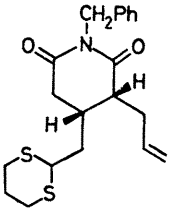
(3); R = H
(4); R = $CH_2CH{=}CH_2$



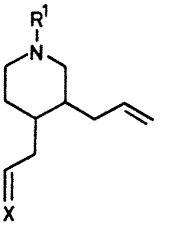
(5), X = H, OH; Y = H_2
(6), X = O; Y = H_2
(7), X = O; Y = –S[CH_2]$_3$S–



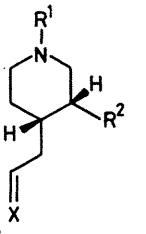
(8)



(9)



(10), *cis* R^1 = CH_2Ph; X = –S[CH_2]$_3$S–
(11), *trans* R^1 = CH_2Ph; X = –S[CH_2]$_3$S–
(12), *cis* R^1 = CO_2CH_2Ph; X = –S[CH_2]$_3$S–
(13), *cis* R^1 = CO_2CH_2Ph; X = O
(14), *cis* R^1 = CO_2CH_2Ph; X = –O[CH_2]$_2$O–



(15), R^1 = CO_2CH_2Ph; R^2 = CH_2CHO; X = –O[CH_2]$_2$O–
(16), R^1 = CO_2CH_2Ph; R^2 = [CH_2]$_2$OH; X = –O[CH_2]$_2$O–
(17), R^1 = CO_2CH_2Ph, R^2 = [CH_2]$_2$Se$C_6H_4NO_2$–*o*; X = –O[CH_2]$_2$O–
(18), R^1 = CO_2CH_2Ph; R^2 = CH=CH_2; X = –O[CH_2]$_2$O–
(19), *trans* R^1 = CO_2CH_2Ph; R^2 = CH=CH_2; X = –O[CH_2]$_2$O–

† About 20% of the starting lactone (**3**) and 10% of the diallyl lactone have been separated. Satisfactory analytical and spectral data were obtained for all new compounds.

1H, C*H*=CH$_2$), in 79% overall yield. Saponification[8] of (**18**) with KOH in Ethyl Cellosolve, followed by benzoylation and deacetalization furnished *N*-benzoylmeroquinene aldehyde (**1**), δ 4·85—5·37 (m, 2H, CH=C*H*$_2$), 5·58—6·25 (m, 1H, C*H*=CH$_2$), and 9·80 (t, 1H, C*H*O) in 35% yield, which, when prepared by a completely different route,[2] has been converted into quinine.[2]

In the *trans*-series (**11**) was converted into the carbamate (**19**), oil, δ 4·80—5·90 (m, 6H, C*H*=C*H*$_2$, *H*COCH$_2$CH$_2$O, and C*H*$_2$Ph), in 46% overall yield *via* the same sequence of reactions as for the *cis*-congener, and after hydrolysis, benzoylation, and deacetalization led to *N*-benzoylepimeroquinene aldehyde (**2**), oil, δ 4·95—5·93 (m, 3H, C*H*=C*H*$_2$) and 9·83 (t, 1H, C*H*O), in 25% yield. Since the corresponding methoxycarbonyl derivative[12] (**2**; CHO replaced by CO$_2$Me) has been converted into the heteroyohimbine alkaloids, (**2**) would also be useful for the synthesis of these alkaloids.

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