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MEROTERPENOIDS—II

PSORALEA CORYLIFOLIA LINN.—2. ABSOLUTE CONFIGURATION OF (+)-BAKUCHIOL*†‡

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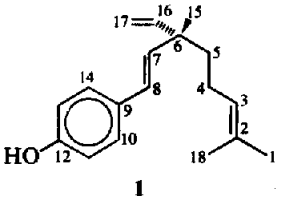
Abstract—Bakuchiol, a terpene phenol from *Psoralea corylifolia* Linn has only one asymmetric centre. By suitable correlation with (+)-linalool on the one hand and, with (+)-3-methyl-3-methoxycarbonyl-n-valeria acid on the other, it has been shown to possess (*S*)-chirality.

In the preceding paper we discussed the structure elucidation of bakuchiol, a monoterpene phenol from *Psoralea corylifolia* Linn. The present communication presents two distinct correlations which enable us to assign the absolute configuration **1** to (+)-bakuchiol.



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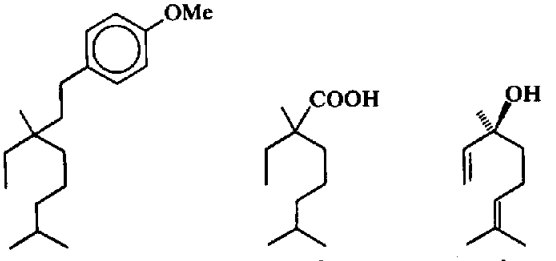
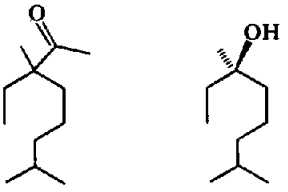
In the first correlation, the degradation of hexahydrobakuchiol methyl ether (**2**) to the C_{11}-acid (**3**) by a sequence of reactions already described,[1] has been exploited to correlate bakuchiol with (*S*)-(+)-linalool (**4**).[2] The C_{11}-acid (**3**) was first converted to the corresponding methyl ketone (**5**) by exposure[3] to methyl lithium. The anticipated Baeyer-Villiger oxidation of this ketone, under a variety of conditions and reagents (perbenzoic acid, *m*-chloroperbenzoic acid, $F_3C{\cdot}COOH$) proved most disappointing as, either no reaction occurred or a complex reaction product resulted. Ultimately, it was found that exposure of the methyl ketone to a $CHCl_3$ soln of *p*-nitroperbenzoic acid at ~ 25° (in the dark) for 30 days resulted in ~ 25% of the desired product, besides unchanged starting ketone. This product was isolated and identified as (+)-tetrahydrolinalool. Since (−)-linalool is known[4] to furnish (−)-tetrahydrolinalool on hydrogenation, (+)-tetrahydrolinalool (**6**) should be likewise related to (*S*)-(+)-linalool (**4**). Further, since Baeyer-Villiger oxidation proceeds with retention of configuration,[5] it follows that (+)-bakuchiol must have (*S*)-chirality at C_6.



2 **3** **4**



5 **6**

Since tetrahydrolinalool has a rather low α_D (0·55),[4]** it appeared desirable to establish the chirality of bakuchiol by another independent method. The second route envisaged degradation of bakuchiol to α-methyl-α-ethyl-glutaric acid (**7**) and its comparison with a synthetic specimen, which should be readily accessible from the

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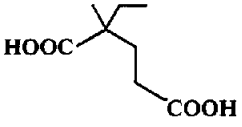
**We did not realise this at the start of the work as $[\alpha]_D$ quoted for tetrahydrolinalool [from hydrogenation of (−)-linalool] in a standard reference text[6] is −24°.

known[7] (*R*)-(+)-α-methyl-α-ethyl-succinic acid (**8**).

For the degradation of bakuchiol (**1**) to **7**, it is imperative that a method for selective hydrogenation of $\Delta^{16,17}$ should be found. Our earlier experience[1] had revealed that with milder, less active hydrogenation catalysts, $\Delta^{7,8}$ in bakuchiol was selectively hydrogenated, rather than the $\Delta^{16,17}$. Fortunately, it was found that bakuchiol acetate on partial (~ two mole H_2 absorption) hydrogenation with a more active (and hence, less selective) catalyst (PtO_2/AcOH) furnished a mixture containing significant quantities of the required 16,17-dihydrobakuchiol acetate (**9**) as revealed by its PMR spectrum; other products were **10** and **11**



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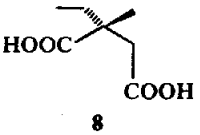

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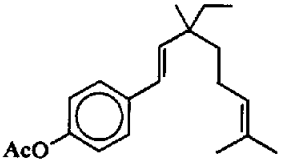

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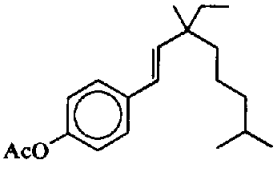

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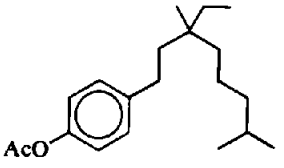

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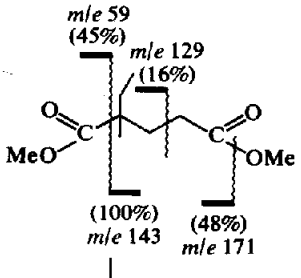
Methyl-α-ethyl-glutaric acid was purified *via* its Me ester by preparative GLC to give the pure dimethyl ester. This compound (or the free acid; **7**) does not appear to have been described in the literature so far, but the structure is fully consistent with its elemental analysis ($C_{10}H_{18}O_4$), PMR spectrum (—CH_2·$C\underline{H}_3$, 3H, t, 0·83 ppm, J = 7H; —$\underset{|}{\overset{|}{C}}$—$C\underline{H}_3$, 3H, s, 1·10 ppm, two —$COOC\underline{H}_3$, 3H singlet at 3·61 and 3·65 ppm) and mass fragmentation (**12** → **13**).

An authentic sample of optically active dimethyl α-methyl-α-ethyl-glutarate was prepared by (from results of ozonolysis; *vide infra*). This hydrogenation mixture was ozonised and the product worked up by Jones oxidation.[8] The acidic fraction consisted of essentially three acids (TLC: solvent, 10% AcOH in C_6H_6) while the neutral fraction (~ 30%) was the hexahydroacetate (**11**). The acid mixture was subjected to inverted-dry-column-chromatography[9] (IDCC) to get somewhat impure α-methyl-α-ethyl-glutaric acid (**7**), besides *p*-acetoxy benzoic acid and the C_{11}-acid (**3**). α-Arndt-Eistert homologation of the known[7b] (*R*)-(+)-3-methyl-3-methoxycarbonyl-n-valeric acid (**14**). The synthetic product (**15**) was fully identical (GLC, PMR, Mass) with the product obtained by degradation of (+)-bakuchiol. Since both the degradation and the synthetic products are dextrorotatory and have almost the same magnitude of $[\alpha]_D$ (+9·7° and +9·8° respectively), it is obvious that (+)-bakuchiol must have the configuration shown in **1**, that is *S*-chirality at C_8.



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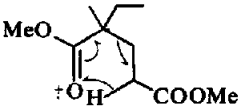

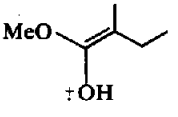

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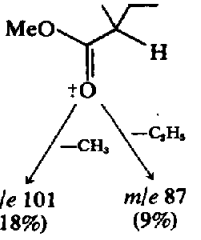

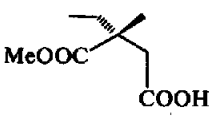

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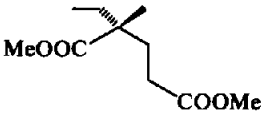

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EXPERIMENTAL

For general remarks see Part I of this series.

Analytical GLC was performed on the 'Aerograph' model A-350-B instrument using a 300 cm × 0·5 cm Al column packed with 20% diethylene glycol polysuccinate (DEGS) on Chromosorb W of 60–80 mesh and H_2 as carrier gas; for preparative GLC a 300 cm × 1 cm Al column packed with 30% DEGS on Chromosorb W (30–60 mesh) was employed.

2,6-Dimethyl-2-ethyl-heptanoic acid (C_{11}*-acid;* **3**)

This acid was prepared either by the method described[1] or better, more conveniently by the following procedure.

Bakuchiol methyl ether (24·0 g) in gl AcOH (100 ml) was partially hydrogenated over Adams' PtO_2 catalyst (233 mg) at 26°/715 mm. After the uptake of ~ 5·5 litres of H_2 (~ 2·3 moles) the product was worked up as usual and distilled (b.p. 150–153°/1 mm) to furnish a mixture of **10** and **2** in 7 : 3 ratio (PMR).

A stream of ozonised oxygen (O_3 conc 1·2 g/hr) was passed through a soln of the above material (10·6 g) in CH_2Cl_2 (100 ml) at −80° (EtOAc-liquid N_2). After the ozonolysis was complete (2·5 hr) the solvent was removed at 40°/50 mm, the resulting 'ozonide' dissolved in Me_2CO (100 ml), cooled to 0° and treated with Jones reagent (30 ml) at 0° (1 hr) and then the mixture left at room temp (~ 25°) for 15 hr. The mixture was poured into water (400 ml), extracted with ether (100 ml × 3) and separated with 10% KOH aq (100 ml × 4) into acidic and neutral fractions. The neutral material (3·87 g) was essentially **2**. The acid part (6·72 g) was triturated with light petroleum (10 ml × 3) and the insoluble acid (2·1 g, *p*-anisic acid) filtered off. The filtrate was freed of solvent and the product (4·5 g) subjected to IDCC separation (SiO_2-gel/3, 250 g, 25 cm × 4·7 cm; solvent: 5% EtOAc in C_6H_6); 3 cm-cuts were made: (i) colourless solid, pure, *p*-anisic acid (1·4 g) (ii) liquid, pure, C_{11}-acid (2·8 g) and (iii) liquid (0·2 g) (rejected).

Fr. (ii) was distilled to furnish the C_{11}-acid (**3**) as a colourless liquid: b.p. 121–123° (bath)/2 mm.

3,7-Dimethyl-3-ethyl-2-oxo-octane **5**

To a stirred soln of the above C_{11}-acid (4·1 g) in dry ether (50 ml) taken in a flask, equipped with a dropping funnel and reflux condenser, was added, dropwise, an ether soln (75 ml, 1·4 molar) of MeLi during 1/2 hr (N_2 atmos, anhyd conditions) and further stirred for 2 hr at room temp. The mixture was diluted with ice water (100 ml), extracted with ether (50 ml × 4) and the unreacted acid (0·93 g) separated by washing with 10% Na_2CO_3 aq. Solvent removal from the ether extract gave the neutral material (2·93 g); TLC (solvent, C_6H_6): 3 spots. This mixture was chromatographed on SiO_2-gel/1 (150 g, 100 cm × 2 cm).

Fr. 1	Light petroleum	200 ml × 6	0·09 g	liquid, higher R_f, rejected
Fr. 2	50% light petrol in C_6H_6	200 ml × 2	2·31 g	liquid, pure, ketone **5**
Fr. 3	50% light petrol in C_6H_6	200 ml × 2	0·23 g	liquid, impure ketone **5**
Fr. 4	MeOH	500 ml	0·23 g	liquid, lower R_f, rejected

Fr. 2 was distilled to furnish **5** as a colourless liquid, b.p. 128–130°/30 mm (2·1 g), n_D^{30} 1·4318, $[\alpha]_D$ +5·0° (*c*, 2·25%); IR (smear): C=O 1710 cm^{-1}; PMR (CCl_4): tertiary Me (3H, s, 1·02 ppm), $C\underline{H}_3CO$ (3H, s, 2·0 ppm), other Me signals at 0·77, 0·82 and 0·92 ppm. (Found: C, 77·64; H, 13·00. $C_{12}H_{24}O$ requires: C, 78·10; H, 13·13%).

Baeyer-Villiger oxidation of **5**

The C_{12}-ketone **5** (530 mg) in $CHCl_3$ (5 ml) was treated with a soln of *p*-nitroperbenzoic acid[10] (1·99 g) in $CHCl_3$ (50 ml) at room temp and left aside in the dark. There was gradual deposition of crystalline *p*-nitrobenzoic acid in the $CHCl_3$ soln; the reaction was monitored by GLC after 2 and 3 weeks when the formation of a small amount of tetrahydrolinalool was indicated. After 30 days the mixture was diluted with more $CHCl_3$ (25 ml) and washed successively with 5% KOH aq (30 ml × 3), water and brine. Solvent removal gave a liquid (0·50 g); TLC (solvent, 5% EtOAc in C_6H_6): 2 spots. This mixture was chromatographed on neutral Al_2O_3/3 (70 g, 30 cm × 1·5 cm).

Fr 1.	light petroleum	200 ml × 3	0·295 g	liquid, pure, C_{12}-ketone **5**
Fr. 2	10% ether in light petrol	200 ml × 2	0·088 g	liquid, pure, alcohol **6**
Fr. 3	Ether	200 ml × 1	0·021 g	rejected.

Fr. 2 [GLC: (temp 90°, flow rate 90 ml/min): single peak] was distilled to furnish pure tetrahydrolinalool (**6**), b.p. 140° (bath)/45 mm, $[\alpha]_D$ +0·2° (*c* 2·4%); identical (IR, PMR) with an authentic sample.

(+)-Dimethyl α-methyl-α-ethyl glutarate (**15**) *from bakuchiol acetate*

Partial hydrogenation. Bakuchiol (25 g) in gl AcOH (100 ml) was partially hydrogenated over PtO_2 catalyst (300 mg) at 27°/715 mm. After the uptake of 5·2 lit of H_2 (~ 2 mole eq) during 75 min the partially hydrogenated product was isolated and the crude material acetylated with Ac_2O (30 ml) and dry pyridine (20 ml) at 27° (16 hr). The acetate mixture, which was rich in **9** and **10**, as revealed by NMR, was distilled to get a liquid (25·6 g), b.p. 150–155°/0·5 mm.

Ozonolysis. The above acetate mixture (10·0 g) in EtOAc was cooled to −20° and a stream of ozonised O_2 (O_3 conc 0·8 g/hr) passed through the soln during 4 hr. After solvent removal at 40°/50 mm, the solid residue was dissolved in acetone (100 ml), cooled to 0° and treated with Jones' reagent (10 ml) till an orange colour persisted. After 20 hr at room temp the mixture was diluted with water (150 ml), extracted with ether (100 ml × 3) and the acidic portion isolated (sat Na_2CO_3 aq 100 ml × 2) as a light brown semi-solid (6·2 g). This was dissolved in ether (25 ml), diluted with light petroleum and the precipitated *p*-acetoxybenzoic acid (1·52 g, m.p. 185°) filtered off. The residue from the filtrate had a complex TLC pattern solvent 10% AcOH in C_6H_6: major 3 spots) and the mixture (3·5 g) was subjected to IDCC (SiO_2-gel/5 500 g, 25 cm × 9·4 cm; solvent,

10% AcOH in C_6H_6):

Fr. 1	1·1 g	Crude *p*-acetoxybenzoic acid.
Fr. 2	1·27 g	(7) + *p*-acetoxybenzoic acid (30–35% by NMR).
Fr. 3	0·464 g	liquid, pure, C_{11}-acid (3).

Fr. 2 (0·756 g) was esterified (CH_2N_2) and distilled: colourless liquid, b.p. 140–145° (bath)/12 mm; GLC (temp 190°; flow rate 100 ml/min): 2 peaks. Preparative GLC (temp 195°; flow rate 150 ml/min; batch size 50 μl) of this material (190 mg) and distillation of the second cut (major) gave **15** (0·031 g), $[\alpha]_D$ +9·7° (*c*, 3·1%). Mass spectrum: important ions at *m/e* 202 M^+ 0·8%), 143 (100%), 83 (100%), 111 (90%), 55 96%), 69 (77%), 171 (48%), 59 (45%), 116 (40%), 142 (36%) and 101 (18%). (Found: C, 59·68; H, 9·20. $C_{10}H_{18}O_4$ requires: C, 59·38; H, 8·97%).

(R)-(+)-3-Methyl-3-methoxycarbonyl-n-valeric acid **(14)**

Ethyl isobutylidene cyanoacetate. Methyl ethyl ketone was condensed with ethyl cyanoacetate in the presence of piperidine acetate-AcOH essentially by the method of Cope *et al.*[11] to give ethyl isobutylidene cyanoacetate (yield, 88%), b.p. 118–120°/10 mm (Lit.[11] b.p. 116–118°/11 mm).

3-Methyl-3-carboxy-n-valeric acid. This compound was prepared essentially by the method of Le Moal[12] in 77% yield, m.p. 101–103° (toluene-ligroin) (Lit.[12]: m.p. 101°).

Methyl-3-methyl-3-methoxycarbonyl-n-valerate. The above diacid (79 g), ethylene dichloride (300 ml), dry MeOH (150 ml) and conc H_2SO_4 (3 ml) were refluxed on the waterbath (48 hr) and worked up to yield the dimethyl ester (67 g): b.p. 85–86°/3 mm; IR (smear): COOMe 1740, 1200 cm^{-1}; PMR (CCl_4): $C\underline{H}_3CH_2$ (3H, t, 0·83 ppm, J = 7 Hz), tertiary Me (3H, s, 1·22 ppm), $MeOOC\cdot C\underline{H}_2\cdot C(Me)$— (2H, q, 2·5 ppm, J = 16 Hz) and two $COO\underline{Me}$ (3H, s, 3·62 and 3·67 ppm respectively); Mass spectrum: important ions at *m/e* 188 (M^+ 2%), 69 (100%), 115 (76%), 87 (61%), 129 (55%), 128 (55%), 59 (50%), 97 (46%), 55 (42%), 157 (39%) and 160 (24%). (Found: C, 57·55; H, 8·07. $C_9H_{16}O_4$ requires: C, 57·43; H, 8·57%).

3-Methyl-3-methoxycarbonyl-n-valeric acid. The above dimethyl ester (56·4 g) was partially hydrolysed with 2·5% aq ethanolic KOH (16·8 g KOH, 60 ml H_2O and 600 ml EtOH) at room temp (15 hr). After removal of EtOH at 50°/50 mm the mixture was diluted with water (150 ml) and extracted with ether (100 ml × 3) to remove the unchanged diester. The aqueous phase, after acidification with conc HCl, was saturated with $(NH_4)_2SO_4$, extracted with ether (300 ml × 4), dried, evaporated and distilled to furnish the half ester (48 g): b.p. 128–130°/3 mm, m.p. 35–36° (Lit.[13]: m.p. 33°); IR (smear): COOH 3200, 2600, 1700 cm^{-1}; COOMe 1740, 1200 cm^{-1}; PMR (CCl_4): $CH_2\cdot C\underline{H}_3$ (3H, t, 0·85 ppm, J = 7 Hz), tertiary $\underline{Me}$ (3H, s, 1·27 ppm), $HOOC\cdot C\underline{H}_2\cdot C(Me)$— (2H, q, 2·57 ppm, J = 16 Hz), $COO\underline{Me}$ (3H, s, 3·67 ppm) and $COO\underline{H}$ (1H, s, 10·67 ppm).

(R)-(+)-3-Methyl-3-methoxycarbonyl-n-valeric acid **14**. The above half ester (3·48 g) in dry MeOH (10 ml) was treated with dehydroabiethylamine (5·70 g) in MeOH (10 ml). After 16 hr at room temp the mixture was cooled to 0° and filtered. The salt (3·24 g, m.p. 130–134°) was recrystallised 5 times from MeOH to a solid m.p. 146–147° (1·28 g). On decomposition with sat Na_2CO_3 aq this salt gave the (+)-enantiomer as a colourless liquid b.p. 125°/0·2 mm (0·456 g), $[\alpha]_D$ +7·6° (*c*, 10·1%, $CHCl_3$) [Lit.[7b] $[\alpha]_D$ +8·2° (*c* 8·5%, EtOH)].

Arndt-Eistert homologation of **14**

(+)-Dimethyl-α-methyl-α-ethyl glutarate **15**. The (+)-half ester **14** (0·374 g), cooled to 0° in an ice-bath was treated with freshly distilled oxalyl chloride (0·5 ml) and left overnight. After removal of excess reagent at 40°/50 mm the crude acid chloride in ether (10 ml) was added dropwise to a thoroughly dried cold conc ethereal soln of CH_2N_2 (excess) and left overnight at room temp. The crude diazoketone, after solvent removal, was treated with dry MeOH (25 ml) and Ag_2O (200 mg) and refluxed for 4 hr. The mixture was filtered, the filtrate taken to dryness and the residue (light petroleum soluble part) was distilled to furnish pure (GLC) **15**: b.p. 140° (bath)/10 mm, $[\alpha]_D$ +9·8° (*c* 4·1%); identical (GLC, PMR, Mass) with the diester obtained by degradation of bakuchiol acetate described earlier.

REFERENCES

[1]G. Mehta, U. R. Nayak and Sukh Dev, *Tetrahedron* **29**, 1119 (1973).

[2a]R. H. Cornforth, J. W. Cornforth and V. Prelog, *Liebigs Ann.* **634**, 197 (1960); [b]R. H. Cornforth, J. W. Cornforth and G. Popjak, *Tetrahedron* **18**, 1351 (1962); [c]G. Ohloff and E. Klein, *Ibid.* **18**, 37 (1962).

[3]See e.g.: H. Gilman and P. R. van Ess, *J. Am. Chem. Soc.* **55**, 1258 (1933); W. G. Dauben, R. C. Tweit and C. Mannerskantz, *Ibid.* **76**, 4420 (1954); C. H. Depuy, G. M. Dappen, K. L. Eilers and R. A. Klein, *J. Org. Chem.* **29**, 2813 (1964).

[4]V. Prelog and E. Watanabe, *Liebigs Ann.* **603**, 1 (1957).

[5]R. B. Turner, *J. Am. Chem. Soc.* **72**, 878 (1950); K. Mislow and J. Brenner, *Ibid.* **75**, 2318 (1953).

[6]J. L. Simonsen, *The Terpenes* Vol. I, p. 61. Univ. Press, Cambridge (1953).

[7a]J. Porath, *Arkiv. Kemi* **3**, 163 (1951); [b]M. R. Cox, G. A. Ellestard, A. J. Hannaford, I. R. Wallwork, W. B. Whalley and B. Sjöberg, *J. Chem. Soc.* 7257 (1965).

[8]A. S. Narula and Sukh Dev, *Tetrahedron Letters* 1733 (1969).

[9]V. K. Bhalla, U. R. Nayak and Sukh Dev, *J. Chromatog.* **26**, 54 (1967).

[10]D. Swern in *Organic Peroxides* (Ed. D. Swern) Vol. I, p. 492. Wiley-Interscience, New York (1970).

[11]A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.* **63**, 3452 (1941).

[12a]H. Le Moal, *Bull. Soc. Chim.* **418** (1956); H. Le Moal, A. Foucaud, R. Carrie', J. Hamelin and C. Sevellec, *Ibid.* 579 (1964).

[13]H. Le Moal, A. Foucaud, R. Carrie, D. Danion and C. Fayat, *Ibid.* 828 (1964).