A NEAT SYNTHESIS OF GEIBALANSINE, O-ACETYLGEIBALANSINE, RIBALININE AND PLATYDESMINE

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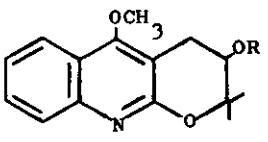
Abstract — A convenient high yield methodology has been evolved for the synthesis of geibalansine, O-acetylgeibalansine, ribalinine and platydesmine starting from atanine.

Two new alkaloids called geibalansine and O-acetylgeibalansine were isolated recently[1] from Geijera Balansae and proved to be the pyranoquinolines 1a and 1b respectively. Even prior to isolation as a natural product, 1a was obtained by Grundon et al.[2], as a minor product, in their synthesis of platydesmine (2a) by way of epoxidation of 4-methoxy-3-(3-methylbut-2-enyl)-2-quinolone (3), now known as



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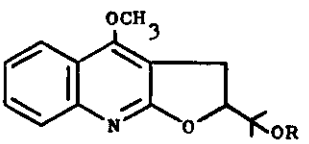
a : R = H; b : R = $COCH_3$

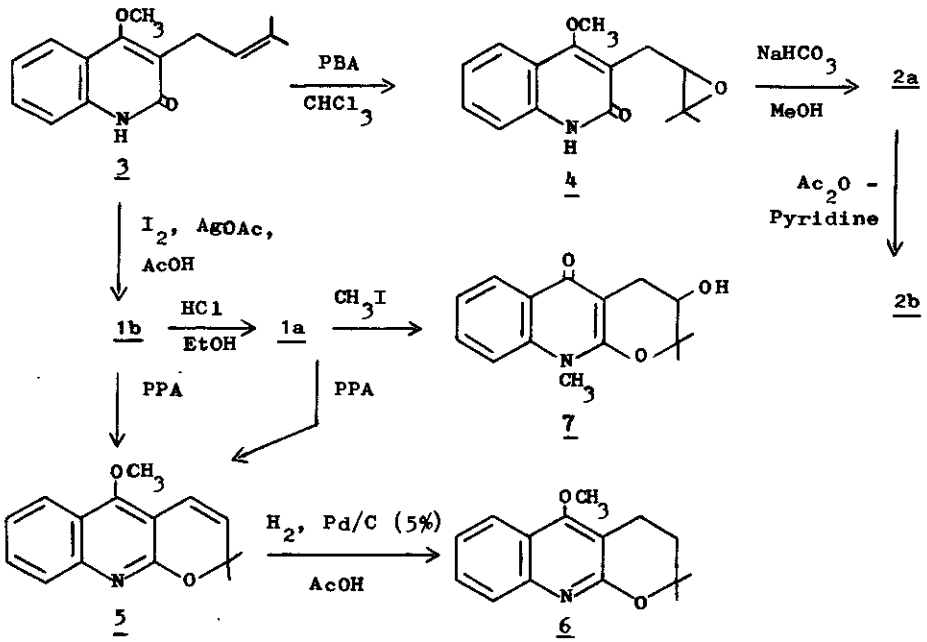


2

a : R = H; b : R = $COCH_3$

the alkaloid atanine[3,4] and treatment of the epoxide (4) with 2N hydrochloric acid. We wish to present now an alternative but elegant methodology for deriving the titled alkaloids from 3, a new synthesis of which has recently been reported[5] from this laboratory. Reaction of 3 with iodine, in the presence of silver acetate (two fold excess) in glacial acetic acid, gave a single product in 80% yield, identified as 3,4-dihydro-3-acetoxy-5-methoxy-2,2-dimethyl-2H-pyrano [2,3-b] quinoline (1b), on the basis of its analytical and spectral data which corresponded to that of acetylgeibalansine[1]. The synthesis of this alkaloid has not hitherto been reported.

On heating with 2% hydrochloric acid in ethanol, 1b readily afforded the alkaloid geibalansine (1a), the mp and spectral data of which corresponded to those reported for the authentic sample[1,2]. With the view to adducing further attestation of



the pyranoquinoline structure assigned for the products 1a and 1b, both were heated with polyphosphoric acid when they readily underwent dehydration and dehydroacetoxylation respectively to give 5-methoxy-2,2-dimethylpyrano [2,3-b] quinoline (5), the structure of which was confirmed by spectral data and by its ready reduction (H_2, Pd/C, 5%) to the known O-methylkhaplofoline (6)[5]. The transformation of 1a and 1b to 5 is similar to that of 3-acetoxy- or 3-hydroxy-2,3-dihydrofuro [2,3-b] quinoline[6] which with the same reagent, gave furo [2,3-b] quinoline.

1a on heating with methyl iodide furnished, as reported by Grundon et al.[2], the hydroxypyranoquinolone 7, the mp and spectral characteristics of which exactly corresponded to that of ribalinine (7)[7].

Interestingly the epoxide 4 (prepared from 3 and perbenzoic acid) when boiled with a solution of sodium bicarbonate in aqueous methanol gave neatly platydesmine (2a) in 70% yield, unlike in the acid-treatment[2] which led to a mixture of 1a (28%) and 2a (40%). Proof of the structure 2a for the product was obtained by its ready conversion to acetylplatydesmine (2b)[8] by heating with acetic anhydride and pyridine[8].

Thus, by choosing proper reagents and conditions, the prenylquinolone 3 can be synthetically manipulated to yield exclusively the pyranoquinoline 1b and from it 1a, or the furanoquinoline 2a.

EXPERIMENTAL

Melting points were determined on a Boetius microheating table and are uncorrected. The ^{1}H-NMR spectra were recorded on a Hitachi R-600 spectrometer (FT). The IR spectra were recorded on a Perkin-Elmer model 597 spectrophotometer.

O-Acetylgeibalansine (1b) - 3 (245 mg, 0.001m) was dissolved in glacial acetic acid (12 ml). After addition of silver acetate (335 mg, 0.002m), iodine (255 mg, 0.001m) was added in small portions to the vigorously stirred mixture over a period of 1 h at room temperature. After the addition, the reaction mixture was stirred for an additional hour. The silver iodide precipitate was filtered and washed with chloroform. The chloroform extract was washed successively with dilute solutions of sodium bicarbonate and sodium thiosulphate and then with water. It was dried over anhydrous sodium sulphate and evaporated. The residue obtained, was placed over a column of alumina and eluted with benzene-ethyl acetate (19:1). Evaporation of the solvent furnished 1b as colourless crystals. It was recrystallised from benzene as colourless needles (240 mg, 80%), mp 138-139°C; ir(CCl_4): $\tilde{\nu}$ 2850, 1720, 1600, 1380, 1360 and 1220 cm^{-1}; nmr(CCl_4): δ 1.45(s,6H, -C(CH$_3$)$_2$), 2.1(s,3H,OCOCH$_3$), 3.2(dd,2H, J = 14 and 5 Hz,-CH$_2$-CHOAc), 3.9(s,3H,OCH$_3$), 5.15 (m,1H,-CHOAc), 7.1-7.7(m,3H,C_7,C_8 and C_9-H) and 7.85(dd,1H, J = 9 and 3 Hz,C_6-H); m/e = 301.

Geibalansine (1a) - A mixture of 1b (300 mg) and 2% ethanolic hydrochloric acid (30 ml) was refluxed for 5 h and thereafter concentrated to a small bulk under reduced pressure. On dilution with ice-cold water a precipitate was formed, which was filtered and dried. Recrystallisation of the solid from benzene-ethanol afforded 1a as colourless crystals (220 mg, 85%), mp 175-176°C; lit[1]. mp 179°C, lit[2]. mp 175-176°C; ir(KBr): $\tilde{\nu}$ 3350 and 1610 cm^{-1}; nmr($CDCl_3$): δ 1.4(s,6H,-C(CH$_3$)$_2$), 2.8(dd,1H, J = 12 and 5 Hz, a 'H' of -CH$_2$-CHOH), 3.25(dd,1H, J = 12 and 5 Hz, a 'H' of -CH$_2$-CHOH), 3.96(m,1H,-CHOH), 4.0(s,3H,OCH$_3$), 7.2-7.9(m,3H,C_7,C_8 and C_9-H) and 8.1(dd,1H, J = 9 and 3 Hz, C_6-H); m/e = 259.

Treatment of 1b with polyphosphoric acid - 1b (150 mg) was mixed with polyphosphoric acid (1 g) and heated on a steam bath for 3 h and then poured into ice water. It was filtered and the clear filtrate was basified with dilute ammoniacal solution and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated. The pale yellow residue obtained was placed over a column of alumina and eluted with benzene. Evaporation of the solvent furnished

5 as colourless crystals. It was recrystallised from petrol-benzene as colourless needles (100 mg, 83%), mp 69-70°C; ir(CCl_4): ν 2900 and 1590 cm^{-1}; nmr(CCl_4): δ 1.5(s,6H,-$\dot{C}(CH_3)_2$), 4.0(s,3H,OCH_3), 5.9(d,1H, J = 9 Hz, Ar-CH=C<u>H</u>-), 7.6-7.8(m,4H, C_7,C_8 and C_9-H and Ar-C<u>H</u>=CH-) and 8.0(dd,1H, J = 9 and 3 Hz, C_6-H); m/e = 241.

<u>Treatment of 1a with polyphosphoric acid</u> - 1a was treated with polyphosphoric acid and the product worked up as in the above case. It was found identical in all respects (mp, ir, nmr) with 5 derived from 1b. Yield : 77%.

<u>Hydrogenation of 5</u> - To a solution of 5 (240 mg) in glacial acetic acid (30 ml) was added Pd/C (5%, 30 mg) and shaken with hydrogen at 60 lb in a Parr hydrogenator for 4 h. The catalyst was filtered off and the solution was diluted with water, neutralised with aqueous ammonia and extracted with chloroform. The chloroform extract after drying was evaporated and the residue was chromatographed over alumina in benzene to furnish 6 as a colourless solid. It was recrystallised from benzene-petrol as colourless needles (180 mg, 75%). It was found identical in all respects with O-methylkhaplofoline[5] (mp, ir, nmr).

<u>Ribalinine (7)</u> - A mixture of 1a (60 mg) and methyl iodide (10 ml) was heated under reflux for 12 h. Evaporation of the excess reagent furnished 7 as an amorphous solid. It was recrystallised from benzene-ethanol as colourless crystals (55 mg, 90%); mp 232 - 234°C(dec); ir(KBr): ν 3200 and 1620 cm^{-1}; nmr($CDCl_3$): δ 1.35 and 1.5(2s,3H each,-$\dot{C}(CH_3)_2$), 2.94(d,2H, J = 4.5 Hz, Ar-CH_2-$\dot{C}$HOH), 3.58(s,3H, NCH_3), 3.92(t,1H,-CH_2-$\dot{C}$HOH), 7.2-7.9(m,3H,C_7,C_8 and C_9-H) and 8.2(dd,1H, J = 9 and 3 Hz, C_6-H).

<u>Platydesmine (2a)</u> - 3 (245 mg) was stirred with perbenzoic acid in chloroform (30 ml) for 30 h at room temperature and was then diluted with more chloroform. It was filtered and the chloroform solution was washed with dilute sodium bicarbonate solution, dried over anhydrous sodium sulphate and then evaporated under reduced pressure. The resulting epoxide was then mixed with methanol(25 ml) to which 6 ml of a 4% solution of sodium bicarbonate in water was added and then refluxed for 8 h. After removal of the solvent under reduced pressure, it was diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulphate and evaporated when a solid product showing a single spot in its tlc analysis (silica gel, chloroform) was obtained. It was further purified by chromatography over alumina in chloroform and recrystallised from chloroform as colourless crystals (180 mg, 70%), mp 137-138°C, lit[2,8] mp

137-138°C; ir(KBr): ν 3200 and 1600 cm^{-1}; nmr($CDCl_3$): δ 1.15 and 1.5(2s,3H each, $-\dot{C}(CH_3)_2$), 3.25(dd,1H, J = 14 and 9 Hz, a 'H' of $-CH_2-$), 3.55(dd,1H, J = 14 and 6 Hz, a 'H' of $-CH_2-$), 4.0(s,3H,OCH_3), 4.7(dd,1H, J = 9 and 6 Hz,$-CH_2-CH-$), 7.0-7.7(m,3H,C_6,C_7 and C_8-H) and 7.9(dd,1H, J = 8 and 6 Hz,C_5-H); m/e = 259.

Acetylplatydesmine (2b) - 2a (260 mg) was refluxed with acetic anhydride (1 ml) in pyridine (2.5 ml) for 5 h and the excess reagents were removed under reduced pressure. The residue obtained was diluted with water and extracted with chloroform. The chloroform extract was washed several times with water and then dried. Evaporation of the solvent furnished 2b. It was recrystallised from benzene as needles, mp 126-127°C, lit[8]. mp 126-127°C; ir(CCl_4): ν 2990, 1730, 1600 cm^{-1}; nmr ($CDCl_3$): δ 1.25 and 1.5(2s,3H each,$-\dot{C}(CH_3)_2$), 1.95(s,3H,$OCOCH_3$), 3.4(d,2H, J = 6 Hz, $-CH_2-CH-$), 4.15(s,3H,OCH_3), 5.4(t,1H, J = 6 Hz,$-CH_2-CH-$), 7.05-7.8(m,3H,C_6,C_7 and C_8-H) and 7.9(dd,1H, J = 8 and 6 Hz,C_5-H); m/e = 301.

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REFERENCES

1) A. Ahond, C. Poupat and J. Pusset, Phytochemistry, 1979, 18, 141.

2) R.M. Bowman and M.F. Grundon, J. Chem. Soc. (C), 1966, 1504.

3) I.T. Eshiett and D.A.H. Taylor, J. Chem. Soc. (C), 1968, 481.

4) B.D. Paul and P.K. Bose, Indian. J. Chem., 1969, 7, 678.

5) M. Ramesh, V. Arisvaran, S.P. Rajendran and P. Shanmugam, Tetrahedron Lett., 1982, 23, 967.

6) P. Shanmugam, R. Palaniappan, N. Soundararajan, T.K. Thiruvengadam and K. Kanakarajan, Mh. Chem., 1976, 107, 259 and references cited therein.

7) R.A. Corral, O.O. Orazi and I.A. Benages, Tetrahedron, 1973, 29, 205.

8) S.R. Johns and J.A. Lamberton, Aust. J. Chem., 1966, 19, 1990.

9) All compounds gave satisfactory C,H analysis (± 0.2).

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