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# A NEW SYNTHESIS OF ATANINE, KHAPLOFOLINE AND THEIR ANALOGUES

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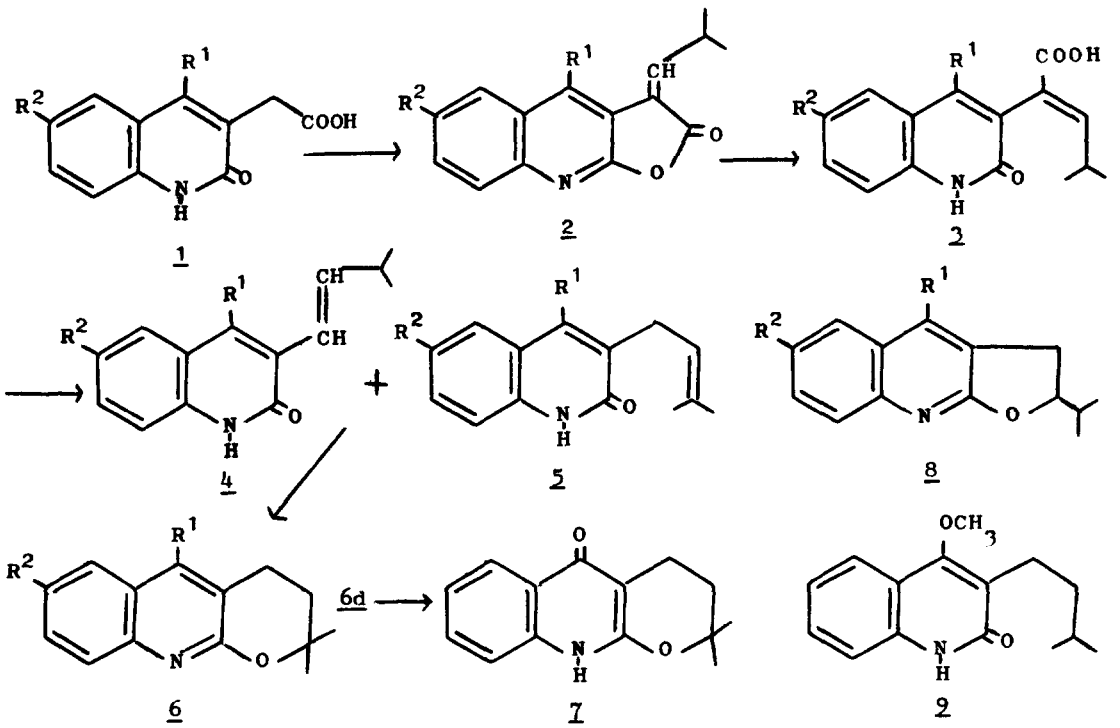
Summary : A facile synthesis of Atanine, Khaplofoline and their analogues is described. The method involves condensation of an appropriately substituted 2-quinolone-3-acetic acid with isobutyraldehyde, as the starting point.

Furoquinolines of the dictamnine group which occur in the Rutaceae[1] are often accompanied by alkaloids of 3-prenyl-2-quinolone (5), 2-isopropyl-dihydrofuroquinoline (8) and 2,2-dimethyldihydropyranoquinoline (7) series.

In connection with our synthetic studies on furo(2,3-b)quinolines, we recently reported[2] an one-step preparation of 2-quinolone-3-acetic acids(1) from N-phenylaconamides. In an effort to investigate their potential for the construction of the other alkaloid systems viz., 5, 7, and 8, we reacted 1a[2a] with isobutyraldehyde by heating with a mixture of acetic anhydride, sodium acetate and acetic acid for 1.5h. The product (m.p.210-211°), obtained in 80% yield, was identified as the isobutylidene-lactone 2a on the basis of elemental analysis ($C_{15}H_{13}O_2N$) and spectral data [$\nu_{max}^{CCl_4}$:1795 and 1635 (  ), 1380 and 1360cm$^{-1}$ (gem-dimethyl); $\delta_{(CCl_4)}$:1.18(d,6H,J=6Hz,-CH(C<u>H</u>$_3$)$_2$), 3.13(m,1H, -C<u>H</u>(CH$_3$)$_2$), 6.9(d,1H,J=7.5Hz,=C<u>H</u>-), 7.12-7.86(m,4H,ArH), 8.0(s,1H,$C_4$-H)ppm; $M^+$:239]. Cleavage of 2a with aqueous alkali, followed by acidification, gave the vinyl acid 3a m.p.234-235° in quantitative yield,($\nu_{max}^{KBr}$:1740,1660cm$^{-1}$), the structure of which was attested by the H.n.m.r. spectrum of its methyl ester m.p.192° [$\delta_{(CDCl_3)}$:0.70(d,6H,J=7.5Hz,-CH(C<u>H</u>$_3$)$_2$), 2.05(m,1H,-C<u>H</u>(CH$_3$)$_2$), 3.79(s, 3H,-COOC<u>H</u>$_3$), 5.55(d,1H,J=8Hz,=C<u>H</u>-), 7-7.75(m,5H,ArH), 13.5(br.s,1H,N<u>H</u>)ppm], derived from 3a by brief treatment with $CH_2N_2$ or from 2a by cleavage with methanol. The acid 3a on decarboxylation (Cu/$Ph_2O$) gave two products, A(24%)

and B(46%), both of which had the molecular formula $C_{14}H_{15}ON$ and were separated by chromatography over silica gel in benzene/ethylacetate. Compound A m.p.193-194° [$\nu_{max}^{CCl_4}$:2975(-NH), 1650(NH-C(=O)-)$cm^{-1}$; $\delta_{(CCl_4)}$: 0.97(d,6H,J=6Hz, $-CH(CH_3)_2$), 2.35(m,1H,$-CH(CH_3)_2$), 6.39(d,1H,J=6Hz,Ar-CH=), 6.9(d.d,1H,J=9; 6Hz,=CH-$CH(CH_3)_2$), 7.2-7.6(m,4H,ArH), 7.75(s,1H,$C_4$-H), 13.17(br.s,1H,NH)ppm; $M^+$:213] and compound B m.p.154-155° [$\nu_{max}^{CCl_4}$:2955(-NH), 1650(NH-C(=O)-)$cm^{-1}$; $\delta_{(CCl_4)}$: 1.48 and 1.54(2s,6H,=C($CH_3$)$_2$), 3.11(d,2H,J=6Hz,$-CH_2$CH=), 5.15(t,1H,J=6Hz, $-CH_2$CH=), 6.85-7.56(m,4H,ArH), 7.63(s,1H,$C_4$-H), 13.00(br.s,1H,NH)ppm; $M^+$:213] were assigned structures 4a and 5a respectively.




a) $R^1 = R^2 = H$; b) $R^1 = H$, $R^2 = CH_3$; c) $R^1 = CH_3$, $R^2 = H$; d) $R^1 = OCH_3$, $R^2 = H$.

Extension of the above synthetic sequence to 1b[2a], 1c[2a], and 1d[2b] gave the corresponding series of compounds : 2b(m.p.183°(dec),90%), 3b(m.p.241° (dec),100%), 4b(m.p.140-141°,28%) and 5b(m.p.115-117°,40%); 2c(m.p.164-165°, 90%), 3c(m.p.234°(dec),100%), 4c(m.p.162-164°,28%), 5c(m.p.213-214°,41%); 2d (m.p.115-116°,85%), 3d(m.p.211°(dec),100%), 4d(m.p.151-152°,28%) and 5d(m.p. 132-134°,42%) respectively. The side-chain moiety in 4b-4d and in 5b-5d was shown, as in 4a and 5a, by H.n.m.r. spectra, to be 3-methylbut-1-enyl and

3-methylbut-2-enyl respectively. The J-value between the vinylic protons was indicative for a cis double bond in 4a(J=6Hz) and 4b(J=8Hz) and a trans double bond in 4c(J=12Hz) and 4d(J=15Hz). 5d corresponds exactly to the alkaloid Atanine[3] in terms of its m.p, ir. and H.n.m.r.[4] It is pertinent to mention here that the vinylquinolone 4d, accessible by the above route, eluded the attempts of Huffman[5] at synthesis.

The allylquinolone 5a when heated with PPA for 3h, gave in 75% yield a base(m.p.94-96°) on workup. It was identified, on the basis of elemental analysis ($C_{14}H_{15}ON$) and spectral data [$\nu_{max}^{CCl_4}$:1610, 1150cm$^{-1}$; $\delta_{(CCl_4)}$=1.5(s,6H, $>C(CH_3)_2$), 1.86(t,2H,J=6Hz,-$CH_2$-$C(CH_3)_2$-), 2.93(t,2H,J=6Hz,Ar-$CH_2$-), 7.2-7.9(m, 4H,ArH), 7.93(s,1H,$C_4$-H)ppm and $M^+$:213], to be the dihydropyranoquinoline 6a. Interestingly, the vinylquinolone 4a gave rise to the same base 6a in 75% yield on heating with PPA; the expected 2-isopropyldihydrofuroquinoline 8a was not obtained. The pyranoquinolines 6b m.p.150-151° [$\nu_{max}^{CCl_4}$:1615, 1150cm$^{-1}$; $\delta_{(CCl_4)}$:1.5(s,6H, $>C(CH_3)_2$), 1.97(t,2H,J=6Hz,-$CH_2$-$C(CH_3)_2$-), 2.6(s,3H,Ar$CH_3$), 3.03(t,2H,J=6Hz,Ar$CH_2$-), 7.4-7.9(m,4H,ArH)ppm and $M^+$:227] 6c m.p.76-77° [$\nu_{max}^{KBr}$: 1615, 1150cm$^{-1}$; $\delta_{(CCl_4)}$:1.5(s,6H, $>C(CH_3)_2$), 2.14(t,2H,J=6Hz,-$CH_2$-$C(CH_3)_2$-), 2.65(s,3H,Ar$CH_3$), 3.15(t,2H,J=6Hz,Ar$CH_2$-), 7.4-8.2(m,4H,ArH)ppm and $M^+$:227] and 6d m.p.115° [$\nu_{max}^{CCl_4}$:1615, 1150cm$^{-1}$; $\delta_{(CCl_4)}$:1.43(s,6H, $>C(CH_3)_2$), 1.79(t,2H,J=6Hz, -$CH_2$-$C(CH_3)_2$-), 2.88(t,2H,J=6Hz,Ar$CH_2$-), 3.93(s,3H,$C_4$-O$CH_3$), 7.1-7.9(m,4H,ArH) ppm and $M^+$:243] were derived likewise from the vinylquinolones 4b-4d as well as from the prenylquinolones 5b-5d in 75-80% yield. The pyranoquinoline 6d which corresponds to the O-methyl derivative of the alkaloid Khaplofoline,[8] readily underwent demethylation on boiling with hydrochloric acid in ethanol solution[9] to give a product in 96% yield, recrystallised from ethyl acetate as prisms m.p.272-274°(dec). The m.p. as well its spectral properties exactly corresponded to those reported[10] for an authentic sample of Khaplofoline (7). Methylation[8] gave its N-methyl derivative, the m.p.(120-121°) and spectral data of which corresponded to those of the authentic sample.[10]

Satisfactory analytical and/or spectral data were obtained for all compounds. Reaction conditions were not optimised.

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