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APPLICATION OF ENAMINE PHOTOCYCLISATION TO A TOTAL SYNTHESIS OF (±)-CRYPTAUSTOLINE

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(±)-Cryptaustoline (1) was synthesised by the route including enamine photocyclisation.

Dibenzopyrrocoline alkaloids, cryptaustoline (1) and cryptowoline (2), were isolated from the bark of Cryptocarya plants[1] and have been synthesised by applying the benzyne cyclisation[2].

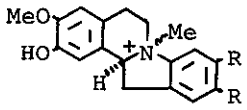
During the course of our study on the application of photocyclisation of nitrogen containing unsaturated systems, we found that the enamine photocyclisation, which was first developed by Chapman[3], could apply to the synthesis of dibenzopyrrocoline skeleton. We now report a new total synthesis of (±)-cryptaustoline (1) by applying the enamine photocyclisation.

First we investigated the stability of the enamine (6) and a possibility of the photocyclisation by using the compound (6a) which was prepared as follows; the phenylacetanilide (3a) [ν max 3400 (NH), 1680 (NCO) cm^{-1}], which was readily prepared by acylation of aniline with 3,4-dimethoxyphenylacetyl chloride in 90 % yield, was reduced with $LiAlH_4$ to afford the sec-amine (4a) [ν max 3400 (NH) cm^{-1}] in 94 % yield which was then acetylated to yield the corresponding N-acetate (5a) [ν max 1650 (NCO) cm^{-1}].

The Bischler-Napieralski reaction of the N-acetate (5a) proceeded smoothly to yield the 1-methylene-2-phenyltetrahydroisoquinoline (6a) quantitatively, which was unstable particularly to moisture, thus forming the ring-opened acetophenone. The spectral data of the enamine (6a) [ν max 1550 (NC=C) cm^{-1}, δ 7.48-6.52 (9H, m, arom. and olefin. H)] established its structure.

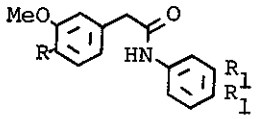
Irradiation of an ethereal solution (0.001-0.002 M) of the enamine (6a) with a high pressure mercury lamp at room temperature afforded a mixture of photocyclised products (7a and 8a) in 10 and 20 % yields respectively, of which the latter product (8a)[4] was readily converted into the former (7a) upon treatment with Sn- HCl. The structures of photoproducts were solidly established from their n.m.r. spectra [(7a), δ 6.67 (1H, s, 1-H), 6.50 (1H, s, 4-H), 4.85 (1H, br dd, J=8 and 4.5Hz, 12a-H); (8a), δ 7.23 (1H, s, 1-H), 6.73 (2H, s, 4- and 12-H)].

With the results obtained from the preliminary experiment, we next carried out total synthesis of cryptaustoline (1),

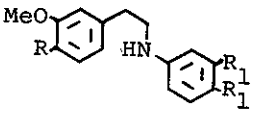


(1) R=MeO cryptaustoline

(2) R=OCH_2O cryptowoline



(3a,b,c)



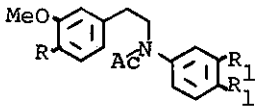
(4a,b,c)

(3,4,5,6)

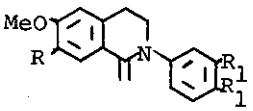
a : R=MeO R_1=H

b : R=$PhCH_2O$ R_1=MeO

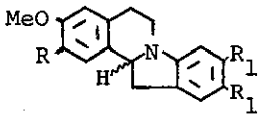
c : R=i-PrO R_1=MeO



(5a,b,c)



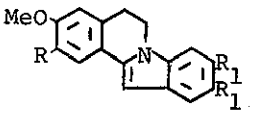
(6a,b,c)



(7a,b)

a : R=MeO R_1=H

b : R=HO R_1=MeO

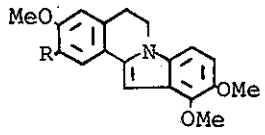


(8a,b,c)

a : R=MeO R_1=H

b : R=HO R_1=MeO

c : R=i-PrO R_1=MeO

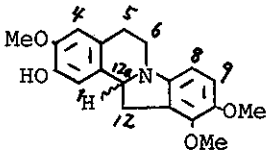


(9a,b,c)

a : R=$PhCH_2O$

b : R=HO

c : R=i-PrO



(10)

in which the protection of a hydroxy group became a crucial problem to overcome for a total synthesis.

First we employed a benzyl as its protective group as in the enamine (6b) which was readily prepared from the corresponding N-phenethylaniline (4b) [ν max 3400 (NH) cm^{-1}] as above.

Irradiation of an ethereal solution of the enamine (6b) [νmax 1550 (NC=C) cm^{-1}] afforded a mixture of two types of photocyclised products (8b, 9a and 9b) in 1, 8 and 1 % yields, respectively, depending on the direction of cyclisation. Their structures were deduced mainly from their spectral data [(8b), ν max 3550 (OH), 1550 (NC=C) cm^{-1}, δ 7.28, 7.09, 6.81, 6.74, 6.63 (each 1H, s, 1-, 4-, 8-, 11-, and 12-H), 5.60 (1H, s, OH); (9a), ν max 1550 (NC=C) cm^{-1}, δ 7.32, 6.80, 6.73 (each 1H, s, 1-,4-, and 12-H), 6.94 (2H, s, 8- and 9-H), 5.22 (2H, s, $-C\underline{H}_2Ph$); (9b), ν max 3550 (OH), 1550 (NC=C) cm^{-1}, δ 7.36, 6.83 , 6.78 (each 1H, s, 1-,4-, and 12-H), 6.97 (2H, s, 8- and 9-H), 5.60 (1H, br s, OH)].

Reduction of the dehydrogenated photoproduct (9a) with Sn-HCl in 95 % EtOH brought about spontaneous debenzylation to afford the dibenzopyrrocoline (10) in 90 % yield, which showed the following spectral data [ν max 3550 (OH) cm^{-1}, δ 6.78 (1H, s, 1-H), 6.69, 6.29 (each 1H, d, J=8Hz, 8- and 9-H), 6.49 (1H, s, 4-H), 5.58 (1H, br s, OH), 4.80 (1H, dd, J=8.5 and 4Hz, 12a-H)].

The dibenzopyrrocoline (10) was converted into the corresponding quaternary salt (methyl iodide), m.p. 184-187°, which was not identical with cryptaustoline[2a], therefore, established the structure (10).

Due to poor yields of the photocyclisation, we next carried out the experiment with the compound having an isopropyl group as the protection of a hydroxy group.

The phenylacetanilide (3c) [ν max 3400 (NH), 1670 (NCO) cm^{-1}] was reduced with $NaBH_4$-AcOH in THF[5] to afford the sec-amine (4c) [ν max 3400 (NH) cm^{-1}], which was then acetylated to give the N-acetate (5c) [ν max 1640 (NCO) cm^{-1}].

The Bischler-Napieralski reaction of the N-acetate (5c) proceeded smoothly to afford the enamine (6c) in 87 % yield [ν max 1560 (NC=C) cm^{-1}].

Irradiation of an ethereal solution of the enamine (6c) yielded a mixture of two types of the dehydrogenated photoproducts (8c and 9c) in 12 and 11 % yields respectively, depending on different directions of cyclisation. Their structures were deduced from their spectral data [(8c), m.p. 160-161°, ν max 1550 (NC=C) cm^{-1}, δ 7.27, 7.11, 6.84, 6.79, 6.65 (each 1H, 1-,4-,8-,11-, and 12-H), 4.62 (1H, septet, J=6Hz, $Me_2\underline{CH}$), 1.40 (6H, d, J=6Hz, $\underline{Me}_2CH$); (9c), m.p. 148-149°, ν max 1550 (NC=C) cm^{-1}, δ 7.33 (1H, s, 1-H), 6.97,(2H, s, 8- and 9-H), 6.82, 6.78 (each 1H, s, 4- and 12-H), 4.62 (1H, septet, J=6Hz, $Me_2\underline{CH}$), 1.39 (6H, d, J=6Hz, $\underline{Me}_2CH$)].

Removal of the protective group of the photocyclised product (8c) was readily achieved by treatment with 48% HBr in AcOH[6] upon heating for 1.5 hr without damaging any methoxy groups present, thus yielding the hydroxydehydrodibenzopyrrocoline (8b) in 61 % yield. Reduction with Sn- HCl in 95% EtOH converted the dehydrodibenzopyrrocoline (8b) into the dibenzopyrrocoline (7b) quantitatively, which was further converted into the corresponding methyl

iodide (1), m.p. 255-256° (lit.[2a] 260°). The identity of the quaternary salt (1) with racemic cryptaustoline furnished a new total synthesis of the dibenzopyrrocoline alkaloids and proved a usefulness of enamine photocyclisation.

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* Unless otherwise mentioned, i.r. spectra were measured in chloroform and n.m.r. in deuteriochloroform with tetramethylsilane as internal standard.

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