Tetrahedron Vol. 34, pp. 3001–3004
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0040-4020/78/1001-3001/$02.00/0

SYNTHESIS OF COMPOUNDS RELATED TO VINCA ALKALOIDS

STEREOSELECTIVE SYNTHESIS OF (±) HOMOEBURNAMINE

A. BUZAS* and C. RETOURNE
Laboratoire de Synthèse Organique, U.E.R. Sciences, 45045, Orléans Cedex, France

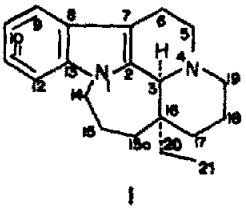
and

J. P. JACQUET and G. LAVIELLE
Laboratoires SAUBA, 260 rue de Rosny, 93104, Montreuil-Sous-Bois, France

(*Received in U.K.* 7 *April* 1978; *Accepted for publication* 8 *May* 1978)

Abstract—Base catalysed addition of acrolein to 1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3a] quinolizine (perchlorate) **5b** gives a pentacyclic alcohol **6b**, which can be reduced in excellent yield to (±) homoeburnamine **7**, a convenient precursor of (±) homoeburnamenine **9** and (±) homoeburnamonine **11**.

It has been shown by Gibson and Saxton[1] that derivatives of homoeburnane **1**, substituted at C-14 and C-15 undergo rearrangement to alkaloids related to vincamine **2** and eburnamonine **3**. Appropriate substitution and reaction conditions enable 7- to 6-membered ring transformation with concomittant functionalisation of C-14 in a desired fashion.[2] Thus (both) homoeburnamenine **9** and homoeburnamonine **11** led to vincamine in two separate synthetic routes.[2a,c] In this paper we wish to report a rapid, stereoselective synthesis of **9** and **11**, starting from a novel compound, i.e. homoeburnamine **7**.†



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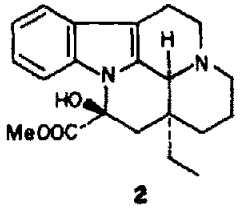

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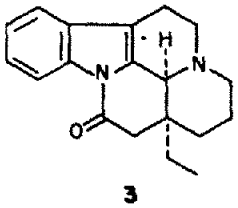

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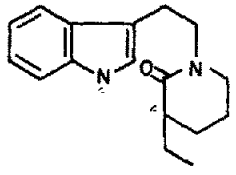
Synthesis of (±) *homoeburnamine and* (±) *epihomoeburnamine*

There is a common method for preparation of the homoeburnane **1** derivatives employing condensation of acrylate with either an anion derived from lactam **4** or enamine **5b**.[3] The acrylic double bond is then inserted into C_{15}–C_{15a}, position of newly created homoeburnane skeleton.



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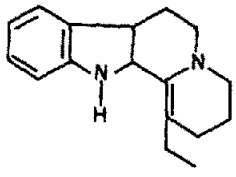


5b

Accordingly Schut *et al.*[4] described the condensation of 2,3,4,6,7,12-hexahydroindolo [2, 3a] quinolizine **5a** with acrolein to give a pentacyclic alcohol **6a** in excellent yield (82%) (Fig. 1). It seems surprising that this reaction apparently has not been extended to 1-substituted enamines, as in such a case the condensation product would be directly related to the natural series, i.e. vinca alkaloids. This extension to **5b** has been the principal aim of our work presented here.

We have confirmed experimentally that the reaction of enamine **5b** with acrolein under condition of Shut (boiling THF-benzene) afforded the condensation product **6b** in an inacceptably low yield. Similarly other aproting solvents (ex. methylene chloride) offered no substantial improvement of the reaction scope.

These results can be interpreted in terms of electrostructural differences between **5a** and **5b**. Intra and intermolecular proton exchange in **5a**-bearing a hydrogen at C-1- enables effective charge dissipation in the reaction course leading ultimately to a pentacyclic enamine **6a**. Contrarily, no such dissipation is possible for the immonium alcoholate **6'b** resulting from **5b** (Fig. 2).

Introduction of an appropriate proton donor would eventually stabilize the immonium carbinoloamine (salt) **6'b**.

Direct preparation of immonium perchlorate **6b**

It seemed both convenient and feasible to utilise a salt of enamine **5b** for protonating effectively the unstable intermediate **6'b**. Indeed, condensation of **5b** perchlorate with acrolein in methylene chloride proceeded smoothly and quantitatively to give **6b** perchlorate if either

†After completion of our work, an article of J. Le Men[16] appeared, describing an alternative synthesis of **7**.

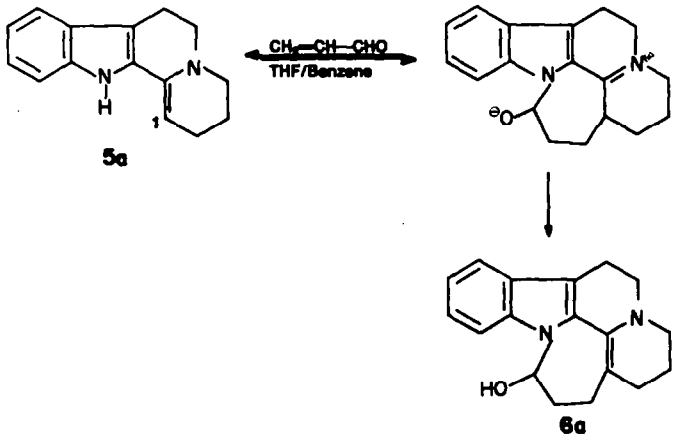


Fig. 1.

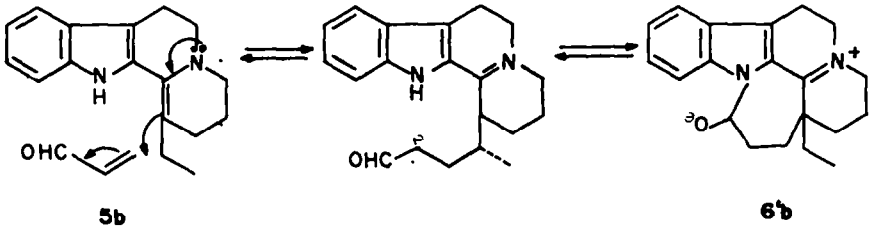


Fig. 2.

triethylamine (1 eq) or a catalytic amount of potassium t-butylate were applied. The reaction mixture turned homogenious before final precipitation of **6b** salt.

The reaction appeared highly stereoselective as the crude product contained ~9:1 ratio of the diastereoisomers (^{1}H NMR data) (Fig. 3).

Reduction of **6b** *to* **7** *or* **8**

Gootjes and Nauta[6] demonstrated that a proper choice of reduction conditions can change the reduction course of immonium indolo or benzo(a) quinolizines. For example, sodium borohydride and hydrogen (evolved *in situ*) reductions give virtually inverse ratios of the appropriate quinolizines (usually with one isomer predominating). These observations were applied successfully during recent synthesis of vincamine[7] and vincamone.[8]

Homoeburnamine **7**

Reduction of **6b** with zinc dust –aqueous acetic acid gave homoeburnamine **7b** (78% yield) stereoselectively (C/E rings). The absence of Bohlmann bands showed its cis-quinolizidine junction as well as a downfield shift of H-3 ($\delta \cong 4$ ppm).

16-*Epi-homoeburnamine* **8**

Reduction of **6b** with sodium borohydride-methanol at 0° yielded exclusively 16-epi-homoeburnamine **8**. The trans-quinolizidine junction was evident from the appearance of Bohlmann bands at 2830 and 2770 cm^{-1} as well as from the upfield shift of H-3 ($\delta = 3.4$ ppm).

Homoeburnamenine **9** *and* 16-*epi-homoeburnamenine* **10**

Refluxing in toluene effects quantitative dehydration of **7** to **9** whereas dehydration of **8** to **10** is much slower and incomplete in the same conditions. The characteristics of **9** and **10** are in agreement with those reported previously.[1]

Oxidation of **7** *and* **8** *to homoeburnamonine* **11** *and* 16-*epihomoeburnamonine* **12**

Hydroxyl oxidation in alkaloid molecule may become sometimes a delicate process; very good results can be often achieved by application of the Fetizon reagent (Ag_2CO_3-celite).[11] Unfortunately, alcohol **7** underwent considerable dehydration during the attempted oxidation in boiling xylene so diminishing considerably the final output of **11**. Similarly the conditions applied by Bartlett and Taylor[12] for eburnamine oxidation did not give in our case reproducible results. Relatively the best yields of the respective lactams **11** and **12** were obtained by oxidation of alcohols **7** and **8** at 25° with CrO_3-pyridine-triethylamine.

Thus alcohol **8** was converted completely into **12**, the alcohol **7** reacted incompletely (~70%) unless the temperature was elevated but then significant decomposition occurred. The date of **11** and **12** corresponded to those reported previously.[2a]

Stereochemical relations of the alcohols **7** *and* **8**

For conclusive clarification of the alcohols **7** and **8** stereochemistry, lactams **11** and **12** were reduced with LAH in mild conditions (THF, 0°).[13] Reduction of **11** gave 4:1 mixture of C-14 epimeric alcohols **7** and **7'**. We ascribed an axial configuration to the prevailing alcohol **7** on the basis of the following data:

(a) Downfield shift of the carbinyl proton of **7** ($\delta = 6.05$ ppm) relatively to that of **7'** ($\delta = 5.7$ ppm), accordingly to the well-known tendency of equatorial protons to appear at the weaker field.[14] (b) Easy dehydration of **7** (vide

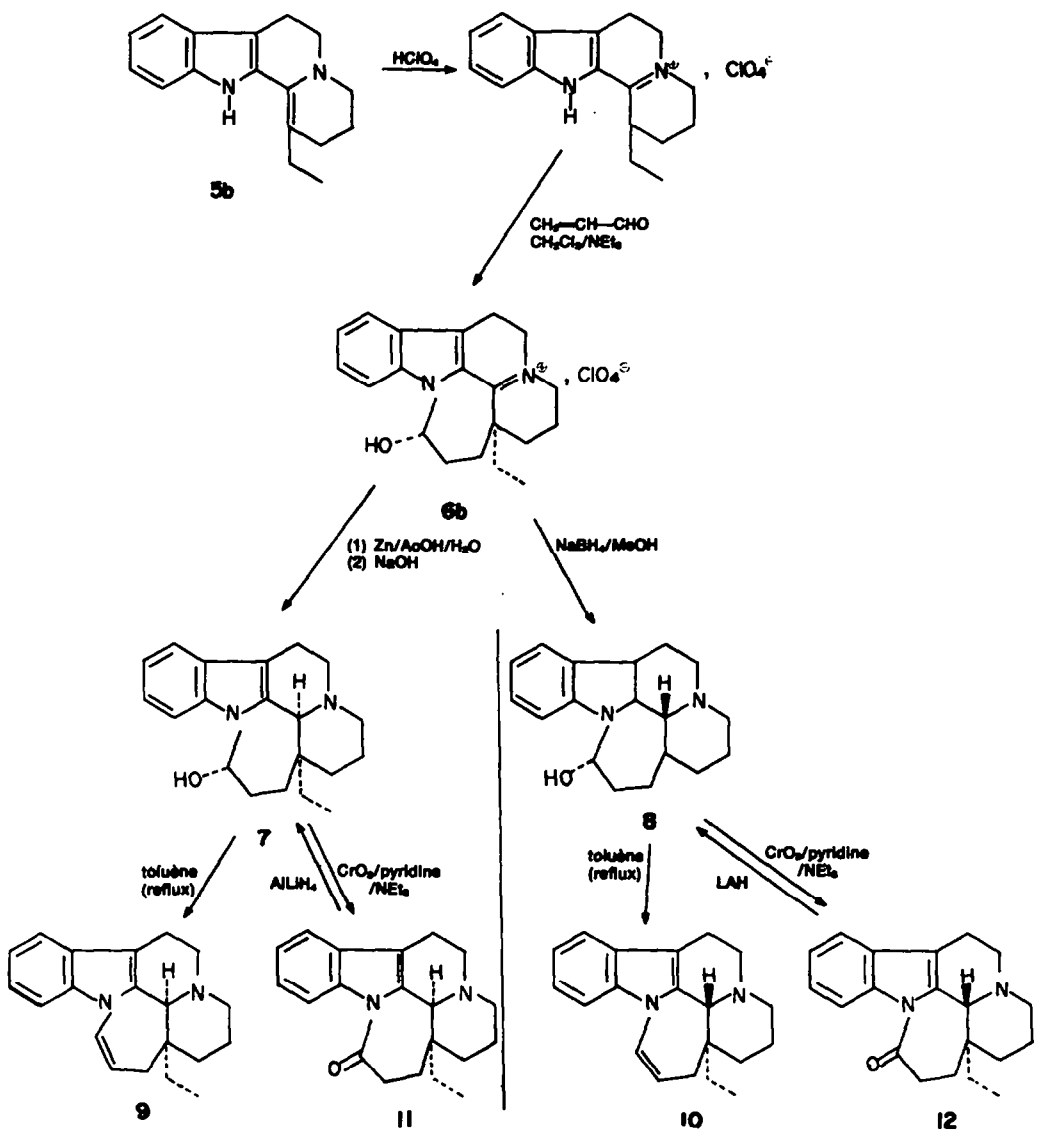
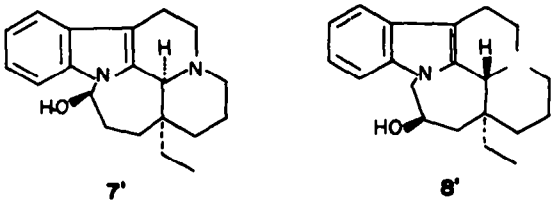


Fig. 3.

supra), also at moderately elevated temperature in vacuum. (c) Higher mobility of 7 relatively to 7' on chromatoplates.[15]

Reduction of 12 produced 1 : 1 mixture of C-14 epimeric alcohols 8 and 8'. The axial one (8) exhibiting downfield position of the carbinyl proton ($\delta = 6.25$ ppm) relatively to the equatorial (8') ($\delta = 5.95$ ppm).



EXPERIMENTAL

M.ps were determined on a Kofler hot-stage apparatus and were uncorrected. Microanalyses were performed by CNRS, Thiais, France. IR spectra were recorded in KBr on a Perkin-Elmer Infracord 257, NMR spectra on Perkin-Elmer R 24 B spectrometer (60 MHz, TMS internal standard). Tlc plates (Merck silica gel 60 F 254) were developed in chloroform - acetone - diethylamine 5 : 4.1 (immonium salts) or methylene chloride-methanol: 1 and visualized by UV or Dragendorff reagent.

Perchlorate 6b. To a suspension of 5b (9.6g) in CH_2Cl_2 Et_3N (2.4g = 0.9 eq) was added and then acrolein (2.6 ml = 2 eq) and the mixture was stirred at room temp for 24 hr. The resulting crystalline material was collected, washed with CH_2Cl_2 and dried giving 10.3 g (94%) of 6b, m.p. : 230°. (Found: C, 58.77; H, 6.14; N, 6.84. $C_{20}H_{23}N_2O_5Cl$ requires: C, 58.74; H, 6.16; N, 6.85%). IR spectrum (KBr) showed prominent bands at 3460 cm^{-1} (OH), 1610 cm^{-1} ($C{=}N^+$).

^1H NMR spectrum (DMSO d_6) : $\delta = 0.8$ (3H, t, CH_2–CH_3); 3.3 (1H, s, OH); 5.9 (0.1H, t, $C_{14}\underline{H}OH$); 6.4 (0.9H, t, $C_{14}\underline{H}OH$).

Homosubmamine 7. A mixture of 6b (10 g) and Zn powder (35 g) in AcOH (250 ml) and water (500 ml) was stirred at room temp. for 24 hr and then filtered to remove Zn and salts. The filtrate was extracted several times with CH_2Cl_2. The extracts were made alkaline with 10% NaOH aq and then washed with water, dried and evaporated in vacuum. Crystallisation of the residue from diisopropylic ether gave 4.5 g (60%) of 7, m.p. : 182°. (Found : C, 77.04; H, 8.75; N, 9.15. $C_{20}H_{26}N_2O$ requires : C, 77.38; H, 8.44; N, 9.03%). IR spectrum (KBr) showed prominent

band at 3340 cm^{-1} (OH). ^1H NMR spectrum ($CDCl_3$): $\delta = 0.9$ (3H, t, CH_2–$\underline{CH_3}$); 4 (1H, s, C_3H); 6.1 (1H, t J = 3Hz, $C_{14}\underline{H}OH$).

16-Epihomoeburnamine **8**. Sodium hydrochloride (2.5 g) was added slowly to a mixture of **6b** (6g) in MeOH (50 ml) cooled in ice. The mixture was stirred at room temp for 6 hr. After removal of MeOH in vacuum, addition of water resulted in white crystals of crude **8**. Recrystallisation from MeOH gave 4.3 g (94%) of pure **8**, m.p.: 191°. (Found: C, 77.21; H, 8.45; N, 9.08. $C_{20}H_{26}N_2O$ requires: C, 77.38; H, 8.44; N, 9.03%). IR spectrum (KBr) showed prominent bands at 3140 cm^{-1} (OH), 2830–2770 cm^{-1} (B.B.). ^1H NMR spectrum ($CDCl_3$): $\delta = 0.8$ (3H, t, CH_2–$\underline{CH_3}$); 3.4 (1H, s, $C_3\underline{H}$); 5.8 (1H, t J = 3Hz, $C_{14}\underline{H}OH$).

Homoeburnamenine **9** *and* *16-epihomoeburnamenine* **10**. A soln of **7** (0.5 g) in dry toluene (400 ml) was refluxed for 2 hr under a water separator. Removal of solvent in vacuum left crude **9** which crystallized from hexane 0.45 g (95%). m.p.: 115°.

Compound **10** was prepared according to the same procedure except that reflexing time was extended to 20 hr (the reaction was not completed). m.p.: 104°. NMR and IR spectrum were identical with those of products described by Gibson.[1]

Homoeburnamonine **11** *and* *16-epihomoeburnamonine* **12**. CrO_3 (1 g) was added in small portions to a solution of **7** (1 g) in pyridine (20 ml) and Et_3N (1.5 ml) with intermittent cooling to keep the temp. below 25°. The mixture was stirred 0.5 hr at room temp. and then filtered through alumina using CH_2Cl_2 as an eluent. The eluate was evaporated in vacuum and dried under reduced pressure. Crystallisation from either gave 0.45 g of pure **11** (45%). m.p.: 164°.

Similar conditions were employed for oxidation of **8** (1 g). Crystallisation from CH_2Cl_2–MeOH gave 0.5 g of pure **12** (50%). m.p.: 152°.

Reduction of **11** *and* **12**. LAH (0.15 g) in dry THF (5 ml) was added slowly at 0° to a stirred soln of **11** or **12** (0.6 g) in dry THF (20 ml). After few min, excess of hydride was destroyed with EtOAc (5 ml), water (5 ml) and 10% NaOH aq (15 ml). Insoluble solid was filtered off and the filtrate concentrated to small volume under reduced pressure. The aqueous layer was then extracted with CH_2Cl_2, washed with water and evaporated giving 0.6 g of crude product.

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