# A Revision of the Synthesis of some Polycyclic Systems Related to Benzoheteroquinolizidines



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The preparation of 3-methoxycarbonyl-*N*-2-(3-benzo[*b*]thienyl)ethylpyridinium bromide, 5-methoxycarbonyl-*N*-2-(3-benzo[*b*]thienyl)ethyl-1,2,3,4-tetrahydropyridine and (1RS,12bRS)-1-methoxycarbonyl(benzo[*b*]thienyl[2,3-*a*]quinolizidine is described. Some observations dealing with different methods discussed in the literature for the synthesis of such polycyclic systems are reported.

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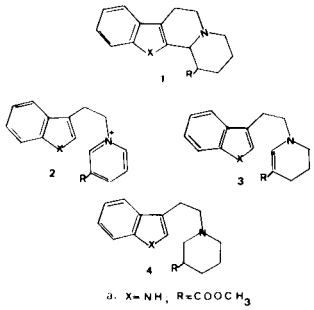
In connection with another study we have had the need to prepare a variety of benzoheteroquinolizidines **1**. In the preparation of these polycyclic systems we have found some differences in the reported methods. Due to the interest in this class of compounds, in the present work we wish to report some observations concerning this topic.

Various methods of synthesis of benzoheteroquinolizidines **1** which are of interest, are based on the reductive cyclisations of derivatives such as **2** *via* $\Delta^2$-piperidine intermediates **3** (*cf.* Scheme 1). Wenkert *et al.*, have

Scheme 1




demonstrated an unusual hydrogenation (the conversion of the pyridinium salt **2a** into the tetrahydropyridine **3a**) as well as acid-induced cyclisation (**3a** to **1a**) as a crucial, two-step reaction sequence in the construction of the alkaloidal indoloquinolizidine skeleton (1). In this hydrogenation, the presence of a pyridine substituent to stabilize the double bond of the piperidine intermediate, and an alkaline medium were considered important requisites for the reaction. Hydrogenation of an ethanolic solution of **2a** and triethylamine over palladium on charcoal yielded predominantly the tetrahydroproduct **3a**.

By contrast, Chapmann, *et al.* (2), have described the **2b** → **3b** transformation by hydrogenation with 5% palladium on charcoal in 50% aqueous ethanol in high yield (73%). In our hands the reduction of compound **2c** under the experimental conditions described by Chapmann allowed us to isolate a substance (70%) yield, the analysis and spectroscopic data of which are in good agreement with the structure **4c** (*cf.* Scheme 1). Compound **3c** was not detected.

In view of these results we tested the reduction by Wenkert's method. Hydrogenation of the pyridinium salt **2c** in methanol at normal pressure and room temperature using triethylamine as a base, yielded exclusively one product **3c** in 41% yield.

3-Methoxycarbonyl-*N*-2-(3-benzo[*b*]thienyl)ethylpyridinium bromide (**2c**) was obtained by condensing 3-(2-bromoethyl)benzo[*b*]thiophene (3) with 3-methoxycarbonylpyridine. The reaction was allowed to stir for 17 hours at 80° under an atmosphere of nitrogen. Subsequently the reaction mixture was cooled and a precipitate was obtained that was identified as the compound **2c**, m.p. 196° dec. (64.8%).

With respect to the second step, the **3** → **1** transformation proceeded for the indoloquinolizidine system (**3a** → **1a**) in methanol saturated with hydrochloric acid at room temperature (1). Chapmann *et al.* (2), have described the preparation of **1b** in 71% yield by refluxing **3b** for 3 hours in concentrated hydrochloric acid. In our laboratory, heating a solution of 500 mg. of **3c** in hydrochloric acid for 1.5 hours led to the isolation of 216 mg. (43%) of starting material following chromatography. A fraction eluted with benzene gave spectroscopic data suggesting fragmentation of compound **3c**. A second run made by heating the reaction mixture at 80° for 30 minutes led after the usual work-up to 5% of compound **1c**.

Subsequently, we prepared **1c** in 83% yield by dissolution of **3c** in a cold solution of methanol saturated with hydrochloric acid under an atmosphere of nitrogen, similar to the preparation of indoloquinolizidines. The **3c** → **1c** cyclisation was accompanied by the creation of two assimetric centers. However, the *trans* C/D ring fusion and the preferential equatorial conformation of the carboxymethyl group in the 1-position led to the stereoselective formation of one of the two possible racemates, *viz.*, the *trans* racemate (4). This conclusion was confirmed by spec-

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Table I

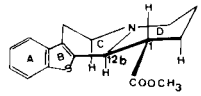
Chemical Shifts of Pyridinic Protons of Salts **2** (a)

| Compound No. | $H_2$ | $H_4$ | $H_5$ | $H_6$ | J (cps) (b) $J_{2,4}$ | $J_{4,5}$ | $J_{5,6}$ |
|---|---|---|---|---|---|---|---|
| **2a** | 9.35 (c) | 8.80 m | 8.20 m | 9.15 m | 3 | 10.5 | 7.5 |
| **2b** | 9.65 (c) | 9.05 m | 8.40 dd | 9.48 dd | 3 | 10.5 | 7.5 |
| **2c** | 9.75 (c) | 9.08 dd | 8.40 dd | 9.35 dd | 3 | 9 | 6 |
| **2d** | 9.05 dd | 8.50 m | 8.10 m | 9 dd | | (d) | |
| **2e** | 9 dd | 8.50 m | 8.10 m | 9 dd | | (d) | |

(a) Measurements were taken in dimethylsulphoxide (δ values). Abbreviations: dd = doublet, m = multiplet. (b) Spectral analysis was possible by 1st order approach. (c) Broad singlet. (d) These values are not directly determined.

tral data. Thus, compound **1c** showed well defined Bohlmann bands at 2760 and 2808 $cm^{-1}$ in the ir, as well as an nmr signal at C(12b)-H at 4 ppm, indicating a *trans*-quinolizidine structure (5). The value of the $J_{12b\text{-}1} = 9$ cps is in good agreement with the equatorial position of the carboxymethyl group (6) (*cf.* Figure 1).

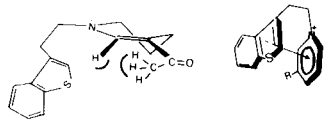
Figure 1




The cyclisation of **3b** to **1b** was investigated using a variety of experimental conditions. Starting products or variable amounts of unidentified products were obtained in the reaction mixture (7).

It seems reasonable to assume that a particular geometry of the molecule can be related to the difficulty of cyclisation. Thus, the shielding effect showed by the absorption of the =C-H tetrahydropyridine proton in **3b** (signal at 7.1 ppm) with respect to the absorption of **3a** (signal at 7.4 ppm) and **3c** (signal at 7.3 ppm), and the shift of the absorption position of $CH_3CO$ to higher field (1.9 ppm as opposed to 2.3-2.5 ppm) could be attributed to the preferential stabilization of the molecule in a conformation such as that indicated in Figure 2 (left side). This conformation is favoured by the presence of the benzothiophene ring, and provokes a steric compression related to the observed shielding effects. In support of this proposal, the allylic protons in **3b** appear as a more complex signal (2.2 ppm, base line width 24 cps). Compounds **3a** and **3c** show a triplet at 2.1 ppm (base line width 19.5 cps). The chemical shifts of the remaining tetrahydropyridine protons are given in the Experimental. A good correlation between the different compounds **3a, 3b,** and **3c** is noted.

Figure 2



The possible participation of the benzothiophene ring in this preferential conformation has been established from the shifts of the pyridine protons of the salts **2**. Thus, compounds **2b** and **2c** show a deshielding effect for such hydrogens with respect to **2a** (see Table I). It may be assumed that this fact is proceeded by interaction between the pairs of electrons of the sulfur atom with the pyridine protons, which is favoured by an intramolecular charge transfer complex, as indicated in Figure 2 (right side). The presence of the group -CO- must be an important requisite in this result, since such differences are not observed in the salts **2d** and **2e** (9a) (see Table I).

## EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12B Spectrometer using TMS as an internal standard. Chemical shifts are reported as δ values in parts per million (ppm). Elemental analyses were performed by Instituto de Quimica Organica, Barcelona.

3-Methoxycarbonyl-*N*-2-(3-indolyl)ethylpyridinium Bromide (**2a**).

Compound **2a** was obtained in 84% yield according to the procedure of Wenkert (1), m.p. 219-220°; nmr (DMSO-$d_6$): 9.35-8.2 (4 pyridine protons, see Table I), 7.4-6.95 (m, 6, indole ring), 5 (t, 2, $-CH_2N$-), 3.60 (t, 2, Ar-$CH_2$-), 3.90 (s, 3, $COOCH_3$).

*Anal.* Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.66; H, 4.12; Br, 21.94; N, 11.18. Found: C, 56.50; H, 4.15; Br, 21.72; N, 10.95.

3-Acetyl-*N*-2-(3-benzo[*b*]thienyl)ethylpyridinium Bromide (**2b**).

Compound **2b** was obtained in 80% yield according to the procedure of Chapmann (2), m.p. 208-209°; nmr (DMSO-$d_6$): 9.65-8.4 (see Table I), 8.1 (m, 2, $C_4$-H, $C_7$-H benzothiophene), 7.5 (m, 3, $C_2$-H, $C_5$-H, $C_6$-H benzothiophene), 5.2 (t, 2, $-CH_2$-N), 3.7 (t, 2, Ar-$CH_2$), 2.8 (s, 3, $COOCH_3$).

*Anal.* Calcd. for $C_{17}H_{16}BrNOS$: C, 56.51; H, 4.43; Br, 21.88; N, 3.87; S, 8.86. Found: C, 56.44; H, 4.41; Br, 21.75; N, 3.80; S, 8.65.

3-Methoxycarbonyl-*N*-2-(3-benzo[*b*]thienyl)ethylpyridinium Bromide (**2c**).

A mixture of 10 g. (0.042 mole) of 3-(2-bromoethyl)benzo[*b*]thiophene (3) and 1.5 g. (0.109 mole) of 3-methoxycarbonylpyridine was heated under an atmosphere of nitrogen for 17 hours at 80° giving a yellow solid. This solid was washed with chloroform giving 9.33 g. (64.8%) of compound **2c**, m.p. 195-196°; nmr (DMSO-$d_6$): 9.6-8.3 (see Table I), 8-7.5 (m, 4, C-H benzothiophene), 7.35 (s, 1, $C_2$-H benzothiophene), 5 (t, 2, $-CH_2$-N-), 4, (s, 3, $COOCH_3$), 3.65 (t, 2, Ar-$CH_2$).

*Anal.* Calcd. for $C_{17}H_{16}BrNO_2S$: C, 54.11; H, 4.24 Br, 20.95; N, 3.71; S, 8.48. Found: C, 54.05; H, 4.24; Br, 20.77; N, 3.69; S, 8.40.

*N*-2-(3-benzo[*b*]thienyl)ethylpyridinium Bromide (**2d**).

Compound **2d** was obtained in 85% yield according to the procedure of Chapmann (2), m.p. 160-162°; nmr (DMSO-$d_6$): 9.1-8.1 (see Table I), 7.9 (m, 2, $C_4$-H, $C_7$-H benzothiophene), 7.35 (m, 3, $C_2$-H, $C_5$-H, $C_6$-H benzothiophene), 4.9 (t, 2, -$CH_2$-N-), 3.45 (Ar-$CH_2$-).

*Anal.* Calcd. for $C_{15}H_{14}BrNS$: C, 56.42; H, 4.38; Br, 24.76; N, 4.38; S, 10.03. Found: C, 56.33; H, 4.29; Br, 24.74; N, 4.38; S, 10.15.

*N*-2-(3-indolyl)ethylpyridinium Bromide (**2e**).

Compound **2e** was obtained in 96% yield according to the procedure of C. Thal (9b), m.p. 230°; nmr (DMSO-$d_6$): 9-8.1 (see Table I), 7.4-6.95 (m, 6, indole ring), 4.92 (t, 2, -$CH_2$-N-), 3.4 (t, 2, Ar-$CH_2$).

*Anal.* Calcd. for $C_{15}H_{15}BrN_2$: C, 62.58; H, 4.96; Br, 26.15; N, 9.27. Found: C, 62.55; Br, 26.13; H, 4.90; N, 9.08.

The tetrahydropyridines **3a**, **3b** and **3c** were obtained according to Wenkert (10).

5-Methoxycarbonyl-*N*-2-(3-indolyl)ethyl-1,2,3,4-tetrahydropyridine (**3a**) was obtained in 76% yield, m.p. 117-118°; nmr (deuteriochloroform): 8.6 (br, s, 1, NH), 7.40 (s, 1, =CH tetrahydropyridyl), 7.2 (m, 4, indole ring), 6.92 (d, 1, Cα-H indole), 3.65 (s, 3, $COOCH_3$), 3.3 (m, 2, $CH_2$-N piperideine), 3 (m, 4, Ar-$CH_2$-$CH_2$-N), 2.1 (t, 2, $CH_2$-allyl), 1.75 (m, 2, -$CH_2$-homoallyl).

*Anal.* Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.60; H, 6.97; N, 9.35.

5-Acetyl-*N*-2-(3-benzo[*b*]thienyl)ethyl-1,2,3,4-tetrahydropyridine (**3b**).

Compound **3b** was obtained in 90% yield, m.p. 110-111°; nmr (deuteriochloroform): 7.8 (m, 2) and 7.4 (m, 2) benzothiophene protons, 7.1 (s, 1, Cα-H thiophene), 3.5 (m, 2, $CH_2$-N piperideine), 3.1 (m, 4, Ar-($CH_2$)-N), 2.2 (m, 2, $CH_2$-allyl), 1.9 (s, 3, $COOCH_3$), 1.75 (m, 2, $CH_2$-homoallyl).

*Anal.* Calcd. for $C_{17}H_{19}NOS$: C, 71.56; H, 6.71; N, 4.91; S, 11.23. Found: C, 71.50; H, 6.63; N, 4.77; S, 11.11.

5-Methoxycarbonyl-*N*-2-(3-benzo[*b*]thienyl)ethyl-1,2,3,4-tetrahydropyridine (**3c**).

A solution of 5 g. (0.013 mole) of **2b** in methanol (300 ml.) was shaken with hydrogen in the presence of 1.3 g. of 10% palladium on charcoal and 3.25 g. of triethylamine. When the reduction was complete, the catalyst was filtered, the solvent was removed under reduced pressure and the oily product was purified by chromatography through an alumina column. On elution with benzene, 1.6 g. (41%) of compound **3c** was obtained, m.p. 88-89°; nmr (deuteriochloroform): 7.75 (m, 2, $C_4$-H and $C_7$-H benzothiophene), 7.3 (m, 3, $C_5$-H, $C_6$-H benzothiophene and =C-H tetrahydropyridine), 3.6 (s, 3, $COOCH_3$), 3.3 (m, 2, $CH_2$N-piperideine), 2.95 (m, 4, Ar($CH_2$)N), 2.1 (t, 2, $CH_2$-allyl), 1.7 (m, $CH_2$-homoallyl).

*Anal.* Calcd. for $C_{17}H_{19}NO_2S$: C, 67.76; H, 6.36; N, 4.65; S, 10.62. Found: C, 67.45; H, 6.29; N, 4.44; S, 10.57.

The reduction of **2c** in 50% aqueous ethanol without triethylamine gave 70% of 3-methoxycarbonyl-*N*-2-(3-benzo[*b*]thienyl)ethylpiperidine **4c**, m.p. 165° dec.; nmr (deuteriochloroform): 7.7 (m, 2) and 7.3 (m, 2, C-H benzothiophene), 7.05 (s, Cα-H benzothiophene), 3.6 (s, 3, $COOCH_3$), 2.9 (complex signal, 8, C-H piperidine and $(CH_2)_2$-), 1.9 (m, 5, C-H piperidine).

*Anal.* Calcd. for $C_{17}H_{21}NO_2S$: C, 67.31; H, 6.98; N, 4.62; S, 10.55. Found: C, 67.15; H, 6.89; N, 4.72; S, 10.50.

(1RS, 12bRs)-1-Methoxycarbonylbenzo[*b*]thieno[2,3-*a*]quinolizidine (**1c**).

A solution of **3b** in methanol (1.36 g. in 100 ml.) under nitrogen was cooled at −40° and then saturated with anhydrous hydrogen chloride (2 hours). The mixture was allowed to rest overnight. The solvent was removed under reduced pressure and the crude dissolved in chloroform, dried with magnesium sulphate and concentrated giving 1.45 g. (83%) of **1c**. This compound is a yellow solid which was recrystallised from acetone, m.p. 144°; nmr (deuteriochloroform): 7.5 (m, 4, C-H benzothiene), 4. (s, 1, $C_{12b}$-H), 3.8 (s, 3, $COOCH_3$), 2.8 (m, 7, C-H quinolizidine ring), 1.7 (m, 5, C-H quinolizidine ring).

*Anal.* Calcd. for $C_{17}H_{19}NO_2S$: C, 67.76; H, 6.36; N, 4.65; S, 10.63. Found: C, 67.54; H, 6.29; N, 4.55; S, 10.60.

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