Benzomorphan Related Compounds. XII (1). 2,5-Methanothieno[3,2-*g*]quinolines as Rigid Bridged Thienomorphans

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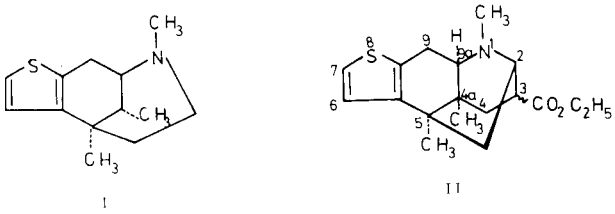
Received December 17, 1979

The preparation of a 1,2,3,4,4a,5,9,9a-octahydro-2,5-methanothieno[3,2-*g*]quinoline, which can be considered as a rigid thieno[3,2-*f*]morphan system due to an additional two-atoms bridge between the 3 and 9 positions of the morphan nucleus, is described. The synthetic route involved the acidic cyclization of a 3-(2-thenyl)-2-azabicyclo[2.2.2]oct-7-ene, obtained by the Diels-Alder reaction between 1,3,4-trimethyl-2-(2-thenyl)-1,2-dihydropyridine and ethyl acrylate.

J. Heterocyclic Chem., **17**, 745 (1980).

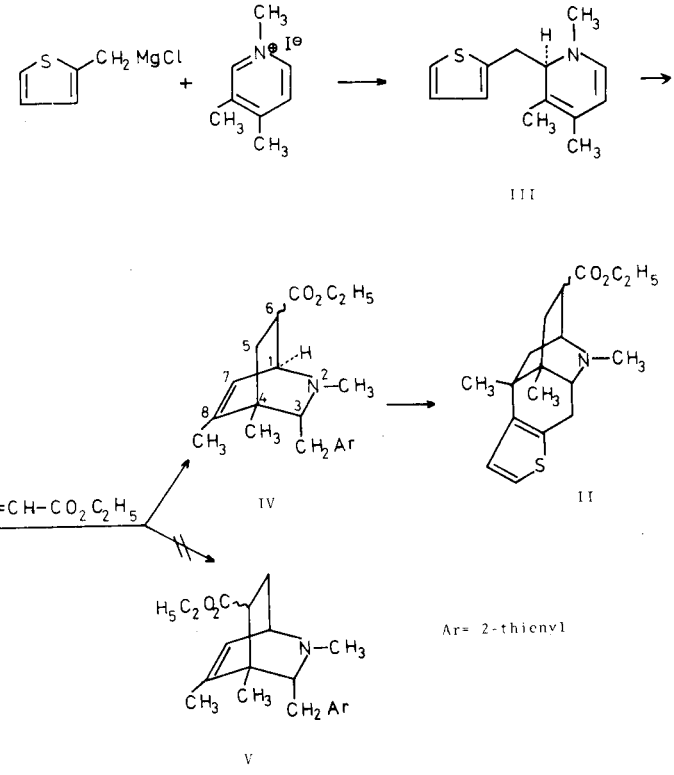
In previous papers (2-5) we have described the synthesis of several thieno[3,2-*f*]morphans (I) (systematic name, 4,5,6,7,8,9-hexahydro-4,8-methanothieno[2,3-*d*]azocines), compounds of interest from a pharmacological standpoint because of their potential activity as analgetics. We now wish to report the preparation of a new system of 1,2,3,4,4a,5,9,9a-octahydro-2,5-methanothieno[3,2-*g*]quinoline (II) which can be considered as a thieno[3,2-*f*]morphan of more rigid structure due to an additional two atoms bridge between the 3 and 9 positions of the morphan nucleus.



Scheme 1

This molecular modification has been tested in the 6,7-benzomorphan series (6,7) in the context of oripavine structurally related compounds synthesis. The introduction of a methylene bridge connecting the 3 and 8 positions of the benzomorphan system has also been described, thus creating another very rigid bridged polycyclic ring structure (8).

As in the synthesis of thienomorphans, the last step in the proposed synthesis of the thieno[3,2-*g*]quinoline II involves the formation of the carbocyclic ring B by acid-induced cyclization over the thiophene ring from a conveniently substituted 3-(2-thenyl)-2-azabicyclo[2.2.2]oct-7-ene (Scheme 2). Condensation of 2-thenylmagnesium chloride, obtained under high dilution conditions, with 1,3,4-trimethylpyridinium iodide affords 1,3,4-trimethyl-2-(2-thenyl)-1,2-dihydropyridine (III) (2), which have a dienamine system suitable to undergo Diels-Alder cycloaddition reactions (9). Some open-chain dienamines, such as *N*-substituted 1-amino-1,3-butadienes, have been utilized in similar reactions for the preparation of pharmacologically interesting 3-amino-4-phenylcyclohexenes (10).



Scheme 2

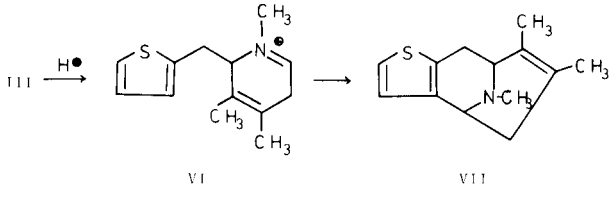
Condensation of III with ethyl acrylate yields, regiospecifically, the expected ethyl 2,4,8-trimethyl-3-(2-thenyl)-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (IV) accordingly with the prediction of the preferred regioisomers in the Diels-Alder reaction between unsymmetrically substituted dienes and dienophiles (11). The formation of the isomeric azabicyclic system V is not detected.

The structural assignation of IV was established from nmr spectral data, including spin-decoupling experiments. Thus, by irradiation of the olefinic proton at δ 5.93 (doublet, J = 6 Hz, with a further splitting, J = 1.5 Hz, by allylic coupling with the methyl group on 8-position) the pair of doublets at δ 3.46 for the C^1 methine proton collapses to a doublet (J = 3 Hz), indicating the existence of

0022-152X/80/040745-03$02.25

only one proton in the adjacent C^6 position. The relative stereochemistry of the carbethoxy group cannot be deduced from the magnitude of this last coupling constant since the dihedral angle H-C^6-C^1-H is almost identical (60°) in any of the two possible configurations at C^6. Other characteristic signals of the nmr spectrum of IV are: (i) a multiplet at δ 7.23-6.53 due to the three aromatic protons, (ii) two singlets at δ 2.00 and δ 1.16 due to the N-CH_3 and C^4-CH_3 groups, respectively, (iii) a doublet (J = 1.5 Hz) at δ 1.63 due to the C^8-CH_3, and (iv) a triplet and a quartet at δ 1.20 and δ 4.00 due to the methyl and methylene protons of the carbethoxy group, respectively. The relative configuration of the 2-thenyl group, *endo* to the double bond, follows from the later cyclization to the tetracyclic system II and can be rationalized from an attack of the dienophile by the less enhanced side of the dihydropyridine III.

Cyclization of 3-(2-thenyl)azabicyclo[2.2.2]oct-7-ene system IV to the thieno[3,2-*g*]quinoline II was first attempted with hydrobromic acid in the conditions described for the cyclization of 2-(2-thenyl)tetrahydropyridines to thienomorphans (2-4). However, the desired compound II was not obtained, but another, VII, the empirical formula of which was coincident with that of the starting dihydropyridine III and whose ir and nmr spectra showed the lack of the carbethoxy group. From its nmr spectrum it was identified as 6,7,10-trimethyl-4,5,8,9-tetrahydro-4,8-iminocycloocta[*b*]thiophene (VII). Thus, the presence of two doublets (J = 5 Hz) in the aromatic region, indicating a disubstituted thiophene ring, and the absence of signals due to olefinic protons shows to be a cyclized product. Other characteristic signals are the singlets at δ 2.35, δ 1.61 and δ 1.51, due to the methyl groups on the nitrogen atom and the olefinic carbons, respectively, and the doublet at δ 3.81 due to the C^4-methine proton.



Scheme 3

The formation of VII (Scheme 3) is interpreted by means of a retro-Diels-Alder reaction leading to the dihydropyridine III which is protonated at the unsubstituted 3-position of the dienamine system (12) in the acidic medium of the reaction. The resulting iminium salt VI acts as an electrophilic agent upon the 3-position of the thiophene ring promoting the cyclization. This interpretation is sustained by the fact that treatment of dihydropyridine III with hydrobromic acid in the conditions of the above reaction gave the same compound VII. The formation of similar compounds, 6,7,10-trimethyl-4,5,8,9-tetrahydro-5,9-iminocycloocta[*b*]thiophene (4) and its furan analog (13), by acidic treatment of the corresponding 2-(3-heteroarylmethyl)-1,3,4-trimethyl-1,2-dihydropyridines has been described.

Treatment of IV with aluminum chloride or bromide, also successfully utilized in the cyclization to thienomorphans (4), failed to give any cyclization product, even after prolonged reaction times. In these cases, the decomposition of the compound is observed and the formation of the compound VII is not detected, probably because of the lower temperature of the process. These results are similar to the described (7) in the cyclization of 3-benzyl-2-azabicyclo[2.2.2]oct-7-enes to 2,5-methanobenzo[*g*]quinoline systems.

As in these cases, the cyclization of IV to ethyl 1,4a,5-trimethyl-1,2,3,4,4a,5,9,9a-octahydro-2,5-methanothieno-[3,2-*g*]quinoline-3-carboxylate (II) occurs satisfactorily with liquid hydrofluroic acid at room temperature. The nmr spectrum of II shows the absence of olefinic protons and are observed as the most characteristic signals: (i) two doublets (J = 5 Hz) in the aromatic region indicating an AB system formed by protons of the disubstituted thiophene ring; (ii) a singlet at δ 0.71 due to the methyl group in the 4a-position, oriented toward the aromatic ring and shielded by it; (iii) two singlets at δ 2.39 and δ 1.28 due to the *N*-methyl and C^5-methyl groups, respectively, and (iv) a triplet and a quartet due to the methyl and the methylene protons of the carbethoxy group, respectively. The stereochemistry of this very rigid bridged thienomorphan is well-defined in all its centers, except that of the carbethoxy group, which is probably (14) *exo* to the nitrogen atom.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-24 B Spectrometer (60 MHz, tetramethylsilane at δ 0.0 ppm as internal standard) with deuteriochloroform as a solvent. Chemical shifts are reported as δ values in parts per million (ppm). Infrared spectra were determined on a Perkin-Elmer model 577 Spectrophotometer. Elemental analyses were performed by Instituto de Química Orgánica Aplicada de Cataluña, Barcelona.

Ethyl 2,4,8-Trimethyl-3-(2-thenyl)-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (IV).

2-Thenyl chloride was converted in a modified cyclic reactor (15) into its Grignard reagent, which was allowed to react with 1,3,4-trimethylpyridinium iodide by a previously described procedure (2)(4)(16). The column of the reactor was packed with magnesium turnings and amalgamated before each run. Then, a solution of 30 g. (0.23 mole) of 2-thenyl chloride in 500 ml. of dry ether was placed in a dropping funnel and 56.5 g. (0.23 mole) of 1,3,4-trimethylpyridinium iodide, suspended in 600 ml. of dry ether, were placed in the reaction flask. This suspension was stirred and heated at reflux temperature. All operations were carried out in atmosphere of dry nitrogen. The rate of addition of the halide to the top of the column was regulated (about 45 mmoles of halide per hour) to allow definite boiling in the column. When the addition was completed the refluxing of ether in the reaction flask was continued for 2 hours. The

resulting solution was poured into ice-water-ammonium chloride, basified with ammonium hydroxide and extracted with ether. The ethereal layer was extracted with 10% hydrochloric acid solution. The combined extracts were basified with ammonium hydroxide and extracted with ether. The extract was dried and evaporated to give the oily dihydropyridine III which was used in the following reaction without purification. Thus, to a stirred solution of III (34 g., 0.15 mole) in anhydrous benzene (400 ml.), 34 ml. (0.31 mole) of ethyl acrylate were added and the mixture was refluxed for 13 hours. After the solvent and the excess of ethyl acrylate were removed an oil was obtained. Distillation (130-140°/0.4 mm. Hg), afforded compound IV (49 g., 66% overall yield); nmr: 7.23-6.53 (m, 3, Ar-H) 5.93 (dd, 1, C^7-H), 4.00 (q, 2, O-CH_2), 3.46 (dd, 1, C^1-H), 2.00 (s, 3, N-CH_3), 1.63 (d, 3, C^8-CH_3), 1.56 (d, 2, C^5-H_2), 1.20 (t, 3, CH_2-CH_3), 1.16 (s, 3, C^4-CH_3); ir (chloroform): 1720 cm^{-1}. Recrystallization of the hydrochloride from acetone-ether gave a product of m.p. 188-190°.

Anal. Calcd. for $C_{18}H_{26}ClNSO_2$: C, 60.78; H, 7.31; Cl, 9.96; N, 3.93; S, 8.99. Found: C, 60.52; H, 7.26; Cl, 10.22; N, 4.01; S, 9.28.

Hydrobromic Acid Cyclization of IV.

A mixture of IV (6 g., 2 mmoles) and 48% hydrobromic acid (56 ml.) were kept at 130-135° (oil-bath temperature) for 3 hours 30 minutes. After cooling the reaction mixture was poured over ice-water, basified with concentrated ammonium hydroxide and extracted with ether. The dried ethereal extracts were evaporated to dryness. The resulting oil was purified by distillation (160-200°/1.6 mm. Hg), affording 1.4 g. (32% yield) of 6,7,10-trimethyl-4,5,8,9-tetrahydro-4,8-iminocycloocta[b]thiophene (VII); nmr: 6.95 (d, 1, Ar-H), 6.66 (d, 1, Ar-H), 3.81 (d, 1, C^4-H), 3.20 (s, 1, C^8-H), 3.00-1.75 (m, 4, C^5-H_2 and C^9-H_2), 2.35 (s, 3, N-CH_3), 1.61 (s, 3, C^6-CH_3), 1.51 (s, 3, C^7-CH_3). Recrystallization of the hydrochloride from acetone-methanol-ether gave a product of m.p. 232-233°.

Anal. Calcd. for $C_{13}H_{18}ClNS \cdot \frac{1}{2}H_2O$: C, 58.99; H, 7.15; N, 5.29. Found: C, 59.09; H, 7.02; N, 5.17.

6,7,10-Trimethyl-4,5,8,9-tetrahydro-4,8-iminocycloocta[*b*]thiophene (VII).

The dihydropyridine III (5.2 g., 16 mmole) prepared as above was treated with 48% hydrobromic acid (71 ml.) at 130-135° (oil-bath temperature) for 3 hours 30 minutes. After work-up the resulting oil was purified by distillation and identified as VII (3.4 g., 65% yield).

Ethyl 1,4a,5-trimethyl-1,2,3,4,4a,5,9,9a-octahydro-2,5-methanothieno-[3,2-*g*]quinoline-3-carboxylate (II).

In a Kel-F screw cap flask provided with a magnetic stirrer was placed IV (2.15 g., 7 mmoles) and added anhydrous hydrofluoric acid until 90 ml. of total volume. This mixture was stirred for 24 hours at room temperature and the excess of hydrofluoric acid was removed. The residue was basified with concentrated ammonium hydroxide, extracted with methylene chloride and the organic layer dried over anhydrous magnesium sulfate. This solution was filtered and the resulting oil distilled (220-250°/0.3 mm. Hg), affording compound II (1.27 g., 59% yield); nmr: 7.01 (d, 1, Ar-H), 6.83 (d, 1, Ar-H), 4.13 (q, 2, O-CH_2), 2.39 (s, 3, N-CH_3), 1.28 (s, 3, C^5-CH_3), 1.23 (t, 3, CH_2-CH_3), 0.71 (s, 3, C^{4a}-CH_3); ir (chloroform): 1715 cm^{-1}. Recrystallization of the hydrochloride from acetone gave a product of m.p. 79-81° (very hygroscopic).

Anal. Calcd. for $C_{18}H_{16}ClNSO_2 \cdot H_2O$: C, 57.81; H, 7.54; N, 3.74. Found: C, 57.43; H, 7.62; N, 3.83.

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(14) This was inferred from the suggestion (7) that the carbethoxy group is probably *endo* to the double bond in ethyl 2-azabicyclo[2.2.2]oct-7-ene-6-carboxylates obtained by analogous Dies-Alder processes.

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