HETEROCYCLIC SPIRO COMPOUNDS.I. SYNTHESIS OF 9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDRO-SPIRO[BENZO[a]QUINOLIZINE-2,3'-PYRROLIDINE]-2',5'-DIONE

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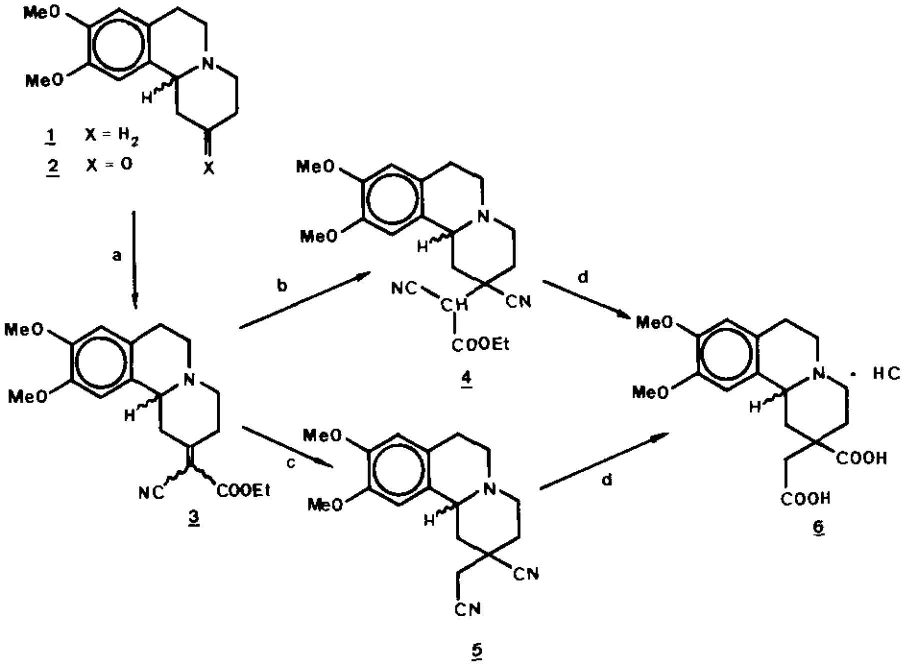
Abstract ——The synthesis of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)-quinolizine-2,3'-pyrrolidine]-2',5'-dione (9) was achieved from the corresponding 2-benzo(a)quinolizidinone (2) by two different routes.

The 1,3,4,6,7,11b-hexahydro-2H-benzo(a)quinolizine system 1 is present in several ipecac alkaloids of well-known amoebicidal properties as well as in some antipsychotic drugs, such as tetrabenazine and benzquinamide[1]. Recent pharmacological studies have shown antihypertensive[2-5], antiinflamatory[6] and anticonvulsivant[7] properties for several benzo(a)quinolizidine derivatives.

Within the scope of our studies on the synthesis of heterocyclic spirans from aminoketones, we considered of interest the preparation of spiro[benzo(a)quinolizidin-2,3'-pyrrolidine]-2',5'-dione 9. The transformation of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizin-2-one[8] 2 into 9 was initially carried out using 2-carboxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizine-2-acetic acid hydrochloride (6) as a synthetic intermediate. The synthesis of 6 was accomplished by two different routes, as shown in Scheme 1.

The Cope condensation[9] between benzo(a)quinolizidin-2-one 2 and cyanoacetic ester in the presence of triethylamine gave 3 in good yield. Addition of hydrogen cyanide to 3 was attempted in a variety of experimental conditions[10-12], among which only the reaction of 3 with two equivalents of hydrogen cyanide in aqueous alcoholic solution at room temperature for 5 days afforded 4 in a sufficiently high yield. Hydrolysis of 4 with concentrated hydrochloric acid gave the dicarboxylic acid 6 in quantitative yield.

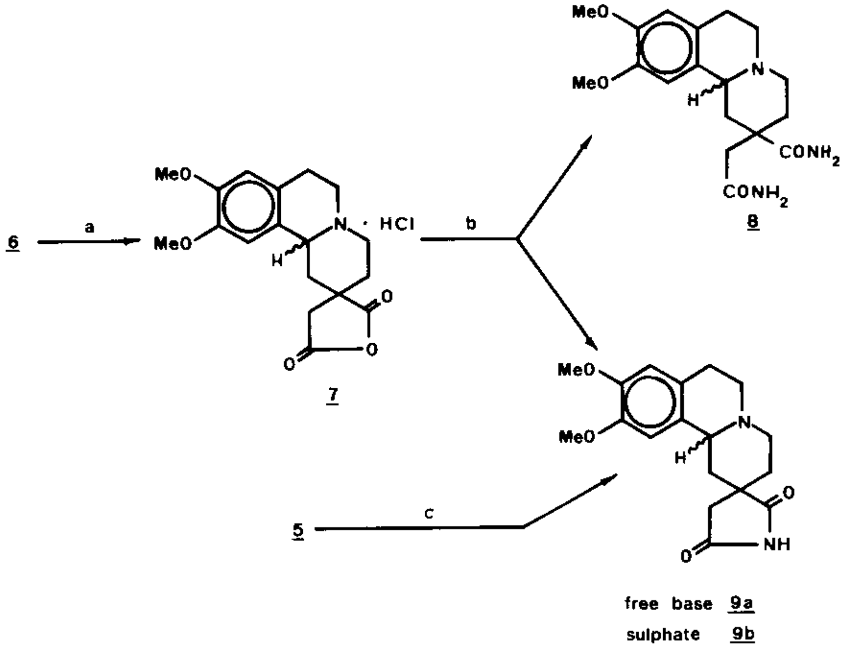
An alternative method was found during the studies on cyanide addition to 3, which on treatment with potassium cyanide in aqueous 2-propanol at 65°C for 16 h yielded dinitrile 5 (88.9%). Compound 5 was identified by spectroscopic methods and assumed to have come probably from the hydrolysis and decarboxylation of the intermediate product 4. Lundahl et al.[12] reported analogous results for a similar reaction of an adamantan-2-one derivative employing a strongly alkaline medium. Finally, acid hydrolysis of 5 quantitatively yielded 6.



a NC-CH$_2$-COOEt
c KCN, 65°C
b KCN, HCl, r.t.
d 35% aqueous HCl

SCHEME 1

The synthesis of the target compound 9 is depicted in scheme 2, both from 5 and 6 as starting materials. Heating 6 with acetic anhydride afforded 7 in quantitative yield. When anhydride 7 was fused with ammonium carbonate, an acceptable yield (30.2%) of spiro compound 9a was obtained, together with some diamide 8 (19.5%). Their different solubilities in acetone allowed an easy separation of 9a. On the other hand, hydrolytic cyclization of dinitrile 5 with a mixture of sulphuric and acetic acids at 120°C during 1 h equally afforded compound 9a as the hydrogen sulphate salt in acceptable yield (40.0%).



a Ac_2O

b Ammonium carbonate

c H_2SO_4, AcOH

SCHEME 2

The quinolizidine system presents a trans conformation in all compounds synthesized, as shown by the ir Bohlmann bands[13] and by the chemical shift of the C-11b proton in the ^{1}H-nmr spectra[14]. Compounds 2,3,4,5,8 and 9a display a multiplet at a field higher than δ 3.8. The displacement of the signal to a lower field (about δ 4.2) observed for the salts 6,7 and 9b is probably due to the deshielding effect of the possitive charge placed on the quaternary nitrogen.

EXPERIMENTAL

Melting points are uncorrected. Spectral data were recorded on the following spectrometers : ir — Perkin Elmer 577 ; ^{1}H-nmr — Hitachi-Perkin Elmer R-24 (60 MHz) (reference, tetramethylsilane) ; ms — Hitachi-Perkin Elmer RMU-6M. Elemental analyses were determined using a Carlo Erba Elemental Analyzer model 1104 equipped with a digital integrator C SI 38.

Ethyl (9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-benzo(a)quinolizinylidene)cyanoacetate (3).

A solution of ketone 2 (3 g, 11.49 mmole)[8], ethyl cyanoacetate (1.3 g, 13.80 mmole), glacial acetic acid (0.3 ml), and Et_3N (0.1 ml) in 25 ml of dry benzene was refluxed for 2 h in an oil bath at 120-125°C, using a Dean-Stark water separator. The cooled reaction mixture was washed with 3 x 15 ml of saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated under reduced pressure, leaving 4.2 g of an orange oil which yielded 3.6 g (87.4 %) of crystals on addition of 5 ml of ethyl ether. Mp 127-128°C (petroleum ether). Ir (KBr) cm^{-1} : 2790, 2760, 2220 (C≡N), 1730 (C=O), 1600. ^1H-nmr ($CDCl_3$) δ : 6.65 (1H,s,11-H) , 6.55 (1H,s,8-H) , 4.40 (2H,q,J=7 Hz) , 3.85 (3H,s,OMe), 3.82 (3H,s,OMe) , 3.65 (1H,m,11b-H) , 3.60-2.20 (10 H,m) , 1.40 (3H,t,J=7 Hz). Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.42 ; H, 6.74 ; N, 7.86. Found : C, 67.64 ; H, 6.71 ; N, 7.71.

Ethyl (2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2-benzo(a)quinolizinyl)cyanoacetate (4).

To an ice-cooled solution of 3 (0.3 g, 0.84 mmole) in a mixture of 2-propanol (15 ml) and 35% aqueous HCl (0.17 ml, 1.68 mmole) was added a solution of KCN (0.11 g, 1.68 mmole) in H_2O (3 ml). The mixture was left at room temperature for 5 days. The yellow needles of 4 that precipitated were filtered off and washed with a small amount of 2-propanol, yielding 0.25 g (76.1 %) of 4. Mp 157-158°C (2-propanol). Ir (KBr) cm^{-1} : 2800, 2765, 2250 (C≡N), 1755 (C=O). ^1H-nmr ($CDCl_3$) δ : 6.60 (2H,broad s, 11-H and 8-H) , 4.40 (2H,q,J=7 Hz) , 3.88 (6H,s,2 OMe) , 3.85 (1H,s,2'-H) , 3.65 (1H,m,11b-H) , 3.10-1.60 (10H,m) , 1.38 (3H,t). Anal. Calcd. for $C_{21}H_{25}N_3O_4$: C, 65.79 ; H, 6.53 ; N, 10.96. Found : C, 65.57 ; H, 6.18 ; N, 10.66.

2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizine-2-acetonitrile (5).

A solution of KCN (1.65 g, 25.32 mmole) in H_2O (5 ml) was added to a solution of 3 (3.6 g, 10.06 mmole) in 2-propanol (40 ml). The mixture was heated at 65°C for 16 h and then cooled to precipitate 2.75 g (88.9 %) of 6. Mp 144-145°C (2-propanol). Ir (KBr) cm^{-1} : 2800, 2760, 2260 (C≡N), 2240 (C≡N). ^1H-nmr ($CDCl_3$) δ : 6.65 (1H,s,11-H) , 6.60 (1 H,s,8-H) , 3.85 (3 H,s,OMe) , 3.80 (3 H,s, OMe) , 3.50 (1 H,broad d,J~12 Hz,11b-H) , 2.75 (2 H,s,2'-H) , 3.20-1.60 (10 H,m). Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.45 ; H, 6.75 ; N, 13.50. Found : C, 69.69 ; H, 6.69 ; N, 13.44. Ms m/e : 311 (M^+), 310, 271, 218, 205, 192, 191.

2-Carboxy-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizine-2-acetic Acid Hydrochloride (6).

a) 6.15 g (15.95 mmole) of 4 was refluxed with 15 ml of 35% aqueous HCl in an oil bath at 120-125 °C for 4 h. The white precipitate formed after cooling was filtered off to yield 4.65 g (76.1 %) of 6. A second crop (1.4 g) was obtained by concentration to dryness of the mother liquors and recrystallization from H_2O. Total yield, 6.05 g (99.0 %). Mp 245-246°C (H_2O). Ir (KBr) cm^{-1} : 3300-2300 (OH, R_3NH^+), 1730 (C=O), 1700 (C=O). ^1H-nmr (d_6-DMSO) δ : 6.77 (1 H,s,11-H) , 6.62 (1 H,s,8-H) , 4.38 (1 H,broad d,J~11 Hz) , 3.76 (6 H,s,2 OMe) , 2.58 (2 H,s,2'-H) , 3.80-2.00 (10 H,m). Anal. Calcd. for $C_{18}H_{24}NO_6Cl$: C, 56.03 ; H, 6.22 ; N, 3.63. Found : C, 55.83 ; H, 5.97 ;

N, 3.88.

b) 0.5 g (1.61 mmole) of 5 was treated in the same manner as described above to give 6 in 98.9 % yield. Mixed mp 245-246°C. Ir and ^1H-nmr, the same as above.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)quinolizine-2,3'-furan]-2',5'(4'H)-dione hydrochloride (7).

The above acid 6 (3 g, 8.16 mmole) was refluxed with acetic anhydride (60 ml) for 6 h. The white solid formed during the reaction was filtered off, yielding 1.5 g (52.4 %) of 7. Additional 1.35 g of 7 was obtained by elimination of the acetic anhydride under reduced pressure, addition of 5 ml of dry toluene, and evaporation to dryness. Total yield, 2.85 g (99.6 %). Mp 249-251°C (decomp.) (acetic anhydride). Ir (KBr) cm^{-1} : 2780-2100 (R_3NH^+), 1855 (-CO-O-CO-, ν_s), 1760 (-CO-O-CO-, ν_{as}), 940. ^1H-nmr (d_6-DMSO) δ : 6.90 (1 H,s,11-H) , 6.82 (1 H,s,8-H) , 4.70 (1 H,m, 11b-H) , 3.75 (6 H,s,2 OMe) , 3.10 (2 H,s,4'-H) , 3.70-2.10 (10 H,m). Anal. Calcd. for $C_{18}H_{22}NO_5Cl$: C, 58.77 ; H, 5.99 ; N, 3.81. Found : C, 58.41 ; H, 5.75 ; N, 3.62.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)quinolizine-2,3'-pyrrolidine]-2',5'-dione (9a).

A magnetically stirred mixture of 7 (1.5 g, 4.08 mmole) and ammonium carbonate (3 g) was melted at 180°C during 2 h under nitrogen atmosphere. After cooling, the solid was crystallized from ethanol and charcoal. The white solid obtained was dissolved in ca. 5 ml of H_2O and precipitated with an equimolecular amount of 15% aqueous NaOH. The first crop obtained was identified as pure 9a ; the successive crops consisted of a mixture of 9a and a secondary product 8. Treatment of this mixture with boiling acetone dissolved 9a and left pure 8 undissolved, which was identified from its spectral and analytical data as 2-carbamoyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizine-2-acetamide (8). The acetone solution of 9a was evaporated under reduced pressure and the residue recrystallized from H_2O. Total yield of 9a, 0.4 g (30.2 %). Mp 230-233°C (decomp.) (H_2O). Ir (KBr) cm^{-1} : 3450 (N-H), 2800, 2750, 1760 (-CO-NH-CO-, ν_s), 1710 (-CO-NH-CO-, ν_{as}). ^1H-nmr (d_6-DMSO) δ : 6.65 (1 H,s,11-H) , 6.55 (1 H,s,8-H) , 3.70 (6 H,s,2 OMe) , 2.52 (2 H,s,2'-H) , 3.60-1.00 (11 H,m). Anal. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.48 ; H, 6.66 ; N, 8.48. Found : C, 65.23 ; H, 6.39 ; N, 8.23. Yield of 8, 0.25 g (19.5 %). Mp 235-237°C (EtOH). Ir (KBr) cm^{-1} : 3480 (N-H), 1680 (C=O). ^1H-nmr (d_6-DMSO) δ : 6.80 (1 H,s,11-H) , 6.70(1 H,s,8-H) , 4.70 (4 H,s,2 $CONH_2$) , 3.80 (6 H, s,2 OMe) , 3.52 (1 H,m,11b-H) , 2.40 (2 H,s,2'-H) , 3.30-1.35 (10 H,m). Ms m/e : 347 (M^+), 331, 330, 288, 191, 190. Anal. Calcd. for $C_{18}H_{25}N_3O_4$: C, 62.25 ; H, 7.20 ; N, 12.10. Found : C, 61.97 ; H, 7.05 ; N, 12.02.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)quinolizine-2,3'-pyrrolidine]-2',5'-dione hydrogen sulphate (9b).

A mixture of the acetonitrile 5 (2.15 g, 6.91 mmole), glacial acetic acid (8 ml), and 75% aqueous H_2SO_4 (2.80 g) was heated at 120-125°C for 1 h. The acetic acid was distilled off under reduced pressure and the residue was treated with hot ethyl acetate. The insoluble fraction was crystallized from 2-propanol. Yield, 0.75 g (40.0 %). Mp 259-261°C (2-propanol). Ir (KBr) cm^{-1} : 3450 (N-H), 1760 (-CO-NH-CO-, ν_s), 1710 (-CO-NH-CO-, ν_{as}). ^1H-nmr (CF_3COOH) δ : 6.80 (2 H,broad s,11-H and 8-H), 3.75 (6 H,s,2 OMe) , 4.90 (1 H,m,11b-H) , 2.65 (2 H,s,4'-H) , 3.65-1.50 (10 H,m). Anal. Calcd. for $C_{18}H_{25}N_2O_8S$: C, 50.94 ; H, 5.66 ; N, 6.60. Found : C, 50.70 ; H, 5.43 ; N, 6.75.

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REFERENCES

1. C. Kaiser, P. E. Setler , "Antipsychotic Agents" in "Burger's Medicinal Chemistry", 4th Ed., ed. by M. E. Wolff, J. Wiley and Sons, N. Y. (1981), p. 859.
2. a) B. Lal, A. N. Dohadwalla, V. A. A. Aroskar, N. K. Dadkar, H. Dornauer, J. Mascarenas, and J. de Souza, Eur. Pat. Appl. EP 75,165 (1983) ; C. A., 1983, 99, 122487h ; b) B. Lal, A. D'Sa, A. N. Dohadwalla, N. J. de Souza, and H. Dornauer, Ger. Offen. DE 3,126,837 (1983) ; C. A., 1983, 98, 198282h.
3. a)J. W. Van Dyke, H. J. Havera, and R. D. Johnson, J. Med. Chem., 1972, 15, 91 ; b) H. J. Havera and W. G. Strycker, Ger. Offen. 2,946,613 (1980) ; C. A., 1980, 93, 168147x.
4. J. M. Caroon, R. D. Clark, A. F. Kluge, C. H. Lee, and A. M. Strosberg, J. Med. Chem., 1983, 26, 1426.
5. J. L. Archibald, R. Beardsley, T. J. Ward, J. F. Waterfall and J. F. White, J. Med. Chem., 1983, 26, 416.
6. C. Szántay, L. Szabó, L. Toeke, I. Toth, S. Virág, E. Kanyó, and A. David, U.S. 4,342,871 (1982); C. A., 1982, 97, 216035r.
7. F. D. Popp and R. F. Watts, J. Pharm. Sci., 1978, 67, 871.
8. N. Whittaker, J. Chem. Soc. (C), 1969, 85.
9. A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, J. Am. Chem. Soc., 1941, 63, 3452.
10. C. A. Eckard, C. A. Grob and W. D. Treffert, Helv. Chim. Acta, 1972, 55, 2432.
11. S. M. McElvain and R. E. McMahon, J. Am. Chem. Soc., 1949, 71, 901.
12. K. Lundahl, J. Schut, J. L. M. A. Schlatmann, G. B. Paerels, and A. Peters, J. Med. Chem., 1972, 15, 129.
13. F. Bohlmann, Chem. Ber., 1958, 91, 2157.
14. M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, J. Am. Chem. Soc., 1964, 86, 3364.

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