# Studies on the Syntheses of Heterocyclic Compounds. Part 724.[1] Total Syntheses of the Quinazolinone Alkaloids Glycorine, Glomerine, Homoglomerine, Crysogine, and Euxylophoricines A and C

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Treatment of the sulphinamide anhydride 1-methyl-3,2,1-benzoxathiazin-4(1*H*)-one *S*-oxide (5), derived from *N*-methylanthranilic acid (1), with amides (9)—(11) gave glycorine (14), glomerine (15), and homoglomerine (16), respectively. Reaction of the *N*-unsubstituted sulphinamide anhydride (6) with *O*-benzyl-lactamide (13), followed by debenzylation of the resulting 2-(1-benzyloxyethyl)quinazolin-4(3*H*)-one (17) yielded crysogine (18). Condensation of the sulphinamide anhydrides (7) and (8), prepared from the corresponding dimethoxy- and methylenedioxy-anthranilic acid derivatives (3) and (4), with 3,4-dihydro-β-carboline (19) furnished euxylophoricines A (20) and C (21). 5,11-Dimethyldibenzo[*b*,*f*][1,5]diazocine-6,12(5*H*,11*H*)-dione (22) was obtained from the *N*-methylsulphinamide anhydride (5).

We have recently developed a new one-step synthesis of quinazolinone derivatives by condensation of sulphinamide anhydrides [(5) and (6), generated from anthranilic acids (1) and (2) and thionyl chloride] with amides [2] or imines.[3,4] We now report the total syntheses of several quinazoline-type alkaloids and the formation of a novel eight-membered-ring lactam (22) from the *N*-methylsulphinamide anhydride (5).

The sulphinamide anhydride (5), prepared from *N*-methylanthranilic acid (1) and thionyl chloride in dry hot benzene,[2,3] was treated with formamide in dry dioxan at room temperature overnight to form the hydrochloride of glycorine (14) (found in *Glycosmis arborea* [5]). The mother liquor yielded a neutral compound, identified as 5,11-dimethyldibenzo[*b*,*f*][1,5]diazocine-6,12(5*H*,11*H*)-dione mainly on the basis of spectral analysis. The i.r. spectrum ($CHCl_3$) showed carbonyl absorption at 1 636 $cm^{-1}$ and the n.m.r. spectrum ($CDCl_3$) exhibited an *N*-methyl signal at δ 3.43. The molecular ion peak was observed at *m/e* 266 in the mass spectrum. Compound (22) was also formed quantitatively from the sulphinamide anhydride (5) when kept at room temperature for several hours in the absence of imines or amides but under moist conditions.

In a similar manner, glomerine (15)[6] and homoglomerine (16),[7] which have been isolated from *Glomeris marginata*, were synthesised by condensation of the *N*-methylsulphinamide anhydride (5) with acetamide (10) or propionamide (11).

Treatment of the sulphinamide anhydride (6),[2,3] prepared from anthranilic acid (2), with (±)-*O*-benzyl-lactamide (13), derived from (±)-lactamide (12), under similar conditions gave (±)-*O*-benzylcrysogine (17) in addition to the benzoxazinone (23). The known dimer (23) [8,9] was formed quantitatively when the sulphinamide anhydride (6) was kept for several hours at room temperature under humid conditions.

Debenzylation of (17) by refluxing with hydrochloric acid in ethanol gave (±)-crysogine (18), whose (−)-isomer has been obtained from a culture broth of *Penicillium chrysogenum*.[10]

2-Amino-4,5-dimethoxybenzoic acid (3) [11] was converted by heating with thionyl chloride in dry benzene into the sulphinamide anhydride (7), which was condensed with 3,4-dihydro-β-carboline (19) at room temperature in dry benzene to afford euxylophoricine A (20) (found in *Euxylophora paraënsis* [12]). Euxylophoricine C (21) [13] was also synthesised, by condensation of 3,4-dihydro-β-carboline (19) with the sulphinamide anhydride (8), derived from 2-amino-4,5-methylenedioxybenzoic acid (4).[14]

## EXPERIMENTAL

I.r. and u.v. spectra were taken with Hitachi 215 and Hitachi 124 recording spectrophotometers, respectively. N.m.r. spectra were measured with a JNM-PMX-60 (60 MHz) instrument (for solutions in deuteriochloroform or [$^2H_6$]dimethyl sulphoxide with tetramethylsilane as internal standard). Mass spectra were measured with a Hitachi RMU-7 spectrometer.

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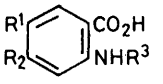
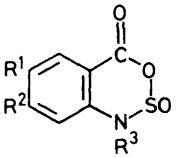
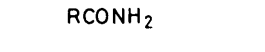
*Glycorine* (14).—A mixture of *N*-methylanthranilic acid (1) (100 mg) and thionyl chloride (500 mg) in dry benzene (10 ml) was refluxed for 2 h. The solvent and the excess of the reagent were then evaporated off under reduced pressure



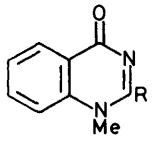
(1) $R^1 = R^2 = H$, $R^3 = Me$
(2) $R^1 = R^2 = R^3 = H$
(3) $R^1 = R^2 = OMe$, $R^3 = H$
(4) $R^1R^2 = OCH_2O$, $R^3 = H$



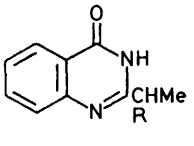
(5) $R^1 = R^2 = H$, $R^3 = Me$
(6) $R^1 = R^2 = R^3 = H$
(7) $R^1 = R^2 = OMe$, $R^3 = H$
(8) $R^1R^2 = OCH_2O$, $R^3 = H$



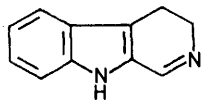
(9) R = H
(10) R = Me
(11) R = Et
(12) R = CH(OH)Me
(13) R = $CH(OCH_2Ph)Me$



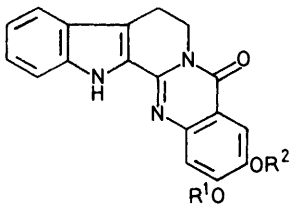
(14) R = H
(15) R = Me
(16) R = Et



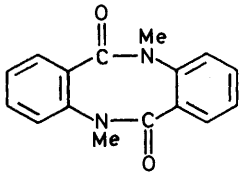
(17) $R = OCH_2Ph$
(18) R = OH



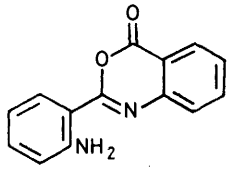
(19)



(20) $R^1 = R^2 = Me$
(21) $R^1R^2 = CH_2$



(22)



(23)

at 30 °C to leave the sulphinamide anhydride (5) as an oily yellow liquid, to which a solution of freshly distilled formamide (9) (29 mg) in dry dioxan (50 ml) was added. The mixture was set aside overnight at room temperature, and the crystals formed were filtered off and recrystallised from ethanol to give glycorine (14) (50 mg) as yellow crystals, m.p. 241.5° (decomp.) [lit.,[5] 242° (decomp.)], the u.v., i.r., and n.m.r. spectral data of which were consistent with those reported.[5]

*Glomerine* (15).—To the sulphinamide anhydride (5), prepared from *N*-methylanthranilic acid (1) (80 mg) as above, was added a solution of acetamide (10) (31 mg) in dry benzene (160 ml). The mixture was set aside overnight at room temperature, then evaporated. The residue was partitioned between aqueous 5% sodium carbonate and chloroform. The chloroform layer was washed with water, dried ($Na_2SO_4$), and evaporated. Recrystallisation of the residue from ethyl acetate gave glomerine (15) (40 mg) as yellow needles, m.p. 203—204.5° (lit.,[6] 204—205°), the u.v. and i.r. spectral data of which were identical with those reported; [15] δ ($CDCl_3$) 2.63 (3 H, s, $CH_3$), 3.76 (3 H, s, $NCH_3$), 7.20—7.86 (3 H, m, 3 × ArH), and 8.23 (1 H, dd, *J* 3 and 7 Hz, 5-H).

*Homoglomerine* (16).—To the sulphinamide anhydride (5), prepared from *N*-methylanthranilic acid (1) (577 mg) as above, was added a solution of propionamide (11) (250 mg) in dry benzene (200 ml). The mixture was set aside overnight at room temperature and then worked up as above. The yellow product was purified by preparative t.l.c. on silica gel [chloroform–methanol (9 : 1 v/v)] to give a powder, which on recrystallisation from ethyl acetate afforded homoglomerine (16) (20 mg) as prisms, m.p. 148—149° (lit.,[7] 149°), the u.v. and i.r. spectral data of which were identical with those reported; [15] δ ($CDCl_3$) 1.41 (3 H, t, *J* 8 Hz, $CH_2{\cdot}CH_3$), 2.90 (2 H, q, *J* 8 Hz, $CH_2{\cdot}CH_3$), 3.75 (3 H, s, $NCH_3$), 7.33—7.80 (3 H, m, 3 × ArH), and 8.33 (1 H, dd, *J* 3 and 7 Hz, 5-H).

*O-Benzyl-lactamide* (13).—A mixture of (±)-lactamide (12) (1.0 g), benzyl chloride (1.4 g), and sodium hydride (0.312 g) in benzene (50 ml) was refluxed overnight. After addition of methanol (5—6 ml), the mixture was evaporated, and the residue was taken up in chloroform. The solution was washed with water, dried ($Na_2SO_4$), and evaporated to leave a viscous syrup, which was triturated with n-hexane and then recrystallised from chloroform–n-hexane to give the benzyl ether (13) (1.2 g) as *needles*, m.p. 101—102° (Found: C, 67.2; H, 7.2; N, 7.9. $C_{10}H_{13}NO_2$ requires C, 67.05; H, 7.25; N, 7.8%), $\nu_{max.}$ ($CHCl_3$) 3 550 and 3 450 ($NH_2$) and 1 680 $cm^{-1}$ (C=O), δ ($CDCl_3$) 1.48 (3 H, d, *J* 7 Hz, $CH_3$), 3.90 (1 H, q, *J* 7 Hz, CH), 4.55 (2 H, s, $OCH_2Ph$), and 7.20—7.50 (5 H, m, Ph).

*2-(1-Benzyloxyethyl)quinazolin-4(3H)-one* (17).—A solution of anthranilic acid (550 mg) and thionyl chloride (5.5 g) in dry benzene (20 ml) was refluxed for 2 h. The mixture was evaporated under reduced pressure at 30 °C to afford the sulphinamide anhydride (6) as an oily yellow liquid, to which a solution of *O*-benzyl-lactamide (13) (700 mg) in dry benzene (40 ml) was added. After being left overnight at room temperature, the mixture was evaporated to give a syrup, which was partitioned between chloroform and aqueous 5% sodium hydrogen carbonate. The chloroform layer was washed with saturated sodium chloride solution, dried ($Na_2SO_4$), and evaporated, and the residue was chromatographed on silica gel. Elution with benzene–ethyl acetate (8 : 2 v/v), followed by recrystallisation from chloroform–n-hexane, yielded the quinazolinone (17) (750 mg) as *needles*, m.p. 180° (Found: C, 71.3; H, 6.0; N, 9.35. $C_{17}H_{16}N_2O_2$, 0.33 $H_2O$ requires C, 71.3; H, 5.85; N, 9.8%), $\nu_{max.}$ ($CHCl_3$) 3 400

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(NH) and 1 660 $cm^{-1}$ (C=O), δ ($CDCl_3$) 1.60 (3 H, d, *J* 7 Hz, $CH{\cdot}CH_3$), 4.60 (2 H, s, $OCH_2Ph$), 4.36—4.73 (1 H, m, $CH_3{\cdot}CHO$), and 7.20—8.20 (9 H, m, 9 × ArH).

*Crysogine* (18).—A mixture of the benzyl ether (17) (400 mg) and concentrated hydrochloric acid (15 ml) in ethanol (15 ml) was refluxed for 28 h and then evaporated. The residue was partitioned between aqueous 5% sodium hydrogen carbonate and chloroform. The chloroform layer was washed with saturated sodium chloride solution, dried ($Na_2SO_4$), and evaporated. Recrystallisation of the residue from methanol–ethyl acetate gave (±)-crysogine (18) (150 mg) as needles m.p. 190—191° (lit.,[16] 190—191°) (Found: C, 62.9; H, 5.15; N, 14.65. Calc. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.25; N, 14.75%), the i.r. and n.m.r. spectra of which were identical with those of the natural product.[10]

*Euxylophoricine A* (20).—A mixture of 2-amino-4,5-dimethoxybenzoic acid (3) [11] (50 mg) and thionyl chloride (250 mg) in dry benzene (5 ml) was refluxed for 2h. The solvent and the excess of reagent were evaporated off under reduced pressure at 30 °C to afford a brown solid, to which a solution of 3,4-dihydro-β-carboline (19) (43 mg) in dry benzene (50 ml) was added. The mixture was set aside overnight at room temperature, then evaporated and the residue was taken up in chloroform. The solution was washed with aqueous 5% sodium carbonate solution and water, dried ($Na_2SO_4$), and evaporated. Recrystallisation of the residue from chloroform–methanol afforded euxylophoricine A (20) (35 mg) as needles, m.p. 296—298° (lit.,[12] 295—298°), the u.v., i.r., and n.m.r. spectral data of which were consistent with those of the natural product.[12]

*Euxylophoricine C* (21).—To the sulphinamide anhydride prepared from 2-amino-4,5-methylenedioxybenzoic acid (4) [14] (100 mg) as above was added a solution of 3,4-dihydro-β-carboline (19) (93 mg) in dry benzene (70 ml). The mixture was set aside overnight at room temperature, and then worked up in a similar manner to give euxylophoricine C (21) (90 mg) as needles, m.p. 310.5—312° (lit.,[13] 310—312°), the u.v., i.r., and n.m.r. spectra data of which were identical with those reported.[13]

5,11-*Dimethyldibenzo*[b,f][1,5]*diazocine*-6,12(5H,11H)-*dione* (22).—A mixture of *N*-methylanthranilic acid (1) (120 mg) and thionyl chloride (1 g) in dry benzene (10 ml) was refluxed for 2 h without moisture. The solvent and excess of thionyl chloride were evaporated off and the residue was set aside at room temperature for 2 h and then dissolved in chloroform. The solution was washed with an aqueous 10% potassium carbonate and water, dried ($Na_2SO_4$), and evaporated. The resulting yellow solid was recrystallised from ether–chloroform to yield the diazocine (22) (90 mg) as *plates*, m.p. 193—195° (Found: C, 72.25; H, 5.35; N, 10.65. $C_{16}H_{14}N_2O_2$ requires C, 72.15; H, 5.3; N, 10.5%), $\nu_{max.}$ ($CHCl_3$) 1 635 $cm^{-1}$, δ ($CDCl_3$) 3.43 (6 H, s, 2 × $NCH_3$), *m/e* 266 ($M^+$).

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