Synthesis of Isoquinobenzodiazepinediones

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1-(2'-Chloroacetylamino)-4,4-dimethyl-1,4-dihydro-3(2*H*)-isoquinolinone (**3**) was cyclised by treatment with sodium hydride in dimethyl sulphoxide containing 0.1% of water to give 10,10-dimethyl-6,7,9,10-tetrahydro-5*H*,14b*H*-isoquino[2,1-*d*][1,4]benzodiazepine-6,9-dione (**4**) in a yield of 80%. In anhydrous dimethyl sulphoxide the main product of the reaction was 5-*N*-(4,4-dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinon-1'-yl)isoquino[2,1-*d*][1,4]benzodiazepine-6,9-dione (**5**), which was also prepared by the reaction of **3** with **4**.

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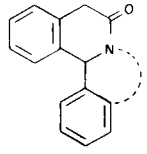
We have earlier described [2] that in the course of the investigation of 3(2*H*)-isoquinolinones we aimed at constructing new ring systems. As a result of this work, a benzene ring was successfully anellated to the homoaromatic ring, to yield benzo[*f*]-, benzo[*g*]- and benzo[*h*]isoquinoline derivatives.

A new possibility for enlarging the ring system is to set up a linkage between the lactam nitrogen of the isoquinoline ring and a suitable substituent, in the present case an amino group in an ortho position to the 1-phenyl group.



Owing to the geometry of 1,4-dihydroisoquinolinones [3], a six-membered ring cannot be formed in this way, only a seven-membered one. In view of this, we attempted to elaborate a method for the synthesis of new isoquinobenzodiazepinediones. As bifunctional partners for the cyclisation chloroacetyl chloride was selected and the starting material was the 1-(2'-aminophenyl)-1,4-dihydro-3(2*H*)-isoquinolinone. It was first acylated with chloroacetyl chloride, as the preparation of the desired product was intended by cyclisation of the resulting derivative with sodium hydride. However, the cyclisation step presented new difficulties, as no homogeneous product could be isolated working either in dimethyl sulphoxide or in dimethyl formamide, under different conditions. This negative result can be explained by the disturbing effect of the methylene group in position 4. Namely, we found in earlier investigations [4] that 1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone reacted in the presence of a strong base, such as sodium hydride, with aromatic aldehydes to yield the corresponding 4-arylidene derivative, which rapidly rearranged in alkaline medium into 4-arylmethyl-3-isoquinolinol. It can be thus supposed that the present failure in obtaining the desired product is also due to some secondary reactions of the carbanion produced on the effect of sodium hydride. Therefore, the further experiments were made with the 4,4-dimethyl derivative (Figure 1).

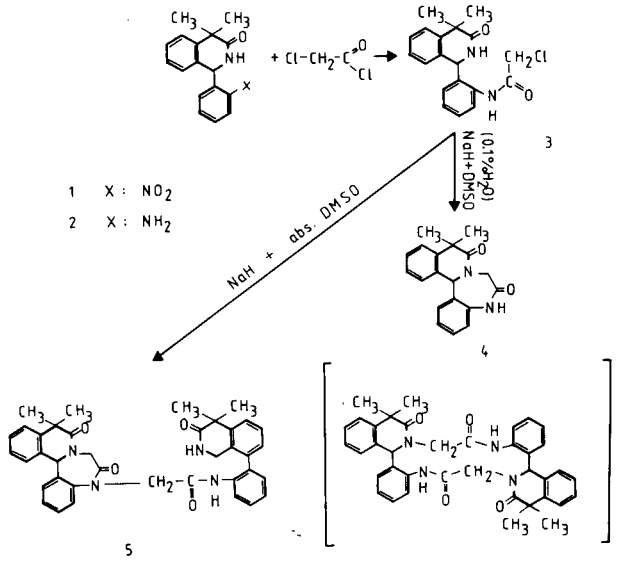


Figure 1

Starting with the amino derivative **2**, obtained from the nitro compound **1** by reduction, the cyclisation of the chloroacetyl derivative **3** could be effected with the best yield in dimethyl sulphoxide solution in the presence of sodium hydride. The reaction afforded the end product **4** in a yield of 75-80% when the dimethyl sulphoxide contained about 0.1% of water. In anhydrous dimethyl sulphoxide the diazepinone **4** could be obtained only in a yield of 20%. The main product of the cyclisation (**5**) did not melt up to 300°, and its ir spectrum had amide-I and ν NH bands. According to the ms, the molecular formula may be $C_{38}H_{36}N_4O_4$ corresponding to a dimer with either of the two alternative structures depicted in Figure 1; the fragmentation pattern did not allow unambiguous decision between them. The ^1H nmr spectrum of the compound

shows four types of CH_3-H, two types of CH_2-H (in the ring as N-CH_2-CO- and in the side chain) two types of NH-H and two types of C_1-H, indicating that the asymmetric structure of **5** is the correct one. In the case of the totally symmetric macrocycle, this doubling in the spectrum would not appear.

The structure of **5** was proved also by synthesis, allowing **4** to react with **3** (Figure 2).

According to our supposition the formation of **5** from **3** is the result of consecutive reactions; the first step is intramolecular alkylation to give **4** by cyclisation; this step is followed by intermolecular alkylation with the chloroacetyl derivative **3** which is still present in the mixture. The problem was to know the factors influencing the relative rates of the two consecutive reactions. Since the dimethyl sulphoxide used as solvent in the cyclisation had been dried over calcium hydride, at first it was supposed that the dissolved calcium salt may have such an effect. To check this

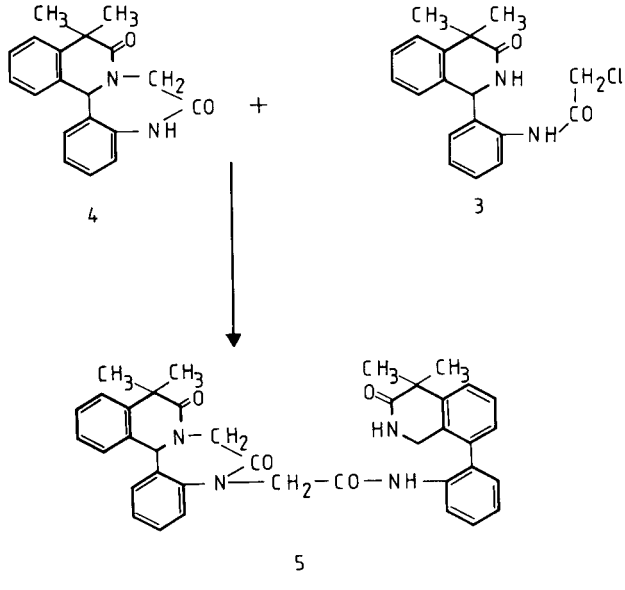


FIG. 2

assumption the calcium content was determined by flame photometry, however it was so low (50 γ/g of DMSO) that the role of calcium in the formation of the dimer could be excluded. Then we supposed that the sodium hydroxide formed in dimethyl sulphoxide from water and sodium hydride was the compound affecting the relative rates of the two reaction steps. Evidence for this was sought by effecting the cyclisation in anydrous dimethyl sulphoxide containing finely pulverized sodium hydroxide equivalent to 0.1% water content. Under such conditions the main product **4** could be prepared in a yield of 79%. This result clearly shows that the ratio of the quantity of **4** and **5** depends on the sodium hydroxide content of the solvent, and in the presence of an appropriate quantity of sodium hydroxide the intermolecular alkylation, that is the production of **5** is suppressed, presumably as a result of some kind of complexation.

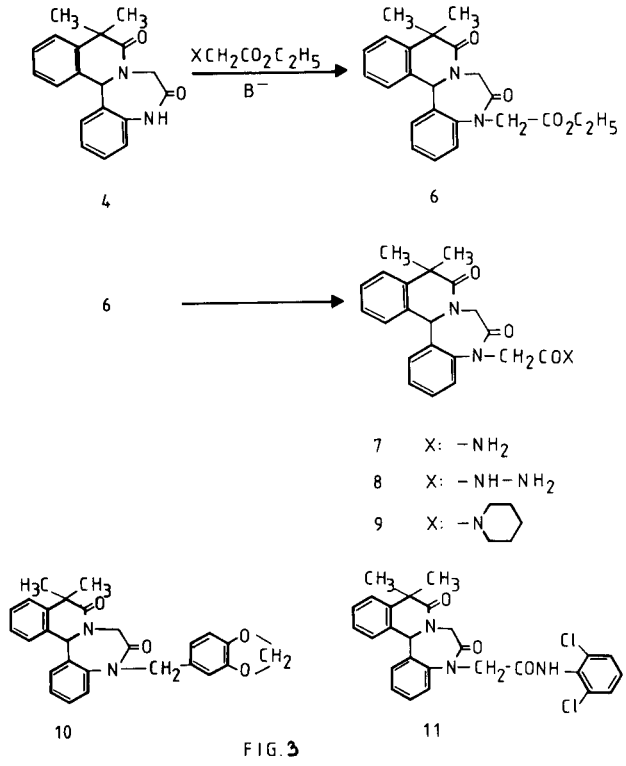


FIG. 3

Finally, for pharmacological testing some new derivatives were synthesized (**6-11**) (Figure 3). Some of these compounds have moderate CNS activity.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide pellets (Perkin Elmer Model 457). The ^{1}H nmr spectra were obtained using a JEOL FX-100 spectrometer and chemical shifts are given in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Mat spectrometer at 70 eV.

4,4-Dimethyl-1-(2'-nitrophenyl)-1,4-dihydro-3(2*H*)-isoquinolinone (**1**).

α-Phenylisobutyric amide (8.15 g, 0.05 mole) was added to polyphosphoric acid (100 ml) and the mixture was heated at 80° for 1 hour, until the amide was completely dissolved. With stirring, 2-nitrobenzaldehyde (7.55 g, 0.05 mole) was added to the solution in small portions during 2 hours, then the mixture was maintained at 77-80° for 3 hours, poured into ice-water (1 litre) and made alkaline (*p*H 8) with concentrated ammonium hydroxide. The brown solid, a mixture of the required product and the unreacted amide, was washed successively with water and diethyl ether (5 × 100 ml). The ethereal solution was clarified with charcoal, dried and evaporated to dryness. The crude product crystallised from ethanol, mp 148-149° (lit [5] mp 150-152°).

1-(2'-Aminophenyl)-4,4-dimethyl-1,4-dihydro-3(2*H*)-isoquinolinone (**2**).

Compound **1** (29.6 g, 0.1 mole) was dissolved in acetic acid (350 ml) at room temperature and hydrogenated in the presence of Pd/C at a pressure of 20-25 bar for 20 minutes. The filtered acetic acid solution was evaporated in vacuum, the solid obtained was washed with water until

free from acid, dried and crystallised from ethanol to obtain ivory crystals (24.5 g, 92%) mp 187°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.51. Found: C, 76.56; H, 6.71; N, 10.48.

1-(2'-Chloroacetylaminophenyl)-4,4-dimethyl-1,4-dihydro-3(2*H*)-isoquinolinone (**3**).

Compound **2** (5.9 g, 0.022 mole) was dissolved in acetic acid (60 ml) at room temperature, triethylamine (2.22 g, 0.022 mole) was added with cooling and stirring followed by the addition, in small portions, of chloroacetyl chloride (2.7 g, 0.024 mole). The mixture was stirred at 50-55° for 6 hours, evaporated in vacuum, the solid was washed with water until free from acid, and crystallised from anhydrous ethanol to give yellow crystals (6.7 g, 90%) mp 232°; ir (potassium bromide): 3260 cm^{-1} (NH), 1690, 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{19}H_{19}ClN_2O_2$: C, 66.56; H, 5.58; N, 8.17. Found: C, 66.76; H, 5.50; N, 10.44.

10,10-Dimethyl-6,7,9,10-tetrahydro-5*H*-14b*H*-isoquino[2,1-*d*][1,4]benzodiazepine-6,9-dione (**4**).

Sodium hydride (0.504 g, 0.21 mole) in the form of a 50% oily suspension was added to dimethyl sulphoxide (50 ml) containing 0.1% of water under stirring. The foaming mixture warmed up to 32-35°. After 5 minutes a solution of **3** (6.85 g, 0.02 mole) in dimethyl sulphoxide (5 ml) was added at such a rate that the temperature did not rise above 35°. Stirring was continued for 1.5 hours, the solid which precipitated was filtered off, washed thoroughly with water, dissolved in ethanol (100 ml) and poured into water (100 ml). The crystalline product (4.95 g, 80%) was isolated by filtration, mp 241°; ir: 3200 cm^{-1} (NH), 1675, 1620 cm^{-1} (amide C=O); nmr (deuteriochloroform): δ 1.37 (3H, s, Me), 1.74 (3H, s, Me), 5.95 (1H, s, H-1), 4.38 (1H, d, $NHCH_2$), 4.80 (1H, d, NCH_2, J_{gem} = 16 Hz), 6.53 (1H, d, ArH, J_{ortho} = 8 Hz), 6.9-7.55 (7H, m, ArH), 10.07 (1H, s, NH = strong H-bridge).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.35; H, 5.82; N, 9.05.

On evaporating the dimethyl sulphoxide mother liquor in vacuum at maximum 30° to dryness a yellow material was obtained that solidified when treated successively with heptane and water. This solid (1.2 g) was boiled with ethyl acetate (50 ml), cooled and the crystalline **5** (1.0 g, 16%) was isolated by filtration. It did not melt up to 280°.

Preparation of **4** in Anhydrous Dimethyl Sulphoxide in the Presence of Sodium Hydroxide.

The experiment described above was repeated in anhydrous dimethyl sulphoxide with the same molar ratios in such a manner that after the addition of the sodium hydride finely powdered sodium hydroxide (0.11 g, 0.028 mole) was added to the solution. The quantity of the latter was equivalent to the sodium hydroxide formed by the reaction of the water content of the dimethyl sulphoxide with the sodium hydride used in excess. As expected, after processing the mixture **4** was obtained in a yield of 80%, mp 240-241°.

5-(*N*-(4,4-Dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinon-1'-yl)carbamoylmethyl)-10,10-dimethyl-6,7,9,10-tetrahydro-5*H*,14b*H*-isoquino-[2,1-*d*][1,4]benzodiazepine-6,9-dione (**5**).

Sodium hydride (0.252 g, 0.011 mole) in the form of an oily 50% suspension was added to dry dimethyl sulphoxide (25 ml) in 5 minutes, then a solution of **3** (3.4 g, 0.01 mole) in dry dimethyl sulphoxide (25 ml) was added at 32-35° and the mixture was stirred for 1.5 hours at room temperature. The solution was then evaporated to dryness in vacuum at maximum 30°. The remaining sticky material was treated successively with heptane and ethanol until it solidified. The solid was washed with water and boiled in ethyl acetate (50 ml). The pure, white microcrystals (2.4 g, 80%) did not melt up to 280°; ir: 3050-3210 cm^{-1} (NH), 1670, 1630 cm^{-1} (amide C=O); nmr (deuteriochloroform): δ 1.73 (3H, s), 1.81 (3H, s), 1.90 (3H, s), 1.99 (3H, s Me), 4.71 (1H, d, J_{gem} = 16 Hz, NCH_2CO in the ring), 5.32 (1H, d, NCH_2CO in the ring), 5.00 (2H, q, NCH_2 (CO)N), 6.40 (1H, s), 6.43 (1H, s) (H-1 and H-1'), 6.8-7.8 (16H, m, ArH), 9.27 (1H, s), 9.87 (1H, s NH).

Anal. Calcd. for $C_{36}H_{36}N_4O_4$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.38; H, 5.88; N, 9.05.

Preparation of **5**. The Reaction of **3** With **4**.

Sodium hydride (0.15 g, 0.03 mole) was stirred in dimethyl sulphoxide (5 ml) at room temperature for 10 minutes, and then **3** (1.03 g, 0.03 mole) in dimethyl sulphoxide (10 ml) was added drop-wise during 3 hours, whereupon the precipitated sodium salt slowly dissolved. The mixture was kept in a refrigerator for 12 hours, then evaporated to dryness in vacuum at maximum 30°. The residue was thoroughly washed first with light petroleum and then with water, dried and boiled in ethyl acetate (10 ml). The white microcrystalline substance (1.65 g, 90%) was identical with **5**.

Ethyl 10,10-dimethyl-6,9-dioxo-5,6,7,9,10-tetrahydro-5*H*,14b*H*-isoquino-[2,1-*d*][1,4]benzodiazepine-5-acetate (**6**).

Compound **4** (3.06 g, 0.01 mole) was dissolved in hot dry benzene with stirring and first sodium hydride (0.48 g, 0.01 mole) in the form of an 50% oily suspension was added followed by the addition of ethyl bromoacetate (1.67 g, 0.012 mole). The solution was refluxed for 9 hours, cooled and washed in a separatory funnel with water (4 × 20 ml) until the aqueous layer was free from chloride ions. The crude product, isolated from the dried benzene solution by evaporation of the solvent, was treated with light petroleum and crystallised from diethyl ether (2.98 g, 76%), mp 163-164°; ir: 1745, 1675, 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.60; H, 6.57; N, 7.44.

10,10-Dimethyl-6,9-dioxo-6,7,9,10-tetrahydro-5*H*,14b*H*-isoquino[2,1-*d*]-[1,4]benzodiazepine-5-acetamide (**7**).

Compound **4** (0.98 g, 0.025 mole) was suspended in methanol (15 ml) and combined with a 22% methanolic solution of ammonia (50 ml). The colourless, clear solution was kept in a bomb tube at 25° for 48 hours, evaporated in vacuum and the residue was crystallised from ethyl acetate, (0.75 g, 83%), mp 185-186°; ir: 1710, 1660, 1630 cm^{-1} (C=O), 3405, 3510 cm^{-1} ($CONH_2$).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.24; H, 6.08; N, 11.70.

10,10-Dimethyl-6,9-dioxo-6,7,9,10-tetrahydro-5*H*,14b*H*-isoquino[2,1-*d*]-[1,4]benzodiazepine-5-acetylhydrazide (**8**).

Compound **4** (1.96 g, 0.05 mole) was dissolved in methanol (60 ml) and combined with hydrazine hydrate (1.0 ml, 0.02 mole). The solution was stirred at room temperature for 36 hours, evaporated in vacuum and treated with diethyl ether to yield the product (1.7 g, 90%), mp 149-151°; ir: 3310 cm^{-1} (NH), 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80. Found; C, 66.62; H, 6.03; N, 14.87.

10,10-Dimethyl-6,9-dioxo-6,7,9,10-tetrahydro-5*H*,14b*H*-isoquino[2,1-*d*]-[1,4]benzodiazepine-5-(*N*,*N*-pentamethylene)acetamide (**9**).

Compound **6** (0.5 g, 0.013 mole) was boiled in distilled piperidine (10 ml) for 32 hours. The solution was evaporated to dryness in vacuum, the residue was triturated with benzene and the white product crystallised from ethyl acetate, (0.25 g, 47%), mp 224° dec; ir: 2930 cm^{-1} (CH_2), 1680, 1650, 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{26}H_{27}N_3O_3$: C, 72.71; H, 6.33; N, 9.78. Found: C, 72.63; H, 6.40; N, 9.79.

10,10-Dimethyl-6,7,9,10-tetrahydro-5-piperonyl-5*H*,14b*H*-isoquino-[2,1-*d*][1,4]benzodiazepine (**10**).

Compound **4** (1.0 g, 0.033 mole) was dissolved in dry dimethyl sulphoxide (20 ml) at room temperature and sodium hydride (0.16 g, 0.33 mole) was added to the solution. After the precipitation of the sodium salt piperonyl chloride (1.8 g, 0.011 mole) was added by drops, and the mixture was heated at 80-85° for 5 hours. After evaporation in vacuum, the

residue was dissolved in chloroform, passed through a column packed with aluminium oxide and eluted with chloroform containing 4% of ethanol. The appropriate fractions were combined, the solvent evaporated and the crude product, a greenish oil, was triturated with diethyl ether and crystallised from acetone (20 ml), (0.82 g, 57%), mp 165°; ir: 1670, 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.39. Found: C, 73.35; H, 5.75; N, 6.45.

10,10-Dimethyl-6,7,9,10-tetrahydro-5-(2,6-dichloroacetanilido)-5*H*,14b*H*-isoquino[2,1-*d*][1,4]benzodiazepine-6,9-dione (**11**).

Compound **4** (1.0 g, 0.033 mole) was dissolved in dry dimethyl sulphoxide (10 ml) at room temperature and then sodium hydride (0.16 g, 0.022 mole) was added to the solution. After the precipitation of the sodium salt, 2,6-dichloro-*N*-(chloroacetyl)aniline (0.8 g, 0.04 mole) in diethylformamide (15 ml) was added to the mixture. It was then maintained at 75-80° for 4 hours and evaporated in vacuum to dryness. The residue was rubbed with water and the solidified crude product crystallised from acetone (25 ml) to give white crystals (0.6 g, 35%), mp 156° dec; ir: 3200 cm^{-1} (NH), 1685, 1670, 1645 cm^{-1} (C=O).

Anal. Calcd. for $C_{27}H_{23}Cl_2N_3O_3$: C, 63.78; H, 4.55; N, 13.95. Found: C, 63.97; H, 4.94; N, 13.93.

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