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Arylation in the 5-Position of 1,4-Benzodiazepine 4-Oxides

POUL NEDENSKOV and MICHAEL MANDRUP

Niels Clauson-Kaas Chemical Research Laboratory, Rugmarken 28, DK-3520 Farum, Denmark

Dedicated to Professor K. A. Jensen on his 70th birthday

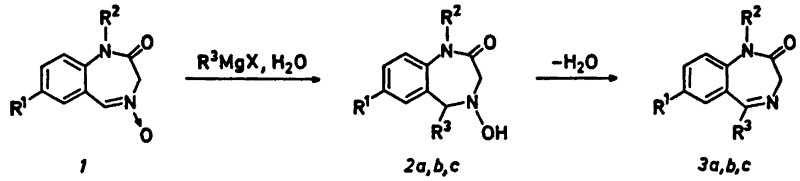
1,3-Addition of arylmagnesium halides to the 4,5-nitrone function in 1,4-benzodiazepine 4-oxides followed by dehydration or oxidation of the resulting substituted hydroxylamines opens up a new synthetic route to the pharmacologically active 1,4-benzodiazepines.

In previously [1] patented syntheses of 1,4-benzodiazepines the substituent in the 5-position was present in the 2-aminobenzophenones, which by various methods were attached to the $C^3-C^5-N^4$ unit before cyclization to the desired 1,4-benzodiazepines. With the present method,* reaction of arylmagnesium halides with 5-unsubstituted 1,4-benzodiazepine 4-oxides, it became possible to obtain 1,4-benzodiazepines with different substituents in the 5-position from the key compounds *1* or *4*.

Previously [2] 1,3-addition of Grignard reagents to nitrones has been described, but only with compounds not containing other "Grignard active" groups.

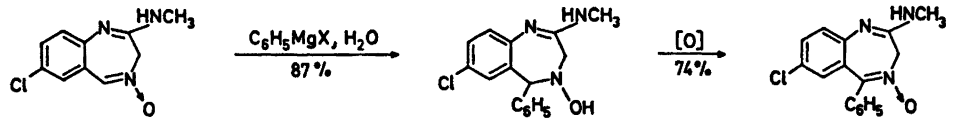
It was thus important to select the proper reaction conditions for the Grignard reaction as it was found that the Grignard-reactive groups R^1, $-N(R^2)-CO$ might have higher reactivity toward Grignard reagents in certain media than the nitrone function had. The stability of the arylating agent might also impose special reaction conditions. The different reaction conditions given here make this arylation method general.

* Patented during 1966—1975 by Grindstedværket A/S, Aarhus, Denmark.



1 *2a,b,c* *3a,b,c*

a, $R^1 = NO_2$; $R^2 = H$; $R^3 = C_6H_5$. *b*, $R^1 = Cl$; $R^2 = CH_3$; $R^3 = C_6H_5$.
c, $R^1 = Cl$; $R^2 = Et_2N(CH_2)_2$-; $R^3 = o$-FC_6H_4.



4 *5* *6*

Scheme 1.

When R^1 in *1* was NO_2 and R^2=H it was found necessary to use the unconventional Grignard reaction medium pyridine in order to get *2a*, which by dehydration gave the sedative *3a* (Nitrazepam). The use of pyridine as solvent in the Grignard reaction also proved to give reasonable yields in 5-phenylation of *1* with R^1=Cl and R^2=CH_3 giving *2b* shown to consist of two isomers, which could not be transformed into each other. The nature of the isomerism was not fully determined, but both isomers could be dehydrated to the well-known psychoactive drug *3b* (Diazepam). A similar case with two isomeric 4-hydroxy-1,4-benzodiazepines was described previously.[11]

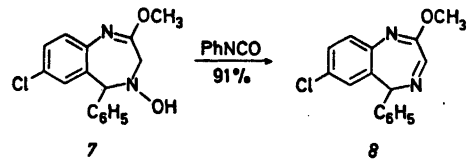
Oxidation of *3b* by *m*-chloroperoxybenzoic acid converted it to the 4-oxide,[7] which by reduction with sodium borohydride gave one of the isomers of *2b* obtained by the Grignard reaction.

The 5-phenylation of *4* gave 5, which was oxidized[12] with potassium hexacyanoferrate(III) to give a mixture of oxidation products, which were isomerized to *6* (Chlordiazepoxide).

When *6* was reduced[8] with lithium aluminium hydride another isomer of *5* was obtained. This isomer could again be oxidized[8] to *6*.

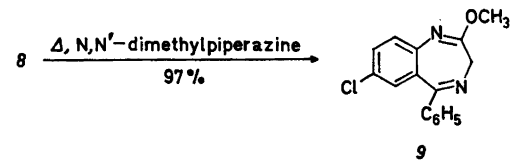
When the aryl group in the arylmagnesium halide contained an *o*-halogen substituent special reaction conditions had to be chosen in order to suppress the transformation of the arylmagnesium halide into a benzyne[9,10] before it reacted with the benzodiazepine 4-oxide. Thus we achieved high yields in the reaction of *1*, R^1=Cl, R^2=$CH_2CH_2N(Et)_2$ with *o*-fluorophenylmagnesium bromide when using the entrainer 1,2-dibromoethane in the *in situ* preparation of the Grignard reagent. The new hydroxylamine *2c* obtained was dehydrated by phenyl isocyanate to *3c* (Flurazepam).

The dehydration of the Grignard products – the cyclic hydroxylamines – was also investigated. Sometimes dehydration with phenyl isocyanate gave the best yields, but in most cases refluxing the hydroxylamine in *N,N'*-dimethylpiperazine gave the expected 3*H*-1,4-benzodiazepine. In the case of 2-alkoxy-4-hydroxy-5-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepines the two dehydration procedures gave either the 5*H*- or the 3*H*-isomer. Thus *7* by dehydration with phenyl isocyanate gave the 5*H*-1,4-benzodiazepine *8*, whereas *7* on refluxing in *N,N'*-dimethylpiperazine gave the 3*H*-1,4-benzodiazepine *9*. Refluxing *8* in *N,N'*-dimethylpiperazine gave isomerization to *9*.



7 8

Scheme 2.



9

Scheme 3.

The structures of *8* and *9* were determined by ^{1}H NMR analysis, whereas other structures followed from syntheses and elemental analyses. The starting materials, *1* and *4*, were prepared by standard reactions from substituted benzaldehydes.[5]

EXPERIMENTAL

Preparation of Nitrazepam (*3a*)

1,3,4,5-Tetrahydro-4-hydroxy-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (2a). (*1*: R^1=NO_2, R^2=H)[13] (4.42 g, 0.0200 mol) was suspended in dry pyridine (140 ml) and the suspension was stirred for 10 min at 35–40 °C and then cooled to 20 °C. A 2.6 M ethereal solution of phenylmagnesium bromide (18.4 ml, 0.0480 mol) was added dropwise at about 20 °C over a period of 7 min in a nitrogen atmosphere. The resulting brown suspension was cooled to 13 °C during the next 7 min. A mixture of ice (70 g) and conc. hydrochloric acid (20 ml) was added with stirring during 2 min. The tea-colored solution was cooled to 0 °C, seeded with *2a*, and stirred for 1 h at 0 °C. Water (225 ml) was added dropwise with stirring over a period of 40 min at 0 °C, whereafter the mixture was stirred overnight at 0 °C. The resulting crystals were isolated by filtration, washed with three 15 ml portions of water, and dried over calcium chloride. The dry crystals [5.26 g, m.p. 207–209 °C (decomp.)] were crystallized from acetone (90 ml) by cooling to –20 °C overnight to give 3.90 g (65 %) of pure *2a*, m.p. 219–220 °C (decomp.). The mother liquor and washings were evap-

orated to dryness from a water bath (40 °C) under reduced pressure, and the residue crystallized from acetone (15 ml) in the same way as above to give another 0.72 g (12 %) of *2a* of the same purity [*m.p.* 219–220 °C (decomp.)]. The total yield of *2a* was thus 4.62 g (77 %). Anal. $C_{15}H_{13}N_3O_4$: C, H, N.

Nitrazepam, 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (3a). *2a* (1.00 g, 0.00334 mol) was suspended in a mixture of anhydrous isobutyl acetate (10 ml) and 1,4-dimethylpiperazine (1 ml) at 20 °C and the suspension stirred for 10 min at 25 °C. Phenyl isocyanate (0.80 ml, 0.0075 mol) was added and the yellowish-white suspension heated to reflux over a period of 15 min. The evolution of carbon dioxide started at about 45 °C and stopped when reflux began. The slightly yellow suspension was cooled to 20 °C and methylene chloride (10 ml) was added with stirring. The white crystals were isolated by filtration, washed with methylene chloride (2+2 ml), and dried (80 °C) to give 0.64 g of 1,3-diphenylurea (90 %), m.p. 242–243 °C. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was crystallized from benzene (5 ml) to give 0.93 g of slightly impure *3a* (99 %), cream-colored crystals, m.p. 218–220 °C. Crystallization from acetonitrile (12 ml) with cooling to −20 °C overnight, filtration, washing with cold acetonitrile (1+1+1 ml), and drying (100 °C, 1 mmHg) gave 0.78 g of *2a* (83 %), almost white crystals, m.p. 226–227 °C. From the mother liquor and washings another crop of *3a*, 0.078 g (8 %), m.p. 225–226 °C was obtained. The total yield of *3a* was thus 0.858 g (91 %). The mixture melting point with an authentic sample was 226–227 °C. The product was further identified by the IR spectrum.

Preparation of Diazepam (*3b*)

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (1: R^1=Cl, R^2=CH_3). (*1*: R^1=Cl, R^2=H)[5] (1.11 g, 0.00525 mol) was suspended in methanol (30 ml) and the suspension heated to 60 °C with stirring. A solution of sodium methoxide [from 0.121 g of sodium (0.00525 mol) and methanol (40 ml)] was added in one portion. The clear solution was heated to boiling, and freshly distilled dimethyl sulfate (0.50 ml, 0.0055 mol) added in one portion. The mixture was heated under reflux for 1 h and then concentrated by distillation under reduced pressure to 3–4 ml. Ether (20 ml) and light petroleum (b.p. 40–60 °C) (30 ml) were added and the mixture cooled to −20 °C. A precipitate of a light reddish powder was isolated by filtration, stirred with water (10+5+5 ml) on the filter, and dried (50 °C, 0.1 mmHg, 1 h). The yield was 0.85 g, the main portion of which melted at 171–175 °C, while a small portion remained solid at 185 °C. Crystallization from ethanol–ether gave 0.65 g of (*1*: R^1=Cl, R^2=CH_3) (55 %), m.p. 175–176 °C. (Found: C 52.9; H 4.0; Cl 15.8 N 12.5. Calc. for $C_{10}H_9ClN_2O_2$: C 53.5; H 4.0; Cl 15.8; N 12.5).

7-Chloro-1,3,4,5-tetrahydro-4-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, isomers A and B (2bA and 2bB). (*1*: R^1=Cl, R^2=CH_3) (7.88 g, 0.035 mol) was dissolved in dry pyridine (100 ml). A 1.37 M solution of phenylmagnesium bromide in ether (35 ml, 0.048 mol) was added dropwise with stirring at about 15 °C for 40 min. The resulting brick-red colored suspension was stirred overnight at room temperature. The next day the suspension was cooled to 0 °C and added with stirring to a mixture of crushed ice (200 g), and concentrated hydrochloric acid (100 ml), while the temperature was kept below −5 °C. Ether (200 ml) was added, and stirring continued for 20 min, while the temperature rose to 20 °C. The mixture was filtered, and the greyish-brown filter cake washed with water (40 ml), ether (40+40+40 ml), and dried (2 h, 80–100 °C). The resulting greyish-brown crystals (2.1 g) were crystallized from boiling benzene (45 ml), crystallization taking place by standing overnight at 5 °C. The crystalline precipitate was isolated by filtration, washed with benzene (2+2 ml), and dried (100 °C, 1 h) to give 1.05 g of grey crystals of *2bB*, m.p. 190 °C (Kofler hot stage). Evaporation of the mother liquor to 10 ml gave another 0.30 g of *2bB* with the same melting point. A sample of *2bB* (100 mg) was crystallized from benzene (3 ml) to give 72 mg of material with the same melting point. This material was analysed. Anal. $C_{16}H_{15}ClN_2O_2$: C, H, N.

The combined aqueous mother liquor and washings were separated from the ether and extracted once more with ether (120 ml). The combined ethereal extracts (about 400 ml) were washed with 6 % sodium hydrogen carbonate solution (35 ml), and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure from a water bath (60 °C), and the residue (9.8 g) stirred with light petroleum (b.p. 40–60 °C) (100 ml) at about 40 °C. The resulting suspension of crystals was filtered, the crystals washed with light petroleum (b.p. 40–60 °C) (20+20+20 ml), and dried at 80 °C to give 7.2 g of a brown powder. Crystallization from benzene (110 ml) then gave 2.68 g of *2bA*, m.p. 208 °C (Kofler hot stage). 100 mg of this product was recrystallized from a 2:3 mixture of benzene and light petroleum (b.p. 40–60 °C) (10 ml) to give 95 mg of *2bA*, white needles, m.p. 209 °C (Kofler hot stage), identical (IR spectra and mixture melting point) with the product obtained by sodium borohydride reduction of 4-oxide[7] of *3b*. Anal. $C_{16}H_{15}N_2O_2$: C, H, N.

Evaporation of the benzene mother liquor from the 2.68 g of *2bA* to 20 ml followed by cooling to 5 °C overnight gave another crop

of crystals (1.57 g) consisting of a mixture of *2bA* and *2bB*. Crystallization experiments showed this mixture to consist of equal amounts of the *A* and *B* isomers, bringing the total yield of *2bA* to 3.46 g (33 %) and of *2bB* to 2.13 g (20 %).

All attempts to transform *2bA* into *2bB*, or *vice versa*, by seeding during crystallization were unsuccessful.

*Diazepam, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (*3b*). 2bA* (1.00 g, 0.00330 mol) was dissolved in dry pyridine (10 ml) at 20 °C. Freshly distilled phenyl isocyanate (0.72 ml, 0.0066 mol) was added in one portion with stirring, The clear colorless solution was heated to 95 °C over a period of 25 min, and kept at this temperature until evolution of carbon dioxide stopped (about 1 h). The reaction mixture was worked up as described above for the dehydration of *2a* to give a voluminous residue, which was recrystallized from methanol (2 ml) at −20 °C to give 0.715 g of *3b* (76 %); white crystals, m.p. 128−130 °C, mixture melting point with an authentic sample 129−131 °C. The product was further identified by the IR spectrum.

When 100 mg of *2bB* was subjected to the above reaction conditions 40 mg of *3b* (43 %), white crystals, m.p. 126−128 °C, mixture melting point 129−131 °C was obtained.The product was further identified by the IR spectrum.

Preparation of Chlordiazepoxide (*6*)

*7-Chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine, isomers* A *and* B *(*5A *and* 5B*). 4*[5] (16.8 g, 0.0750 mol) was suspended in technical methylene chloride (150 ml) and the suspension cooled to 0 °C with stirring. A 2 M ethereal solution of phenylmagnesium bromide (82 ml, 0.164 mol) was added dropwise at about 5 °C over a period of 90 min. The resulting suspension was allowed to warm to room temperature with stirring over a period of 1 h. The suspension was then cooled to 0 °C and N hydrochloric acid (165 ml, 0.165 mol) added dropwise with stirring at about 5 °C over a period of 20 min. The mixture was stirred 20 min at 0−5 °C and the resulting white crystals filtered off, washed with methylene chloride (25+25 ml) and water (30+30+30 ml), and dried in the air at 60 °C for 2 h to give 16.9 g of *5A* (75 %), m.p. 180−184 °C. From the organic phase of the combined filtrate and washings another crop of *5* (4.4 g) was obtained, which contained about 1 g (5 %) of the starting material. Crystallization from methylene chloride (100 ml) gave 2.8 g of *5A*, m.p. 180 °C (Kofler hot stage), the total yield of *5A* thus being 19.7 g (87 %).

500 mg of the above 16.9 g *5A* was dissolved in boiling acetone (5 ml) the solution filtered, and the filtrate concentrated to 1.5 ml and left overnight at −20 °C. The resulting crystals were isolated by filtration, washed with cold acetone (1 ml), and dried at 60 °C to give 425 mg, m.p. 185−188 °C (decomp.). Anal. $C_{16}H_{16}ClN_3O$: C, H, Cl, N.

Reduction of purified, commercial chlordiazepoxide (1.0 g) with lithium aluminium hydride according to Sternbach [8] gave 0.38 g of *5B* (38 %), m.p. 196−198 °C (decomp.). The sample showed the same infrared absorption as our sample above. Anal. $C_{16}H_{16}ClN_3O$: C, H, Cl, N.

*Chlordiazepoxide, 7-chloro-3-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (6).* Oxidation of *5A* or *5B* with potassium hexacyanoferrate (III) according to the directions given previously [12] gave a 74 % yield of *6*, m.p. 238−239 °C (lit.[8] 236 °C).

Preparation of Flurazepam (*3c*, 2HCl)

*7-Chloro-1-[2-(diethylamino)ethyl]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide (*1: R^1=Cl, R^2=$(CH_2)_2NEt_2$). (*1*: R^1=Cl, R^2=H) (80.0 g, 0.380 mol) was added to a solution of sodium methoxide [from 9.66 g of sodium (0.420 mol) and methanol (200 ml), followed by evaporation of 150 ml of methanol] in methanol (50 ml) and *N,N*-dimethylformamide (800 ml). The clear solution, which became turbid after 30 s, was stirred for 30 min at room temperature. A solution of 2-chlorotriethylamine [prepared from the hydrochloride (72.3 g, 0.420 mol)] in dry toluene (440 ml) at 5 °C was added in one portion. The mixture was heated with stirring for 1 h on the water bath (100 °C). The resulting light orange suspension was evaporated to dryness under reduced pressure from a water bath (70 °C). Methylene chloride (300 ml) was added to the residue and the suspension poured on to a mixture of ice (1000 g), water (1000 ml), and 3 N hydrochloric acid (133 ml, 0.400 mol). The aqueous phase was removed, washed with methylene chloride (200+200 ml), and adjusted to pH 9−10 at 0 °C with 3 N sodium hydroxide (133 ml, 0.400 mol). The oil which separated was extracted with methylene chloride (200+200+200 ml). The combined methylene chloride extracts were dried with Drierite (Sikkon, Fluka). Removal of the methylene chloride by distillation from a water bath (40 °C), finally at 15 mmHg, gave 99.3 g (84 %) of a tea-colored oil.

The oil (99.3 g) was dissolved in warm ether (200 ml) and left for 48 h at −30 °C. The resulting cake of crystals was separated by decantation of the supernatant ether, washed with cold ether (15+15 ml), and dissolved in warm methanol (30 ml). Ether (300 ml) was added and the solution left overnight at −20 °C. The resulting crystalline precipitate was isolated by filtration, washed with cold ether

(25+25 ml), and dried (20 °C, 0.5 mmHg) to give 48.0 g of (*1*: R^1=Cl, R^2=$(CH_2)_2NEt_2$) (41 %) as white crystals, m.p. 87–89 °C. The mother liquor and washings were evaporated to dryness from a water bath (45 °C) under reduced pressure, and the residue crystallized from ether (100 ml) at −20 °C and isolated as above to give another 23.4 g of (*1*: R^1=Cl, R^2=$(CH_2)_2NEt_2$) (20 %) as slightly yellow crystals, m.p. 86–88 °C. The total yield of (*1*: R^1=Cl, R^2=$(CH_2)_2NEt_2$) was thus 71.4 g (61 %). A sample melting at 88–90 °C was analysed. Anal. $C_{15}H_{20}ClN_3O_2$: C, H, Cl, N.

Crude 7-chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3,4,5-tetrahydro-4-hydroxy-2H-1,4-benzodiazepin-2-one (2c). A stirred suspension of magnesium turnings (1.18 g, 0.0049 mol) in a mixture of 1,2-dibromoethane (1.5 g, 0.008 mol) and tetrahydrofuran (20 ml, free of water and peroxide), was heated under nitrogen in a dry flask to about 60 °C to initiate evolution of ethylene. A solution of (*1*: R^1=Cl, R^2=$(CH_2)_2NEt_2$) (1.49 g, 0.0048 mol) in a mixture of 1,2-dibromoethane (2.5 g, 0.013 mol), 1-bromo-2-fluorobenzene (1.22 g, 0.007 mol), and tetrahydrofuran (20 ml, free of water and peroxide) was then added dropwise with stirring at 40–42 °C over a period of 45 min. The resulting dark, red-brown solution was heated to 50 °C and stirred at this temperature for 30 min. The viscous mixture was added in one portion to ice-cold 0.14 N hydrochloric acid (150 ml, 0.021 mol). The resulting red-yellow, turbid solution was filtered to remove 0.4 g unreacted magnesium. The pH of the solution was adjusted to about 5 with 3 N NaOH (2 ml), and it was then extracted continuously with methylene chloride for 6 h.

The methylene chloride extract was washed with 20 % $KHCO_3$ (50 ml+50 ml) and dried over anhydrous calcium sulfate. The light brown filtrate was evaporated to about 150 ml. Methanol (50 ml) was added. Carbon black (0.2 g) was added, and the suspension was stirred under gentle reflux for 40 min. The filtrate was stirred with silica gel (3 g, Merck type G) for 10 min. The filtrate was evaporated to dryness (70 °C/10 mmHg), and the remaining oil was used in the next reaction without further purification.

Flurazepam, 7-chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride (3c), 2HCl. The impure *2c* was dehydrated with phenyl isocyanate according to the directions given above, and the crude oil was treated with a solution of hydrogen chloride in 2-propanol to give a 46 % overall yield of *3c*, 2HCl, m.p. 199–203 °C. Previously [14] found 190–220 °C.

Dehydration experiments with 7-chloro-2-methoxy-4-hydroxy-5-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine (*7*).

7 was prepared by a Grignard reaction in tetrahydrofuran in a 70 % yield after directions given previously.[15]

7-Chloro-2-methoxy-5-phenyl-5H-1,4-benzodiazepine (8). *7* (6.2 g, 0.0205 mol) was dissolved in a mixture of isobutyl acetate (60 ml) and 1,4-dimethylpiperazine (6 ml) at 20 °C and the solution stirred for 5 min at 25 °C. Phenyl isocyanate (4.85 ml, 0.0456 mol) was added and the solution heated to reflux over a period of 15 min. The evolution of carbon dioxide started at about 40 °C and stopped when reflux began. The yellow suspension was cooled to 25 °C and methylene chloride (100 ml) was added with stirring. The white crystals were isolated by filtration, washed with methylene chloride (30+30 ml), and dried (60 °C) to give 4.0 g of 1,3-diphenylurea (92 %), m.p. 243 °C. The combined filtrate and washings were evaporated to dryness under reduced pressure from a water bath (70 °C). Boiling cyclohexane (100 ml) was added to the yellowish brown residue whereby most of the residue dissolved. The mixture was left overnight at 5 °C and the solution decanted from insoluble, oily material. The cyclohexane solution was evaporated to dryness under reduced pressure from a water bath (90 °C). The light yellow, very viscous residue (6.45 g) was distilled from an oil bath (178–182 °C) to give 5.29 g (91 %) of *8*, $b.p._{0.3}$ 162–165 °C. Anal. $C_{16}H_{13}ClN_2O$: C, H, Cl, N.

The ^1H NMR spectrum ($CDCl_3$) of *8* showed a singlet at δ 6.5 and a doublet at δ 4.8–4.9 representing, respectively, one proton at position 3 and one proton at position 5.

7-Chloro-2-methoxy-5-phenyl-3H-benzodiazepine (9). *8* (2.0 g, 0.0070 mol) and 1,4-dimethylpiperazine (3.5 ml) were heated under reflux over a period of 1 h. The tea-colored solution was evaporated to dryness under reduced pressure from a water bath (100 °C). The very viscous residue was distilled from an oil bath (175–185 °C) to give 1.93 g (97 %) of *9*, $b.p._{0.1}$ 141–148 °C. The product crystallized on standing at 60 °C for three days, whereafter it was powdered in a mortar and homogenized to give a slightly yellow powder, m.p. 85–87 °C (softening from 79 °C). (Found: C 67.4; H 4.6; Cl 12.4; N 10.1; OCH_3 10.0. Calc. for $C_{16}H_{13}ClN_2O$: C 67.5; H 4.6; Cl 12.5; N 9.9; one OCH_3 10.8).

100 mg of the above material was crystallized from light petroleum (1 ml) (b.p. 50 °C) to give 55 mg of *9*, m.p. 86–88 °C. (Found: C 67.6; H 4.8; Cl 12.3; N 9.7; OCH_3 10.5).

The ^1H NMR spectrum ($CDCl_3$) of both samples of *9* showed a singlet at δ 4.0 representing two protons at position 3.

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