SYNTHESIS OF 7-CHLORO-5-(4-CHLOROPHENYL)-1-METHYL-1,3-DIHYDRO-1,4-BENZODIAZEPIN-2-ONE

Zdeněk VEJDĚLEK, Zdeněk POLÍVKA and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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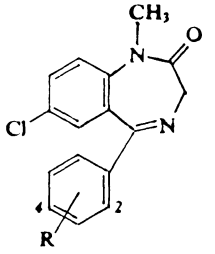
The synthesis of the title compound *II* was carried out from 5-chloro-3-(4-chlorophenyl)-2,1--benzisoxazole (*III*) by two methods proceeding *via* new intermediates *V* and *VI*. 5-(2-Fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*VII*) was synthesized from 2-amino-2'-fluorobenzophenone *via VIII*.

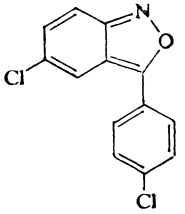
In contradistinction of 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-1,4-benzodiazepin-2-one (*I*) (experimental agent Ro 5-3448) (ref.[1]), which has strong central depressant, anticonvulsant and anxiolytic activity, its position isomer *II* (the 4-chlorophenyl compound), known under the code number Ro 5-4864, is indeed likewise a ligand for the central and peripheral benzodiazepine binding sites but its pharmacodynamic potency is considerably lower and is partly reverted to the antagonistic one (convulsant action) (ref.[2-5]); in the form of its tritiated analogue, the compound is an excellent tool for localization and characterization of the benzodiazepine receptors[6,7]. The substance was needed in our pharmacological laboratory and, therefore, its synthesis has to be considered. This was described by several methods[8-15] which mostly appeared tedious and little effective. For this reason, we prepared compound *II* using two further methods, and the description of this work is the main object of this communication.



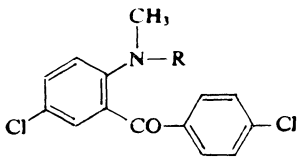
I, R = 2-Cl
II, R = 4-Cl

5-Chloro-3-(4-chlorophenyl)-2,1-benzisoxazole (*III*) was chosen as the starting compound being easily accessible by reaction of 4-chlorophenylacetonitrile[16] with 4-chloronitrobenzene in methanolic potassium hydroxide under cooling[17]. The

described procedure was modified by substantial reduction of the used amount of potassium hydroxide. For the direct conversion of compound *III* to 5,4'-dichloro--2-methylaminobenzophenone (*IV*) (ref.[18]) we used the method, described in[19] for the preparation of the corresponding 4'-dechloroanalogue, consisting in treating compound *III* with dimethyl sulfate and in the following reduction of the nonisolated quaternary salt with iron and hydrochloric acid in boiling ethanol.

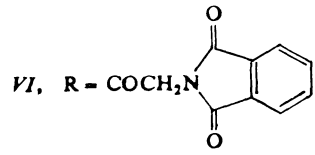


III



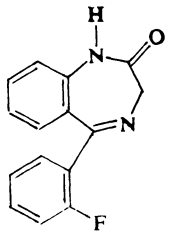
IV, R = H

V, R = $COCH_2Cl$

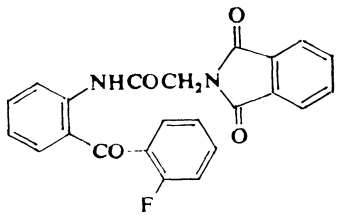


VI, R = $COCH_2N$

For concluding the synthesis of compound *II*, two methods were used. In the first one the intermediate *IV* was acylated with chloroacetyl chloride in benzene in the presence of ice and in a high yield amide *V* was obtained. Treatment with hexamethylenetetramine in boiling aqueous methanol (method[20,21]) gave the compound *II* in a yield of 94%. The second procedure used the Podešva's approach[22] (*cf.* our preceding papers[23-25]): treatment of the intermediate *IV* with phthalimidoacetyl chloride[26-28] in boiling chloroform resulted in the phthalimide derivative *VI* which was transformed to compound *II* by hydrazinolysis in methanol at 60°C. The product *II*, obtained in a yield of 80%, melted by 6°C higher than described in the literature[8] and its identity was confirmed by analysis and by spectra.



VII



VIII

In a different connection we used Podešva's method[22] in the synthesis of 5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*VII*) (ref.[29]) which is an important intermediate. 2-Amino-2'-fluorobenzophenone[29] afforded by treatment with phthalimidoacetyl chloride[26-28] in boiling chloroform the phthalimide derivative *VIII* (was claimed in a patent[30] but not described) which was subjected to hydrazinolysis in aqueous ethanol at 60°C to yield *VII* (94%).

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C or at room temperature. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra with a Perkin Elmer 298 spectrophotometer and ^1H NMR spectra (mostly in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

5-Chloro-3-(4-chlorophenyl)-2,1-benzisoxazole (*III*)

A solution of 438 g 85% KOH in 865 ml methanol was stirred and treated at 17–20°C with a solution of 99 g 4-chloronitrobenzene and 105 g 4-chlorophenylacetonitrile[16] in 300 ml benzene, added dropwise over 75 min. The mixture was stirred for 3 h at room temperature and poured into a stirred solution of 430 g NH_4Cl in 3 l water, it was stirred for 1 h and allowed to stand overnight. The precipitated product was filtered, washed with a mixture of benzene and hexane, then with hexane, and dried *in vacuo*; 66·0 g, m.p. 214–215°C. The organic layer of the filtrate was separated, the aqueous layer was extracted with 500 ml benzene, the organic layers were combined and evaporated *in vacuo*. The residue was stirred with 150 ml ether and the second crop was obtained by filtration; 5·2 g, m.p. 215–216°C. The total yield was thus 71·2 g (43%). Lit.[17], m.p. 214–215°C.

5,4'-Dichloro-2-methylaminobenzophenone (*IV*)

A mixture of 52·8 g *III* and 200 g dimethyl sulfate was stirred for 5 h at 80°C. The warm mixture was treated with 480 ml ethanol, 20 ml water and 26 g Fe fillings, it was heated to reflux and over 90 min 150 ml hydrochloric acid were added dropwise. The mixture was refluxed for 3 h, filtered while hot, the solid was washed with 60 ml ethanol and the filtrate was poured under stirring into 3 l cold water. It was stirred for 1 h, allowed to stand overnight, the yellow product was filtered, washed with water and dried *in vacuo*; 53 g (95%), m.p. 119–121°C. Lit.[18] (different synthetic method), m.p. 123°C.

N-[4-Chloro-2-(4-chlorobenzoyl)phenyl]-N-methylchloroacetamide (*V*)

A mixture of 28·0 g *IV* and 500 ml benzene was stirred and treated over 50 min with 18·0 g chloroacetyl chloride at 10°C; the cooling was achieved by slow addition of ice (totally 400 g ice added). It was stirred for 90 min, the benzene layer was separated, filtered, washed with 250 ml cold 5% NaOH and water, dried (Na_2SO_4) and benzene was partly evaporated. The residue was warmed to 75°C and allowed to crystallize in a refrigerator. The product was filtered, washed with a mixture of benzene and hexane, and dried; 28·5 g, m.p. 160–161°C. Evaporation of the mother liquor gave another 2·1 g product, the total yield being 30·6 g (86%). Analytical sample, m.p. 161–162°C (benzene–hexane). UV spectrum: λ_{max} 263 nm (log ε 4·26). IR spectrum: 779,

790, 805, 899 (2 adjacent and solitary Ar—H), 1 567, 1 585, 3 070, 3 090 (Ar), 1 645 (ArCOAr'), 1 668 cm^{-1} (N—CO). ^1H NMR spectrum: δ 7·70 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in 4-chlorobenzoyl), 7·20—7·52 (m, 5 H, remaining ArH), 3·90 and 3·70 (ABq, 2 H, $COCH_2Cl$), 3·35 and 2·98 (2s, 3 H, NCH_3). For $C_{16}H_{12}Cl_3NO_2$ (356·6) calculated: 53·89% C, 3·38% H, 29·83% Cl, 3·93% N; found: 53·66% C, 3·35% H, 30·00% Cl, 3·99% N.

N-[4-Chloro-2-(4-chlorobenzoyl)phenyl]-N-methylphthalimidoacetamide (*VI*)

A solution of 22·0 g *IV* in 100 ml chloroform was treated with 17·5 g phthalimidoacetyl chloride[26-28] and the mixture was refluxed for 8 h. Chloroform was evaporated and the warm residue slowly treated with 120 ml ethanol; crystallization took place and was concluded by standing in a refrigerator. The product was filtered, washed with a 1 : 8 mixture of chloroform and ethanol, finally with 50 ml cold ethanol, and was dried; 34·7 g (95%), m.p. 180—182°C. Analytical sample, m.p. 182—183°C (ethanol). UV spectrum: λ_{max} 263 nm (log ε 4·28), infl. 238 nm (4·35). IR spectrum: 742, 765, 810, 852 (4 and 2 adjacent and solitary Ar—H), 1 480, 1 567, 1 585, 3 030, 3 060, 3 090 (Ar), 1 680 (ArCOAr', NCOR), 1 715, 1 772 cm^{-1} [1,2-$C_6H_4(CO)_2N$]. ^1H NMR spectrum: δ 7·30—7·90 (m, 11 H, ArH), 4·41 and 4·04 (ABq, J = 13·0 Hz, 2 H, $COCH_2N$), 3·35 and 3·00 (2 s, 3 H, NCH_3). For $C_{24}H_{16}Cl_2N_2O_4$ (467·3) calculated: 61·67% C, 3·45% H, 15·18% Cl, 6·00% N; found: 61·63% C, 3·45% H, 15·21% Cl, 6·02% N.

N-[2-(2-Fluorobenzoyl)phenyl]phthalimidoacetamide (*VIII*)

A solution of 26·6 g 2-amino-2'-fluorobenzophenone[29] in 165 ml chloroform was treated with 27·6 g phthalimidoacetyl chloride[26-28], the mixture was refluxed with stirring for 6 h, allowed to stand overnight at room temperature, evaporated *in vacuo* and the residue was treated with 200 ml boiling ethanol. Crystallization and processing of the mother liquor gave 43·0 g (86%) *VIII*, m.p. 177—179°C. Analytical sample, m.p. 180—182°C (chloroform–ethanol). UV spectrum: λ_{max} 230 nm (log ε 4·63), 265 nm (4·11), 305 nm (3·68). IR spectrum: 752 (4 adjacent Ar—H), 1 522, 1 710 (RCONHAr), 1 581, 1 610, 3 068, 3 100 (Ar), 1 640 (ArCOAr'), 1 720 [1,2-C_6H_4··$(CO)_2N$], 3 280 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 10·71 (s, 1 H, NH), 7·00 to 8·00 (m, 12 H, ArH), 4·29 (s, 2 H, $COCH_2N$). For $C_{23}H_{15}FN_2O_4$ (402·4) calculated: 68·65% C, 3·76% H, 4·72% F, 6·96% N; found: 68·38% C, 3·78% H, 4·69% F, 6·86% N.

7-Chloro-5-(4-chlorophenyl)-1-methyl-1,3-dihydro-1,4-benzodiazepin-2-one (*II*)

A) A mixture of 12·0 g *V*, 11·0 g hexamethylenetetramine, 150 ml methanol and 15 ml water was stirred and refluxed for 22 h, it was filtered while hot and the filtrate was allowed to crystallize; 10·0 g (94%), m.p. 161—162°C (aqueous ethanol), UV spectrum: λ_{max} 317 nm (log ε 3·41), infl. 253 nm (4·30). IR spectrum: 745, 822, 835, 890 (4 and 2 adjacent and solitary Ar—H), 1 482, 1 560, 1 590 (Ar), 1 608 (C=N in conjugation), 1 675, 1 690 cm^{-1} (N—CO). ^1H NMR spectrum: δ 7·30—7·70 (m, 6 H, ArH), 7·20 (d, J = 2·5 Hz, 1 H, 6-H), 4·80 and 3·75 (ABq, J = 13·0 Hz, 1 + 1 H, 3,3-H_2), 3·38 (s, 3 H, NCH_3). For $C_{16}H_{12}Cl_2N_2O$ (319·2) calculated: 60·20% C, 3·79% H, 22·22% Cl, 8·78% N; found: 59·96% C, 3·86% H, 22·42% Cl, 8·91% N. Lit.[8] (different method of synthesis), m.p. 154—156°C.

B) A suspension of 34·0 g *VI* in 520 ml methanol was treated with a solution of 4·75 g N_2H_4 in 24 ml water and the mixture was stirred for 3 h at 60°C. After standing overnight the precipitated solid was filtered and combined with the residue, obtained by evaporation of the filtrate *in vacuo*. The solid was suspended in a mixture of 300 ml water and 100 ml NH_4OH, the suspension was stirred for 30 min at room temperature, the undissolved product was filtered, washed

with diluted NH_4OH and water, and dried; 22·6 g crude product, m.p. 160—162°C. Crystallization from aqueous ethanol gave 18·6 g (80%) pure *II*, m.p. 161—162°C, identical with the substance, obtained under *A*.

5(2-Fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*VII*)

A suspension of 43·0 g *VIII* in 910 ml methanol was treated with a solution of 11·1 g N_2H_4 in 28 ml water and the mixture was stirred at 60°C for 3 h. Similar processing like in the preceding case gave 25·5 g (94%) homogeneous (TLC) *VII*, m.p. 180—183°C. Lit.[29], m.p. 180—181°C (different method of preparation).

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REFERENCES

1. Babbini M., Gaiardi M., Bartoletti M.: Life Sci. *25*, 15 (1979).
2. Braestrup C., Albrechtsen R., Squires R. F.: Nature (London) *269*, 702 (1977); Chem. Abstr. *88*, 45 132 (1978).
3. File S. E., Pellow S.: Psychopharmacology *80*, 166 (1983).
4. Weissman B. A., Cott J., Paul S. M., Skolnick P.: Eur. J. Pharmacol. *90*, 149 (1983).
5. File S. E., Green A. R., Nutt D. J., Vincent N. D.: Psychopharmacology *82*, 199 (1984).
6. Schoemaker H., Boles R. G., Horst W. D., Yamamura H. J.: J. Pharmacol. Exp. Ther. *225*, 61 (1983).
7. Marangos P. J., Patel J., Boulenger J. P., Clark-Rosenberg R.: Mol. Pharmacol. *22*, 26 (1982).
8. Sternbach L. H., Fryer R. I., Metlesics W., Reeder E., Sach G., Saucy G., Stempel A.: J. Org. Chem. *27*, 3 788 (1962).
9. Reeder E., Sternbach L. H. (Hoffmann-La Roche Inc.): U.S. 3 136 815 (Swiss Appl. 02.12.60); Chem. Abstr. *61*, 9 515 (1964).
10. Reeder E., Sternbach L. H. (Hoffmann-La Roche Inc.): U.S. 3 270 053 (Swiss Appl. 02.12.60); Chem. Abstr. *66*, 28 808 (1967).
11. Reeder E., Sternbach L. H. (Hoffmann-La Roche Inc.): U.S. 3 344 183 (Swiss Appl. 02.12.60); Chem. Abstr. *68*, 95 869 (1968).
12. Reeder E., Sternbach L. H. (Hoffmann-La Roche Inc.): U.S. 3 402 171 (Swiss Appl. 02.12.60); Chem. Abstr. *70*, 37 850 (1969).
13. Yamamoto H., Inaba S., Kume Y., Izumi T., Hirohashi T., Yamamoto M., Ishizumi K., Maruyama I., Akatsu M., Mori K. (Sumitomo Chemical Co., Ltd.): Ger. Offen. 2 017 060 (Japan. Appl. 18.04.69—03.07.69); Chem. Abstr. *74*, 22 904 (1971).
14. Von Brachel H., Graewinger O. (Cassella Farbwerke Mainkur A.-G.): Ger. Offen. 1 942 743 (Appl. 22.08.69); Chem. Abstr. *74*, 100 116 (1971).
15. Aki O., Nakagawa Y., Shirakawa K., Yamamoto M. (Takeda Chemical Industries, Ltd.): Japan. 73/21 114 (Appl. 21.10.70); Chem. Abstr. *79*, 105 306 (1973).
16. Mndzhoyan A. L., Papayan G. L., Bagoyan M. A.: Izv. Akad. Nauk Arm. SSR, Khim. Nauki *16*, 359 (1963); Chem. Abstr. *60*, 11 933 (1964).
17. Davis R. B., Pizzini L. C.: J. Org. Chem. *25*, 1 884 (1960).
18. Mouzin G., Cousse H., Autin J.-M.: Synthesis *1981*, 448.
19. Lugenheim W., Heidrich H. J.: Ger. (East) 69 134 (Appl. 20.03.68); Chem. Abstr. *72*, 90 064 (1970).

20. Blaževič N., Kajfež F.: J. Heterocycl. Chem. *7*, 1 173 (1970).
21. CRC Compagnia di Ricerche Chimiche S. A.: Fr. Demande 2 123 218 (Appl. 29.01.71); Chem. Abstr. *78*, 97 727 (1971).
22. Podešva C. (Delmar Chemicals Ltd.): Neth. Appl. 65/446 (Brit. Appl. 14.01.64 and 07.04.64); Chem. Abstr. *64*, 5 120 (1966).
23. Vejdělek Z., Rajšner M., Dlabač A., Ryska M., Holubek J., Svátek E., Protiva M.: This Journal *45*, 3 593 (1980).
24. Vejdělek Z., Protiva M.: This Journal *48*, 1 477 (1983).
25. Polívka Z., Holubek J., Svátek E., Metyš J., Protiva M.: This Journal *49*, 621 (1084).
26. Balenović K., Bregant N., Cerar D., Tkalčic M.: J. Org. Chem. *16*, 1 308 (1951); Chem. Abstr. *46*, 3 005 (1952).
27. Foye W. O., Lange W. E.: J. Amer. Pharm. Assoc. *45*, 742 (1956).
28. King F. R., Clark-Lewis J. W., Wade R., Swindin W. A.: J. Chem. Soc. *1957*, 873.
29. Keller O., Steiger N., Sternbach L. H. (Hoffmann-La Roche Inc.): U. S. 3 203 990 (Appl. 20.04.61 and 21.03.62); Chem. Abstr. *64*, 3 576 (1966).
30. Podešva C., Kohan G. (Delmar Chemicals Ltd.): Can. 871 117 (Appl. 09.09.67); Chem. Abstr. *75*, 88 346 (1971).

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