SYNTHESIS OF TWO 1-SUBSTITUTED 8-BROMO-6-(2-CHLOROPHENYL)-4*H*-*s*-TRIAZOLO[4,3-*a*]--1,4-BENZODIAZEPINES*

Zdeněk VEJDĚLEK and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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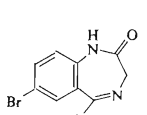
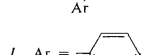
2-Amino-5-bromo-2'-chlorobenzophenone (*VII*) afforded by a reaction with phthalimidoacetyl chloride the phthalimido derivative *VIII* which was transformed by hydrazinolysis to 7-bromo--5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*II*). A reaction with phosphorus pentasulfide in pyridine gave the thiolactam *IX* which reacted with hydrazides of acetic and methylthioacetic acid in boiling 1-butanol and gave the title compounds *V* and *VI*. Compound *V* is very potent in pharmacological tests for anticonvulsant, central depressant and discoordinating activity in mice; compound *VI* is somewhat weaker.

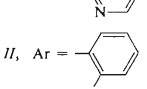
While the atom of chlorine as a 7-substituent appears in molecules of a number of tranquillizers, anxiolytics, anticonvulsants and hypnotics of the 1,4-benzodiazepine series, the use of the atom of bromine in the same position is rather rare[1]. Bromazepam (*I*) was the first practically used 7-bromo-1,4-benzodiazepine (its molecule contains the 2-pyridyl residue in position 5) finding a growing usage as anxiolytic with some advantages over diazepam[2,3]. Fenazepam (*II*) has been developed as an anxiolytic (2-chlorophenyl in position 5) (refs[4,5]) and quite recently the 7-bromo--5-(2-chlorophenyl)-1,4-benzodiazepine derivative *III* has been announced as an anxiolytic with the generic names metaclazepam or brometazepam[6].

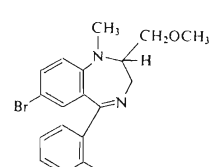


I, Ar =



II, Ar =

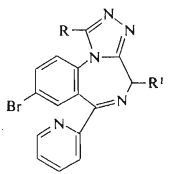




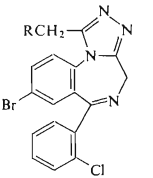
III

* Part XVIII in the series Benzocycloheptenes and Heterocyclic Analogues as Potential Drugs; Part XVII: This Journal *48*, 123 (1983).

There are reports in the literature[7] and especially in patents (*e.g.*[8–10]) about 6-aryl--8-bromo-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepins, containing similarly like the molecule of bromazepam (*I*), the 2-pyridyl residue in position 6 and corresponding thus to the general formula *IV*. Phenyl as the 6-aryl appeared only in a few cases[7] and we did not meet at all with a combination of the atom of bromine in position 8 with the 2-chlorophenyl in position 6 which could be considered especially promising from the point of view of the central activity. We carried out, therefore, the synthesis of compounds *V* and *VI* which is described in the present communication. Compound *V* is a bromo analogue of 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]--1,4-benzodiazepine, *i.e.* the hypnotically extremely potent triazolam[11–15] and compound *VI* is a bromo analogue of a substance described in the preceding communication of this series[16].

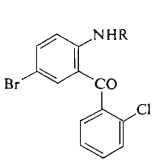


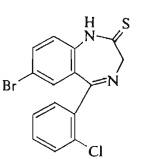
IV



V, R = H
VI, R = SCH_3

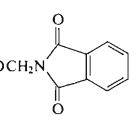
In the synthesis of compounds *V* and *VI* we used similar methods like in previous communications of this series[16,17]. The starting 2-amino-5-bromo-2'-chlorobenzophenone (*VII*) (ref.[4]) was transformed by treatment with phthalimidoacetyl chloride[18–20] in boiling chloroform to compound *VIII* which was subjected to hydrazino-





VII, R = H

VIII, R = —$COCH_2$N



IX

lysis with a solution of hydrazine in aqueous methanol at 60°C. The primarily formed aminoacetamido derivative underwent cyclization to compound *II*, *i.e.* the already mentioned fenazepam, the synthesis of which has been described by a different method[4]. The following reaction with phosphorus pentasulfide in boiling pyridine gave the thiolactam *IX*. The final steps were reactions of *IX* with acethydrazide[21] and methylthioacethydrazide[22] in boiling 1-butanol resulting directly in the desired *s*-triazolo[4,3-*a*]-1,4-benzodiazepines *V* and *VI*.

Compounds *V* and *VI* were pharmacologically evaluated in a similar manner like substances described in our preceding communication[16]; they were administered orally. The acute toxicity of both compounds in mice is very low; the values of LD_{50} are above 1 g/kg. Doses of 0·2–1·0 g/kg, bring about a strong central depression, ataxia and convulsive reactions; these symptoms last longer than 24 h. On the rotarod both compounds bring about ataxia in very low doses; the ED_{50} values are 0·31 mg/kg for compound *V* and 1·0 mg/kg for compound *VI*. In the test of inhibition of the spontaneous locomotor activity in mice using the photocell method of Dews only compound *V* was evaluated; its medium effective dose D_{50} is 0·073 mg/kg. Both compounds are highly potent in the test of inhibition of the convulsant effect of the electroshock; the medium protective doses (PD_{50}) are 0·14 mg/kg for compound *V* and 0·18 mg/kg for compound *VI*. In the test of pentetrazole convulsions in mice compound *V* in a dose of 0·03 mg/kg had a statistically significant protective effect towards the convulsant as well as lethal action of pentetrazole. In comparison with triazolam[16] both compounds have a similarly low toxicity, compound *V* has a similar anticonvulsant effect towards pentetrazole, it has some 25% of the triazolam activity in the test of electroshock, 12% of the locomotor inhibiting effect and some 40% of the discoordinating activity. Compound *VI*, for which only fragmentary data on activity are available, appears less active than compound *V*. From the point of view of intensity of the central effects the substitution of the chlorine atom with the bromine atom in the important position 8 of the *s*-triazolo[4,3-*a*]-1,4-benzodiazepine skeleton appears as mildly unfavourable.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer and the IR spectra (in Nujol) with a Perkin Elmer 298 spectrophotometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel.

5-Bromo-2′-chloro-2-(phthalimidoacetamido)benzophenone (*VIII*)

A mixture of 130 g *VII* (ref.[4]), 580 ml chloroform and 94 g phthalimidoacetyl chloride[18–20] was refluxed for 5 h and 500 ml chloroform were distilled off. The warm residue was diluted with 600 ml ethanol and the mixture was allowed to crystallize overnight in a refrigerator; 202 g

(97%), m.p. 168–169°C (chloroform–ethanol) with first melting and resolidification at 90–95°C. UV spectrum: λ_{max} 240 nm (log ε 4·63), 267·5 nm (4·13) and 347 nm (3·65); infl. at 295 nm (3·50). IR spectrum: 755, 770, 835, 892 (4 and 2 adjacent and solitary Ar—H), 1 510, 1 577, 1 644 (Ar.

.NHCOR), 1 720, 1 772 (C_6H_4  N), 3 055 (Ar), 3 208 and 3 235 cm^{-1} (NH). For $C_{23}H_{14}$.

.$BrClN_2O_4$ (497·7) calculated: 55·50% C, 2·83% H, 16·05% Br, 7·12% Cl, 5·64% N; found: 55·91% C, 2·91% H, 15·71% Br, 6·95% Cl, 5·55% N.

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

A mixture of 199 g *VIII*, 2·9 l methanol and 140 ml 18% aqueous N_2H_4 was stirred for 3 h at 60°C, for further 30 min at room temperature and it was then allowed to stand overnight at room temperature. The separated phthalylhydrazine was filtered off and methanol was distilled off from the filtrate under reduced pressure. The residue was diluted with 680 ml water, treated with 60 ml NH_4OH and stirred for 30 min at room temperature. After 30 min standing the liquid was separated from the heavy precipitate which was treated once more with 680 ml water and 60 ml NH_4OH and the stirring for 30 min was repeated. It was then filtered, the solid product washed with a solution of 50 ml NH_4OH in 500 ml water, and dried; 126 g (90%), m.p. 223–224°C (ethanol). UV spectrum: λ_{max} 231 nm (log ε 4·53), 321 nm (3·27), infl. at 255 nm (4·09). IR spectrum: 752, 793, 828, 847, 870 (4 and 2 adjacent and solitary Ar—H), 1 480, 1 570, 1 590, 3 030, 3 073 (Ar), 1 615 (Ar—C=N), 1 694 (ArNHCOR), 3 110, 3 200 cm^{-1} (NH). For $C_{15}H_{10}$ $BrClN_2O$ (349·6) calculated: 51·53% C, 2·88% H, 22·86% Br, 10·14% Cl, 8·01% N; found: 51·89% C, 2·94% H, 22·40% Br, 9·83% Cl, 8·07% N. Lit.[4]. m.p. 228–230°C.

7-Bromo-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*IX*)

A mixture of 26·0 g *II*, 150 ml pyridine and 18 g P_2S_5 was stirred and refluxed under nitrogen for 45 min. After cooling below 22°C the mixture was poured into a solution of 250 g NaCl in 850 ml water at 5°C, the mixture was stirred for 30 min and the crude product was filtered, washed with water and dried. It was dissolved in 500 ml dichloromethane and the solution was filtered through a column of 50 g neutral Al_2O_3 (activity II). The column was washed with 4 l dichloromethane and the combined filtrates were evaporated. The residue was heated with 50 ml ethanol, the suspension was cooled, filtered, the solid was washed with a mixture of 50 ml ethanol and 10 ml hexane and then with 50 ml hexane, and dried; 16·2 g (60%), m.p. 238–240°C. Analytical sample, m.p. 241–242°C (yellow needles from a mixture of chloroform and ethanol). UV spectrum: λ_{max} 305 nm (log ε 4·42), infl. 344 nm (3·68). IR spectrum: 749, 832, 880 (4 and 2 adjacent and solitary Ar—H), 1 375 (NHCS), 1 525, 1 580 (Ar), 1 613 cm^{-1} (Ar—C=N). For $C_{15}H_{10}$.$BrClN_2S$ (365·7) calculated: 49·27% C, 2·75% H, 21·86% Br, 9·90% Cl, 7·66% N, 8·76% S; found: 49·32% C, 2·79% H, 21·46% Br, 9·46% Cl, 7·57% N, 8·85% S.

8-Bromo-6-(2-chlorophenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*V*)

A mixture of 5·48 g *IX*, 2·95 g acethydrazide[21] and 110 ml 1-butanol was stirred and refluxed under nitrogen for 7 h. The solvent was evaporated *in vacuo*, the residue was stirred with 80 ml water, the solid product was filtered, washed with water, dried, and dissolved in 850 ml boiling ethyl acetate, The solution was filtered, 730 ml ethyl acetate were distilled off from the filtrate and the residue was allowed to crystallize under cooling; filtration and processing of the mother liquor gave 4·7 g (81%) product, m.p. 274–275°C (chloroform–ethyl acetate). UV spectrum: λ_{max} 285 nm (log ε 3·17), infl. at 250 nm (4·11). IR spectrum: 752, 832, 881 (4 and 2 adjacent

and solitary Ar—H), 1 475, 1 532, 1 560, 1 590, 3 005, 3 050 (Ar), 1 618 cm^{-1} (C=N). For $C_{17}H_{12}BrClN_4$ (387·7) calculated: 52·67% C, 3·12% H, 20·61% Br, 9·15% Cl, 14·45% N; found: 52·21% C, 3·24% H, 20·77% Br, 9·22% Cl, 14·30% N.

8-Bromo-6-(2-chlorophenyl)-1-(methylthiomethyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*VI*)

A mixture of 2·0 g *IX*, 1·8g methylthioacethydrazide[22] and 50 ml 1-butanol was stirred and refluxed under nitrogen for 7 h. The solvent was evaporated *in racuo*, the residue mixed with 60 ml water and extracted with chloroform. The extract was washed with water, dried with Na_2SO_4 and evaporated. The residue was dissolved in 7 ml boiling ethyl acetate and the solution was cooled for 48 h to −5°C. The precipitated product was filtered, washed with ethyl acetate and dried; 2·1 g (89%), m.p. 215–216°C (chloroform–ethyl acetate). UV spectrum: λ_{max} 285 nm (log ε 3·24), infl. at 250 nm (4·18). IR spectrum: 745, 815, 842, 885 (4 and 2 adjacent and solitary Ar—H), 1 480, 1 528, 1 560, 1 590, 3 008, 3 040, 3 055, 3 085 (Ar), 1 610 cm^{-1} (C=N). For $C_{18}H_{14}BrClN_4S$ (433·8) calculated: 49·84% C, 3·26% H, 18·42% Br, 8·17% Cl, 12·92% N, 7·39% S; found: 50·08% C, 3·33% H, 18·30% Br, 8·09% Cl, 13·13% N, 7·64% S.

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