ACTA CHEMICA SCANDINAVICA 23 (1969) 971–974

New Methods for the Preparation of 1,4-Benzodiazepinones, Carbostyrils and Indolo[2,3-c]quinolones

JOHN BRAMMER PETERSEN* and KARL HEINZ LAKOWITZ

Rexolin Chemicals AB, Högastensgatan, Hälsingborg, Sweden

Azidoacetylation of 2-aminobenzophenones gives 2-azidoacetamidobenzophenones, from which 1,4-benzodiazepinones, carbostyrils and indolo[2,3-c]quinolones were prepared in high yields in simple one step syntheses.

Our attempts to find a new and convenient synthesis for the pharmaceutical 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, Valium (IV), originally prepared by Sternbach and Reeder,[1] have resulted in the synthetic sequences I→II→III→IV and I→III→IV shown below.

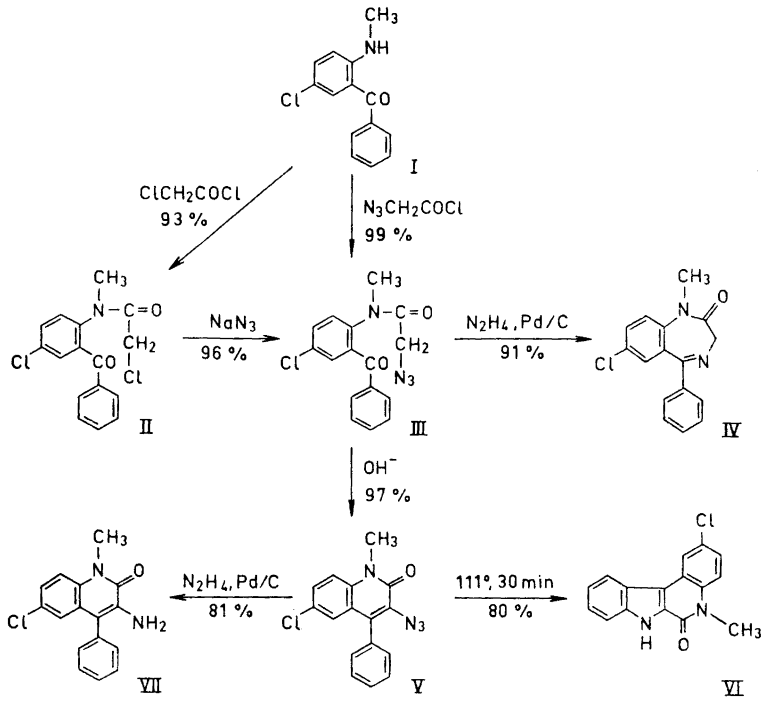
Besides giving rise to the compound primarily desired (IV) through reduction, the azido-compound, III, was found to cyclize readily to the azidocarbostyril, V, when treated with a trace of alkali in ethanolic solution. V is stable at room temperature. When heated in boiling toluene, it splits off nitrogen (like similar azides [2]) and cyclizes to the indolo[2,3-c]quinolone VI. The aminocarbostyril, VII, was obtained by catalytic reduction of V.

In order to demonstrate the generality of the above syntheses a set of compounds (IIIa—VIIa) derived from the unsubstituted 2-aminobenzophenone, were also prepared.

The structures of the compounds were proved by elementary analysis and infrared spectroscopy; that of compound VIa additionally by comparison with a sample prepared according to Clemo and Felton.[3]

The compounds IIa, III, IIIa, V, Va, VI and VIIa are not previously recorded in the literature.

* Present address: Israel Institute of Technology, Haifa, Israel.



EXPERIMENTAL

2-Chloroacetamidobenzophenone (IIa). A solution of chloroacetyl chloride (3.36 g, 0.0297 mole) in chloroform (5 ml) was added in one portion to a solution of 2-aminobenzophenone (3.95 g, 0.0200 mole) in chloroform (20 ml). The resulting solution was heated under reflux for 30 min and evaporated from a water bath (60°, 10 mm). The crystalline residue formed was crystallized from ethanol (20 ml). After drying at 80°, 5.10 g (93 %) of slightly yellow IIa melting at 104–108° was obtained. A sample was crystallized from ethanol to constant melting point (108–109°). [Found: C 65.7; H 4.4; Cl 13.0; N 5.1. Calc. for $C_{15}H_{12}ClNO_2$ (273.7): C 65.8; H 4.4; Cl 13.0; N 5.1.].

2-(2-Azido-N-methylacetamido)-5-chlorobenzophenone (III) from I. Azidoacetyl chloride (7.17 g, 0.060 mole) was poured into a stirred solution of I (12.28 g, 0.050 mole) in chloroform (25 ml). The temperature of the solution rose to 40° and hydrogen chloride was evolved. The solution was kept at 40°–50° for 1 h and evaporated from a water bath (60°, 10 mm). The resulting hot oily residue was dissolved in ethanol (25 ml) and cooled (−10°). The crystalline precipitate of III was filtered off, washed with ethanol (10 ml) and dried at 60°, whereby 16.22 g (99 %) of III was obtained as white crystals melting at 111–113°. A sample was crystallized to constant melting point (112–113°) from ethanol. [Found: C 58.3; H 4.0; Cl 11.0; N 17.3. Calc. for $C_{16}H_{13}ClN_4O_2$ (328.8): C 58.5; H 3.9; Cl 10.8; N 17.0.]

2-(2-Azido-N-methylacetamido)-5-chlorobenzophenone (III) from II. Sodium azide (1.43 g, 0.022 mole) was added to a stirred solution of II [4] (6.44 g, 0.020 mole) in dimethylformamide (25 ml). The temperature of the mixture increased and was brought to 60° by additional heating. After stirring at this temperature for 30 min, cold water (30 ml) was added dropwise to the warm reaction mixture whereby crystalline III precipitated. Cooling to room temperature, removal of the solvent by decantation and recrystallization from ethanol (10 ml) gave 6.30 g (96 %) of white III melting at 111.5–113.0°.

2-Azidoacetamidobenzophenone (IIIa). IIIa was prepared from sodium azide (0.715 g, 0.0110 mole) and IIa (2.74 g, 0.0100 mole) according to the directions given for the preparation of III. 80 ml of water was used to precipitate IIIa from the dimethylformamide solution. 2.40 g (86%) of white crystalline IIIa melting at 79.5—80.2° was obtained. A sample was crystallized from ethanol to constant melting point (79.9—80.5°). [Found: C 64.4; H 4.3; N 19.9. Calc. for $C_{15}H_{12}N_4O_2$ (280.3): C 64.3; H 4.3; N 20.0].

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (IV). A solution of hydrazine hydrate (3.13 g, 0.0626 mole) in ethanol (100 ml) was added in one portion to a stirred suspension of III (32.88 g, 0.100 mole) and palladium catalyst (2.00 g of 5 % Pd/C) in ethanol (300 ml) at room temperature. The reaction mixture was heated to 40° and kept there for 1 h with slow stirring. Nitrogen was evolved and the slightly exothermic reaction made cooling necessary. The catalyst was filtered off, the solvent evaporated from a water bath (100°, 20 mm) and the remaining yellow oily residue dissolved in 2-propanol (100 ml). Cooling (—20°) gave crystalline IV which was filtered off and washed with 2-propanol (25 ml, —20°). After drying at 80°, 25.80 g (91 %) of slightly yellow crystalline IV melting at 130.2—131.5° (previously found [1] 125—126°) was obtained. [Found: C 67.5; H 4.8; Cl 12.5; N 10.0. Calc. for $C_{16}H_{13}ClN_2O$ (284.7): C 67.4; H 4.6; Cl 12.5; N 9.9.]. The product was crystallized three times from 2-propanol (100 ml). The two last crystallizations included treatment with activated carbon (1.25 g of Norit SX Ultra, no boiling). Hereby 22.60 g (88 %) of white IV melting at 131.4—132.6° was obtained. Further purification did not change the melting point.

1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IVa). A solution of hydrazine hydrate (0.130 g, 0.00260 mole) in ethanol (5 ml) was added in one portion to a stirred suspension of IIIa (1.40 g, 0.0050 mole) and palladium catalyst (0.20 g of 5 % Pd/C) in ethanol (15 ml). The reaction mixture was kept at room temperature for 90 min with slow stirring, then the initially lively nitrogen evolution ceased and stirring was continued at 50° for further 30 min. The catalyst was filtered off, the filtrate evaporated (80°, 10 mm) and the resulting yellow oily residue dissolved in toluene (5 ml). Cooling (—20°) gave crystalline IVa which was filtered off and washed with toluene (2 ml, —20°). After drying at 80°, 0.75 g (64 %) yellowish IVa melting at 177—180° was obtained. A sample was crystallized to constant melting point from toluene (180.5—181.5°, previously found [5] 179—180°). [Found: C 76.3; H 5.1; N 11.9. Calc. for $C_{15}H_{12}N_2O$ (236.3): C 76.3; H 5.1; N 11.9].

3-Azido-6-chloro-1-methyl-4-phenylcarbostyril (V). A solution of III (5.00 g, 0.0152 mole) in ethanol (50 ml) was heated to 55° with stirring and one drop of 40 % aqueous sodium hydroxide was added. Precipitation of V started immediately after the addition and the temperature rose to 60°. The suspension was stirred for 5 min, cooled (0°) and filtered. The precipitate was washed with ethanol and ether and dried at room temperature. 4.58 g (97 %) of slightly yellow crystals of V was obtained. [Found: C 61.8; H 3.6; Cl 11.3; N 18.1. Calc. for $C_{16}H_{11}ClN_4O$ (310.7): C 61.8; H 3.6; Cl 11.4; N 18.0.]. White V is obtained by rapid crystallization from benzene. V does not melt but gives off nitrogen at around 125°.

3-Azido-4-phenylcarbostyril (Va). A solution of IIIa (3.00 g, 0.0107 mole) in ethanol (45 ml) was heated to 60° with stirring and one drop of aqueous 40 % sodium hydroxide was added. The colourless solution turned yellow and after a short while precipitation of Va started. Stirring at 60° was continued for a total of 60 min, whereafter the suspension was cooled (—20°) and the precipitate was filtered off. Washing with ethanol (25 ml, —20°) and ether (15 ml) and drying at room temperature gave 2.40 g (86 %) of crystalline slightly yellow Va. [Found: C 68.8; H 3.8; N 21.2. Calc. for $C_{15}H_{10}N_4O$ (262.3): C 68.7; H 3.8; N 21.4]. Va does not melt but gives off nitrogen above 100°.

2-Chloro-5,6-dihydro-5-methyl-7H-indolo[2,3-c]quinoline-6-one (VI). A solution of V (1.00 g, 0.00322 mole) in toluene (10 ml) was heated under reflux for one half hour. Precipitation of VI and evolution of nitrogen started before the temperature of the solution had reached the boiling point of toluene. The suspension was cooled (10°) and the white precipitate of I was removed by filtration, washed with toluene (2 ml) and ether (two 2 ml portions), and dried at 80°. Hereby 0.73 g (80 %) of white crystalline VI was obtained. [Found: C 67.8; H 4.0; Cl 12.5; N 10.0. Calc. for $C_{16}H_{11}ClN_2O$ (282.7): C 67.8; H 3.9; Cl 12.5; N 9.9]. A sample was crystallized from dimethylformamide whereby a product having elementary analysis and infrared spectrum identical with the above was obtained. VI does not melt below 350°.

5,6-Dihydro-7H-indolo[2,3-c]quinoline-6-one (VIa). A solution of Va (0.250 g, 0.000955 mole) in toluene (20 ml) was heated under reflux for 2 h. Precipitation of VIa occurred after about 15 minutes. After cooling (0°) the precipitate was filtered off, washed with toluene (5 ml, 0°) and ether (10 ml), and dried at 80°. 0.18 g, (81 %) of slightly yellow VIa was obtained, melting at 312—313°. A sample was crystallized from pyridine-ether. Melting point 312.7—313.0°, previously found [3] 313°, mixed melting point with an authentic sample 312.7—313.0. [Found: C 76.8; H 4.3; N 12.2. Calc. for $C_{15}H_{10}N_2O$ (234.3): C 76.9; H 4.3; N 12.0].

3-Amino-6-chloro-1-methyl-4-phenyl-carbostyril (VII). V (3.11 g, 0.0100 mole) and palladium catalyst (0.100 g of 5 % Pd/C) were suspended in ethanol (5 ml) and hydrazine hydrate (0.50 g, 0.0100 mole) was added dropwise in about 1 min. A lively evolution of nitrogen took place during which the temperature rose to 50° and VII precipitated. After 5 min the reaction was over. Ethanol (65 ml) was added and the suspension was heated to its boiling point and filtered hot through asbestos to remove the catalyst. Upon cooling (0°) filtration, washing with ethanol, and drying at 80°, 2.31 g (81 %) of white crystals of VII melting at 136—138° was obtained. A sample was crystallized from ethanol to constant melting point, 138—139° (reported [6] 130—133°), and analysed. [Found: C 67.5; H 4.7; Cl 12.4; N 9.8; Calc. for $C_{16}H_{13}ClN_2O$ (284.7): C 67.4; H 4.6; Cl 12.5; N 9.9].

3-Amino-4-phenylcarbostyril (VIIa). A solution of hydrazine hydrate (0.100 g, 0.00200 mole) in ethanol (5 ml) was added in one portion to a stirred suspension of Va (0.68 g, 0.00259 mole) and palladium catalyst (0.040 g of 5 % Pd/C) in ethanol (10 ml). The suspension was stirred for 30 min and filtered. The filtercake containing catalyst and undissolved material was extracted with hot ethanol (30 ml) and the combined filtrates evaporated to dryness from a water bath (80°, 10 mm). Crystallization of the solid residue from ethanol (40 ml) gave 0.50 g (82 %) of white crystalline VIIa melting at 246.6—250.8°. A sample was crystallized from ethanol to constant melting point (247.5—248.3°) and analysed. [Found: C 76.3; H5.2; N 11.9. Calc. for $C_{15}H_{12}N_2O$ (236.3): C 76.3; H 5.1; N 11.9].

REFERENCES

1. Sternbach, L. H. and Reeder, E. *J. Org. Chem.* **26** (1961) 4936.
2. Mueller, E., (Ed.), *Methoden der Organischen Chemie* (Houben-Weyl), 4th Ed., Georg Thieme Verlag, Stuttgart 1965, Vol. 10/3, p. 824.
3. Clemo, G. R. and Felton, D. G. I. *J. Chem. Soc.* **1951** 671.
4. Sternbach, L. H., Fryer, R. I., Metlesics, W., Reeder, E., Sach, G., Saucy, G. and Stempel, A. *J. Org. Chem.* **27** (1962) 3788.
5. Bell, S. C., Sulkowski, T. S., Gochman, C. and Childress, S. J. *J. Org. Chem.* **27** (1962) 562.
6. Fryer, R. I., Brust, B. and Sternbach, L. H. *J. Chem. Soc.* **1964** 3097.

Received July 11, 1968.