Notes

[Chem. Pharm. Bull. 23(12)3279—8282(1975)] UDC 547.892.057 : 547.752.04

Benzodiazepines. XII.[1] Synthesis of 5-(2-Pyridyl)- and 3-Methyl-1,4-benzodiazepin-2-ones

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(Received February 27, 1975)

The synthesis of 5-(2-pyridyl)- and 3-methyl-1,4-benzodiazepin-2-ones by oxidative ring enlargement of the corresponding 2-aminomethyl- and 2-(1-aminoethyl)indoles is described.

In previous publications,[3] it was reported that 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones could be synthesized by oxidative ring enlargement of the corresponding 2-aminomethyl-3-phenylindoles. As an extension of this work, we have applied this method to the synthesis of 5-(2-pyridyl)- and 3-methyl-1,4-benzodiazepin-2-ones.

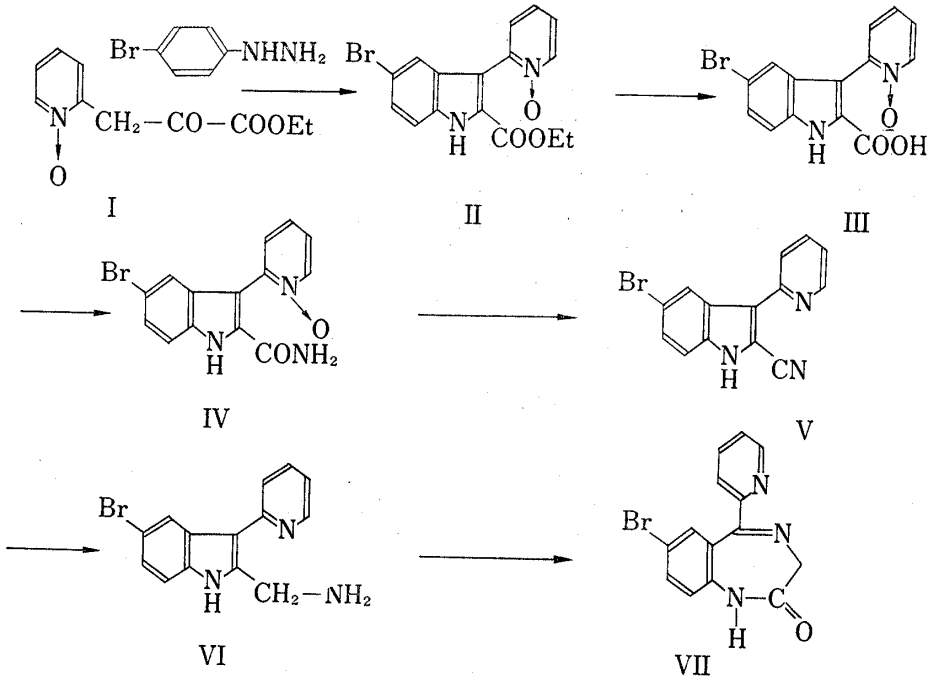

Chart 1

Ethyl 5-bromo-3-(2-pyridyl)indole-2-carboxylate 1′-oxide (II) was prepared directly by heating ethyl 2-pyridylpyruvate 1-oxide (I)[4] with a mixture of *p*-bromophenylhydrazine hydrochloride, acetic acid and concentrated sulfuric acid, without isolation of the hydrazone.

1) Part XI: S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 2421 (1975).
2) Location: *2-1, Takatsukasa-4-chome, Takarazuka-shi, Hyogo.*
3) *a*) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); *b*) S. Inaba, T. Hirohashi, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1263 (1969); *c*) S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 263 (1971); *d*) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 722 (1971).
4) R. Adams and S. Miyano, *J. Am. Chem. Soc.* **76**, 3168 (1954).

The ester II was hydrolysed with base to give acid (III), which was converted to amide (IV) *via* acid chloride by treatment with thionyl chloride followed by ammonia. Treatment of IV with phosphorous trichloride followed by phosphorous oxychloride gave 5-bromo-3-(2-pyridyl)indole-2-carbonitrile (V). The nitrile V was converted to the desired 2-aminomethyl-5-(2-pyridyl)-indole (VI) by reduction with lithium aluminum hydride.

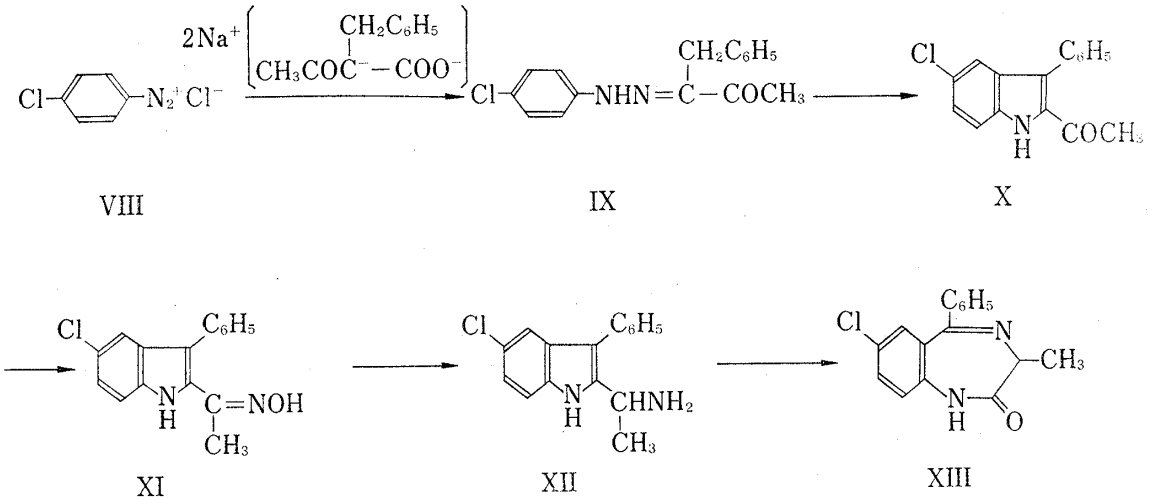

Chart 2

On the other hand, 2-(1-aminoethyl)-5-chloro-3-phenylindole (XII) was prepared from the corresponding 2-acetylindole (X) as shown in Chart 2. The 2-acetylindole X was obtained from the Japp-Klingemann reaction of *p*-chlorobenzenediazonium chloride (VIII) and the sodium salt of α-benzylacetoacetic acid followed by the Fischer indole cyclization of the resulting hydrazone (IX). Oximation of X with hydroxylamine led to 2-acetyl-5-chloro-3-phenylindole oxime (XI). Reduction of XI with lithium aluminum hydride gave XII.

Oxidation of VI and XII with chromic acid resulted in ring enlargement and formation of the expected 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones VII and XIII, respectively.

Experimental

All melting points were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra were measured on a Hitachi Model EPI-G3 spectrophotometer, and nuclear magnetic resonance (NMR) spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. All solvents used for extraction were dried over anhydrous Na_2SO_4 after extraction and evaporated on a rotary evaporator under water aspirator pressure.

Ethyl 3-(2-Pyridyl)-5-bromoindole-2-carboxylate 1′-Oxide (II)——To a solution of ethyl 2-pyridylpyruvate 1-oxide[4] (23.1 g, 0.11 mole) and *p*-bromophenylhydrazine hydrochloride (24.5 g, 0.11 mole) in AcOH (17.4 g) was added dropwise conc. H_2SO_4 (30.4 g) at about 50° and the mixture was heated under reflux for 2.5 hr. After the solvent was removed *in vacuo*, the residue was diluted with H_2O (100 ml) and chloroform (50 ml), and made basic with 20% NaOH (200 g). The precipitate was collected by filtration, washed with water followed by chloroform and dried to give 25.4 g (63.9%) of II, mp 235—245° (decomp.). Recrystallization from EtOH gave colorless prisms, mp 259.5—260° (decomp.). IR ν_{max}^{Nujol} cm^{-1}; 3050, 1670. *Anal.* Calcd. for $C_{16}H_{13}O_3N_2Br$: C, 53.21; H, 3.63; N, 7.76; Br, 22.12. Found: C, 53.48; H, 3.53; N, 7.60; Br, 22.32.

3-(2-Pyridyl)-5-bromoindole-2-carboxylic Acid 1′-Oxide (III)——To a solution of KOH (8.2 g) in EtOH (300 ml) was added the ester II (30.0 g) and the mixture was heated under reflux for 1.5 hours. The mixture was cooled to 5°, and the precipitate was collected by filtration, suspended in H_2O (200 ml) and made acidic with conc. HCl under cooling. The precipitate formed was collected by filtration, washed thoroughly with H_2O and dried to give 27.4 g (99%) of III, mp 242—246° (decomp.). Recrystallization from EtOH gave colorless needles, mp 258—260° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3380, 3050, 1680. *Anal.* Calcd. for $C_{14}H_9O_3N_2Br$: C, 50.48; H, 2.72; N, 8.41; Br, 23.98. Found: C, 50.56; H, 2.58; N, 8.34; Br, 24.21.

3-(2-Pyridyl)-5-bromoindole-2-carboxamide 1′-Oxide (IV)——A mixture of the carboxylic acid III (22.0 g, 0.066 mole) and $SOCl_2$ (47.6 g, 0.66 mole) was refluxed for 0.5 hr. The excess $SOCl_2$ was removed *in vacuo* and the residue was suspended in dry toluene (200 ml). Ammonia was introduced into the suspension below

10°. The precipitate was collected by filtration, washed with toluene followed by H_2O, dried, and recrystallized from a mixture of dimethylformamide and EtOH to give 8.93 g of IV, mp 252.2—254° (decomp.). From the mother liquors an additional 11.41 g of product was obtained for a combined yield of 20.34 g (94%). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1640. *Anal.* Calcd. for $C_{14}H_{10}O_2N_3Br$: C, 50.63; H, 3.03; N, 12.65; Br, 24.06. Found: C, 51.00; H, 2.98; N, 12.61; Br, 24.03.

3-(2-Pyridyl)-5-bromoindole-2-carbonitrile (V)——To a suspension of the amide IV (83.1 g, 0.25 mole) in dry toluene (830 ml) was added dropwise PCl_3 (408.5 g, 2.85 mole) at about 20°. The mixture was heated under reflux for 1 hr. To the mixture was added dropwise $POCl_3$ (213.5 g, 1.25 mole) and heated under reflux for 2.5 hr. After cooling, the precipitate was collected by filtration, washed with toluene, suspended with ice-water and made basic with 20% NaOH (250 ml). The precipitate was collected by filtration, washed with water and dried to give 60.1 g (80.6%) of V, mp 213.5—215°. Recrystallizations from EtOH gave colorless needles, mp 224—224.5°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 2220. *Anal.* Calcd. for $C_{14}H_8N_3Br$: C, 56.40; H, 2.70; N, 14.09; Br, 26.80. Found: C, 56.35; H, 2.69; N, 14.07; Br, 26.78.

2-Aminomethyl-5-bromo-3-(2-pyridyl)indole Dihydrochloride (VI)——To a suspension of $LiAlH_4$ (0.64 g) in dry ether (30 ml) was added portionwise V (1.0 g) and the mixture was stirred at room temperature for 3 hr and heated under reflux for 0.5 hr. After cooling and cautious addition of H_2O (7 ml), the ether layer was separated by decantation, dried and evaporated. The residue was dissolved in EtOH (10 ml) and to this solution was added 16% EtOH–HCl (2 ml). After cooling the resulting precipitate was filtered off and dried to give 0.69 g of the hydrochloride of VI, mp 256—265° (decomp.). From the filtrate, a second crop (0.24 g) was obtained for a combined yield of 0.93 g (74%). Recrystallizations from EtOH gave colorless fine needles, mp 274—277° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 2730, 2680, 2600, 2450, 2050, 1990, 1650. *Anal.* Calcd. for $C_{14}H_{14}N_3BrCl_2$: C, 44.83; H, 3.76; N, 11.20. Found: C, 45.22; H, 3.64; N, 11.11.

7-Bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one (VII)——To a suspension of the dihydrochloride of VI (1.0 g) in AcOH (20 ml) was added dropwise with stirring a solution of CrO_3 (1.6 g) in H_2O (1.2 ml) at 15—27°. After stirring at 40° for 2.5 hr, the reaction mixture was poured into ice-water (50 g), made basic with 28% NH_4OH below 20° and extracted with chloroform. The chloroform layer was washed with saturated aq. NaCl solution, dried, and evaporated. The residue was recrystallized from EtOH (10 ml) to give 0.59 g (70%) of VII, mp 225—226°. Recrystallizations from EtOH gave colorless prisms, mp 246—248° (lit.[5] mp 237—238.5°). IR ν_{max}^{Nujol} cm^{-1}: 3150, 3030, 1670. NMR (DMSO-d_6) δ: 4.25 (2H, s, CH_2), 7.1—8.8. (7H, m, aromatic H), 1.06 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd. for $C_{14}H_{10}ON_3Br$; C, 53.19; H, 3.19; N, 13.29, Br, 25.27. Found: C, 53.62; H, 3.23; N, 13.28; Br, 25.33.

1-Phenyl-2,3-butanedione 2-(*p*-Chlorophenylhydrazone) (IX)——A solution of NaOH (18 g) in H_2O (50 ml) was added to a solution of ethyl α-benzylacetoacetate (88 g) in MeOH (100 ml) and the mixture was stirred for 20 min. A semisolid gelatinous mass formed. After the addition of H_2O (1 liter) the mixture was stirred until only a small amount of oil remained unreacted upon. The solution was filtered and the filtrate was added at 0—5° to a solution of *p*-chlorobenzene-diazonium chloride (VIII) prepared by diazotization of *p*-chloro-aniline (48.5 g) in conc. HCl (100 ml) with $NaNO_2$ (26 g) in H_2O (47 ml) at 0—10°. To the mixture was added AcONa (200 g). After stirring below 10° for 30 min, the precipitate that formed was collected by filtration, washed successively with H_2O, 5% $NaHCO_3$ and H_2O, and dried to give 79.8 g (73.2%) of IX, mp 88—93°. Recrystallization from EtOH afforded red prisms, mp 109—110°. IR ν_{max}^{Nujol} cm^{-1}: 3260, 1665, 1650. NMR ($CDCl_3$) δ: 2.53 (3H, s, CH_3), 3.95 (2H, s, CH_2), 7.55—6.85 (9H, m, aromatic H), 8.10 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd. for $C_{16}H_{15}ON_2Cl$: C, 67.02; H, 5.27; N, 9.77; Cl, 12.36. Found: C, 66.84; H, 5.25; N, 9.81; Cl, 12.47.

2-Acetyl-5-chloro-3-phenylindole (X)——A mixture of IX (71.7 g), conc. HCl (300 ml) and iso-PrOH (300 ml) was refluxed with stirring for 4 hr. The reaction mixture was cooled and the precipitate formed was collected by filtration and washed with iso-PrOH followed by H_2O to give 47.0 g of X, mp 94—111°. From the mother liquor a second crop (6.6 g) was obtained for a combined yield of 53.6 g (79.5%). Recrystallization from MeOH yielded colorless needles, mp 137—138°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1640, 1600. NMR ($CDCl_3$) δ: 2.20 (3H, s, CH_3), 7.72—6.83 (8H, m, aromatic H), 9.82 (1H, s, NH). *Anal.* Calcd. for $C_{16}H_{12}ONCl$: C, 71.25; H, 4.48; N, 5.19; Cl, 13.14. Found: C, 71.05; H, 4.48; N, 5.19; Cl, 13.01.

2-Acetyl-5-chloro-3-phenylindole Oxime (XI)——To a stirred suspension of X (40 g) and $NH_2OH \cdot HCl$ (103.0 g) in EtOH (200 ml) was added dropwise a solution of NaOH (166.4 g) in EtOH (800 ml), and the mixture was refluxed for 5 hr. The reaction mixture was poured into a mixture of conc. HCl (140 ml) and H_2O (560 ml) and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated. The oily residue (41.3 g) was crystallized from petroleum-ether to give 34.3 g (81.4%) of XI, mp 113—126°. Recrystallization from benzene–hexane (1:1) gave colorless prisms, mp 137—139°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3350, 3250, 1600. NMR ($CDCl_3$) δ: 1.90 (3H, s, CH_3), 6.73—6.92 (8H, m, aromatic H), 7.13 (1H, s, D_2O exchangeable, OH), 9.13 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd. for $C_{16}H_{13}ON_2Cl$: C, 67.49; H, 4.60; N, 9.84; Cl, 12.45. Found: C, 67.56; H, 4.40; N, 9.69; Cl, 12.38.

5) I. Fryer, R.A. Schmidt, and L.H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

2-(1-Aminoethyl)-5-chloro-3-phenylindole (XII)——A solution of XI (32 g) in dry ether (300 ml) was added dropwise to a suspension of $LiAlH_4$ (10.6 g) in dry ether (500 ml) below 10°. The mixture was heated under reflux for 9 hr. After cooling, H_2O (100 ml) was added cautiously, followed by conc. HCl (150 ml). The precipitate was collected by filtration and washed succesively with ether, 5% HCl and H_2O to give 19.0 g (55.2%) of the hydrochloride of XII, mp 171.5—175° (decomp.). The hydrochloride (0.3 g) was suspended in CH_2Cl_2 and made basic with 28% NH_4OH. After stirring, the CH_2Cl_2 layer was separated and evaporated. The residue was recrystallized from isopropyl ether to give the free base of XII (0.18 g) as colorless prisms, mp 119.5—120.5°. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3140, 3000, 1600. NMR ($CDCl_3$) δ: 1.42 (3H, d, J=6 Hz, CH_3), 1.77 (2H, s, D_2O exchangeable, NH_2), 4.60 (1H, q, J=6 Hz, CH), 7.60—7.11 (8H, m, aromatic H), 9.20 (1H, s, D_2O exchangeable, indole NH). *Anal.* Calcd. for $C_{16}H_{15}N_2Cl$: C, 70.98; H, 5.58; N, 10.35; Cl, 13.09. Found: C, 70.86; H, 5.60; N, 10.55; Cl, 13.09.

7-Chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XIII)——A solution of chromium trioxide (2.9 g) in H_2O (3 ml) was added dropwise to a mixture of the hydrochloride of XII (0.5 g) in acetic acid (15 ml) with stirring. The mixture was stirred at room temperature for 24 hr. The reaction mixture was neutralized with 28% NH_4OH (15 ml) and extracted with benzene. After evaporation of the solvent, the residue was crystallized from petroleum ether to give 0.35 g (75.4%) of XIII, mp 199.5—201.5°. Recrystallization from EtOH gave colorless prisms, mp 222—223° (lit[6] mp 220—221°). IR ν_{max}^{Nujol} cm^{-1}: 3180, 3100, 3020, 1680. NMR ($CDCl_3$) δ 1.75 (3H, d, J=6.5 Hz, CH_3), 3.75 (1H, q, J=6.5 Hz, CH), 7.75—7.11 (8H, m, aromatic H), 10.01 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd. for $C_{16}H_{13}ON_2Cl$: C, 67.49; H, 4.60; N, 9.84; Cl, 12.45. Found: C, 67.17; H, 4.73; N, 9.99; Cl, 13.18.

Acknowledgement The authors wish to thank Mr. Isao Katsuki and Mr. Kazuo Mori for skillful technical assistance.

6) S.C. Bell, T.S. Sulkowski, C. Gochman, and S.J. Childress, *J. Org. Chem.* **27**, 562 (1962).

Chem. Pharm. Bull. 23(12)3282—3285(1975)

UDC 547.918.02.04 : 581.192

Studies on the Constituents of Himalayan Ginseng, *Panax pseudoginseng*. II.[1] The Structures of the Saponins (2)

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(Received April 15, 1975)

The chemical structures of saponin B (I) (=chikusetsusaponin IV), $C_{47}H_{74}O_{18}$, $[\alpha]_D^{18}$ −9.10° (pyridine) and saponin C (III) (=desarabinofuranosylchikusetsusaponin IV), $C_{42}H_{66}O_{14}$, $[\alpha]_D^{18}$ +15.8° (MeOH), which were isolated from *Panax pseudoginseng* subsp. *himalaicus* var. *angustifolius* (Araliaceae), were established on the basis of physical data and chemical investigations.

In our previous paper,[1] we reported the structural elucidation of saponin A(=chikusetsusaponin V[3]) and saponin D(=ginsenoside Rb_1[1,4]), which were isolated from the rhizoma of *Panax pseudoginseng* subsp. *himalaicus* var. *angustifolius*. The present paper deals with the structure determination of saponin B(I) and C(III).

Saponin B(I), $C_{47}H_{74}O_{18}\cdot 4H_2O$, $[\alpha]_D^{18}$ −9.10° (in pyridine) forms a white powder reprecipitated from methanol–ethyl acetate. The infrared (IR) spectrum of I shows the presence

1) Part I: N. Kondo, J. Shoji, and O. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **21**, 2705 (1973).
2) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
3) N. Kondo, Y. Marumoto, and J. Shoji, *Chem. Pharm. Bull.* (Tokyo), **19**, 1103 (1971).
4) S. Sanada, N. Kondo, J. Shoji, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **22**, 421 (1974).