Synthesis of Carbon-14 Labeled 1,4-Benzodiazepines. III. 2-Allyloxyamino-7-chloro-5-(2-chlorophenyl)-3H-1,4-benzodiazepine-2-^{14}C, 8-Chloro-1-dimethylamino-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-3a-^{14}C, and 8-Chloro-2,4-dihydro-2-methyl-6-phenyl-1H-s-triazolo[4,3-a][1,4]benzodiazepin-1-one-3a-^{14}

Richard S. P. Hsi and Tommy D. Johnson
Research Laboratories, The Upjohn Company,
Kalamazoo, Michigan 49001, U.S.A.
Received on November 12, 1975
Revised on April 19, 1976

SUMMARY

A group of radioactive 1,4-benzodiazepine derivatives have been synthesized from glycine-1-^{14}C. The subject compounds are labeled with carbon-14 in the 2-position of the 1,4-benzodiazepine ring system.

Key Words: Synthesis, Carbon-14, 1,4-Benzodiazepines, Glycine

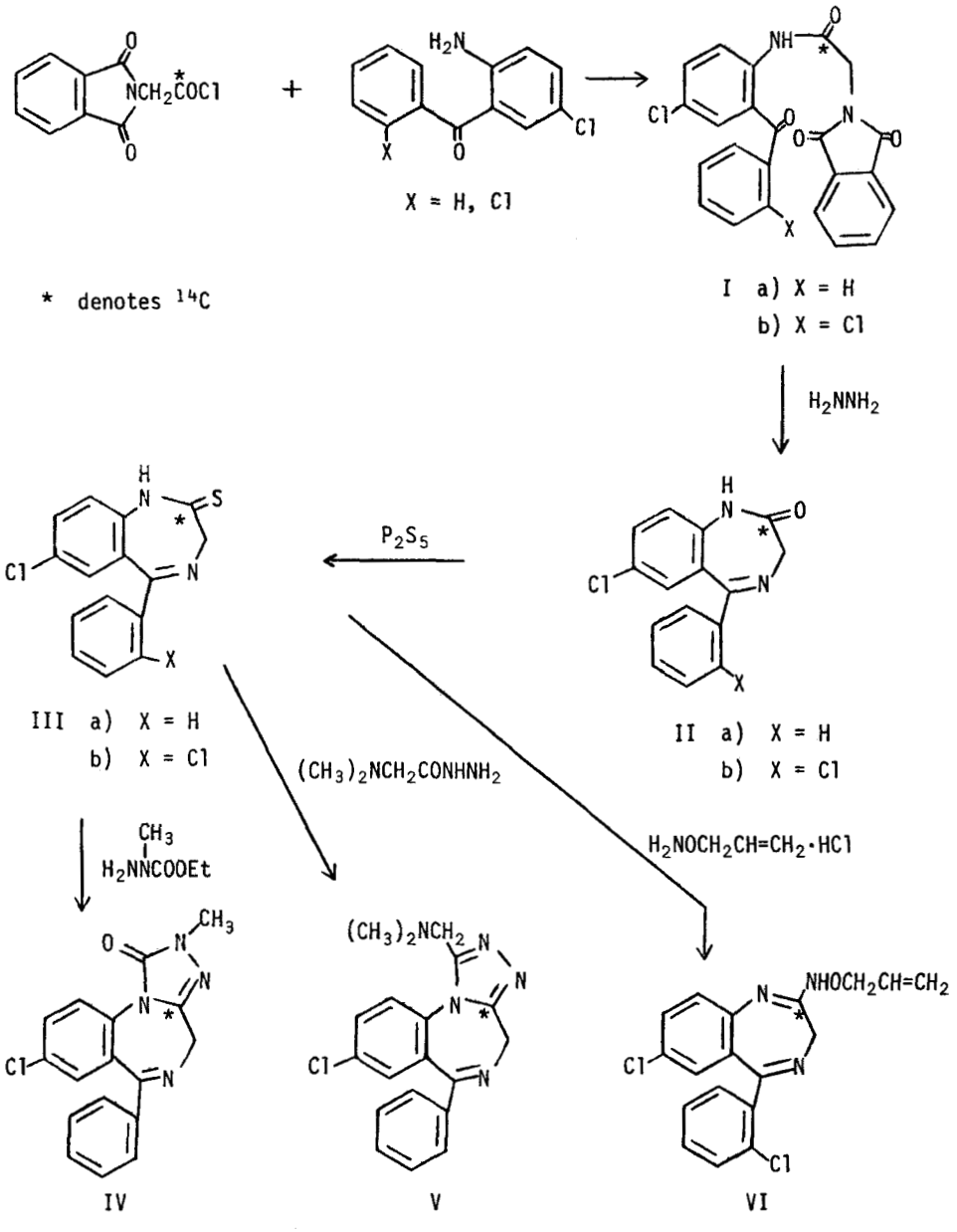
INTRODUCTION

We reported earlier (1) the synthesis of several carbon-14 labeled 1,4-benzodiazepine derivatives. This report describes the preparation of three more carbon-14 labeled compounds selected from a large group of substituted 1,4-benzodiazepines which exhibit interesting biological effects on the central nervous system. Radioactive forms of these three compounds, 8-chloro-2,4-dihydro-2-methyl-6-phenyl-1H-s-triazolo[4,3-a][1,4]benzodiazepin-1-one (IV), 8-chloro-1-dimethylaminomethyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (V), and 2-allyloxyamino-7-chloro-5-(2-chlorophenyl)-3H-1,4-benzodiazepine (VI), are needed for conducting absorption, distribution, metabolism, and excretion studies in animals and man.

Compounds IV, V, and VI can all be prepared from appropriately substituted carbon-14 labeled 1,4-benzodiazepin-2-ones II. We previously reported(1b) the synthesis, from glycine-1-^{14}C, of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-2-^{14}C (IIa), the intermediate for IV and V. 7-Chloro-1,3-dihydro-5-(2-

SCHEME 1

Synthesis of 1,4-Benzodiazepines-2-^{14}C



chlorophenyl)-2H-1,4-benzodiazepin-2-one-2-^{14}C (IIb), the intermediate for VI, was prepared in a similar manner. Acylation of 2-amino-5, 2'-dichlorobenzophenone with phthalimidoacetyl chloride-1-^{14}C gave 5,2'-dichloro-2-(2-phthalimido--acet-1-^{14}C-amido)benzophenone (Ib). Removal of the protecting phthalimide group

in Ib followed by thermal cyclization produced IIb. The conversion of the benzodiazepinones IIa and IIb to the corresponding thiones IIIa and IIIb was carried out according to a modification of known procedures(2,3), as shown in Scheme 1.

The preparation of s-triazolo[4,3-a][1,4]-benzodiazepines from the thiones III was reported by Hester *et al.*(3,4). Condensation of IIIa with ethyl 2-methylcarbazate occurred at 140°-150°C, and the resulting intermediate 2-methyl-3-(7-chloro-5-phenyl-3H-1,4-benzodiazepin-2-yl)carbazic acid ethyl ester could be cyclized thermally at 170°-180°C to give IV. However best yields of IV were obtained by carrying out the condensation-cyclization in a large excess of ethyl 2-methylcarbazate as solvent at 200°C. The synthesis of V from IIIa and dimethylaminoacethydrazide, on the other hand, was best carried out in refluxing n-butanol. Treatment of IIIb with allyloxyamine hydrochloride according to a modified literature procedure(5) afforded compound VI.

EXPERIMENTAL

Radioactivity determinations were carried out with a Packard Tri-Carb Model 2425 liquid scintillation spectrometer using Diotol scintillation(6) solvent and the external standard method. Thin layer chromatographic (tlc) analyses were done on 2.5 x 10 cm glass plates coated with a 250 μm thick layer of silica gel GF (Analtech). Developed zones were visualized under uv (254 nm) light illumination. Radioactive zones in developed plates were detected with a Vanguard Model 880 Autoscanner equipped with Model 885 Glass Plate Scanner. Uv spectra were obtained with a Cary Model 15 spectrometer. Melting points were determined in capillary tubes and were uncorrected. Microanalyses were obtained for the listed elements and all results were within ±0.4% of theory.

Preparation of Ia and Ib

Phthaloylglycine-1-^{14}C was prepared as described previously(1b). From 269 mg of glycine-1-^{14}C (nominally 27.8 mCi/mM)(7), 113 mg of non-labeled glycine (5.08 mmoles total), and 1.169 g (5.33 mmoles) of N-carbethoxy-phthalimide(8), there was obtained 840 mg (4.09 mmoles, 80.6% yield) of phthaloylglycine-1-^{14}C. A mixture of this material and 10 ml of $SOCl_2$ was refluxed under N_2 with stirring for 2 hrs. To the solution was added 10 ml of dry $PhCH_3$ and the mixture was distilled with intermittent addition of more $PhCH_3$ until bp of distillate reached

109°C. The remaining solution was cooled to ambient temperature and 952 mg (4.11 mmoles) of 2-amino-5-chloro-benzophenone was added. The mixture was stirred for 18 hrs. and the resulting precipitates were filtered, washed with 10 ml each of 1:1 $PhCH_3$-hexane and hexane, and dried to give 1.535 g (89.6% yield) of Ia, sp act 45.8 μCi/mg or 19.2 mCi/mM; radiochromatographically homogeneous by tlc (2% v/v MeOH in CH_2Cl_2).

Another sample of phthaloylglycine-1-^{14}C, obtained from 339 mg of glycine-1-^{14}C (nominally 20.0 mCi/mM)(7), 412 mg of glycine (10.0 mmoles total), and 2.411 g (11.0 mmoles) of N-carbethoxyphthalimide, was similarly converted to the acid chloride and the latter used to acylate 2-amino-5,2'-dichlorobenzophenone and give Ib in 97.5% yield, radiochromatographically homogeneous by tlc (CH_2Cl_2).

Preparation of IIa and IIb

A modification of the previously described procedure(1b) was used to obtain IIa in better yields. A solution of 1.535 g (3.66 mmoles) of Ia in 22 ml (4.62 mmoles) of 0.210 M solution of $H_2NNH_2 \cdot H_2O$ in abs EtOH was refluxed with stirring under N_2 for 18 hrs. The mixture was concentrated and the residue was chromatographed on a column of 80 g of silica gel (70-230 mesh) eluted with 1 l. of 2% v/v MeOH in CH_2Cl_2. The eluate was collected in 15 ml fractions. The pooled residues from fractions 27 through 43 were recrystallized from Me_2CO-hexane to give 795 mg (80.2% yield) of IIa, mp 213-124.5°C; sp act 71.1 μCi/mg or 19.3 mCi/mM; radiochromatographically homogeneous by tlc (5% v/v MeOH in CH_2Cl_2).

Similarly, from 1.247 g (2.75 mmoles) of Ib and 13.8 ml (2.90 mmoles) of 0.207 M solution of $H_2NNH_2 \cdot H_2O$ in abs EtOH, there was obtained, after chromatography on a 175 g column of silica gel eluted with 5% v/v MeOH in CH_2Cl_2, 681 mg (81.2% yield) of IIb, mp 200-202°C; sp act 30.8 μCi/mg or 9.38 mCi/mM; radiochromatographically homogeneous by tlc (5% v/v MeOH in CH_2Cl_2).

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-thione-2-^{14}C (IIIa)

A suspension of 703 mg (3.15 mmoles) of P_2S_5 and 17 ml of pyridine was stirred under N_2 at 86-90°C for 45 min and a solution of 774 mg (2.86 mmoles) of IIa in 7.5 ml of pyridine was added. The mixture was refluxed with stirring under N_2 for 70 min, cooled to RT and treated with stirring with 30 ml of H_2O in portions to give precipitates which were filtered, washed with H_2O and dried,

595 mg of IIIa (72.5% yield), mp 238-9°C (dec); sp act 67.6 μCi/mg or 19.4 mCi/mM; radiochromatographically homogeneous by tlc (5% v/v MeOH in CH_2Cl_2).

7-Chloro-1,3-dihydro-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-thione-2-^{14}C (IIIb)

A mixture of 641 mg (2.10 mmoles) of IIb, 515 mg (2.31 mmoles) of P_2S_5 and 15 ml of pyridine was gently refluxed (oil bath at 120°C) with stirring under N_2 for 25 min. The dark red solution was concentrated at 40°C and 1 mm Hg pressure to give a glass-like residue which was triturated with 75 ml of boiling CH_2Cl_2. The solution was decanted from the insoluble reddish brown syrup, treated with activated charcoal (Darco G-60) and filtered. The filtrate was concentrated and the residue was chromatographed on a 2 x 60 cm column of 180 g of silica gel eluted with 5% v/v Me_2CO in CH_2Cl_2. The crude product obtained was recrystallized from a mixture of 7 ml each of Me_2CO and H_2O to give 531 mg (78.5% yield) of IIIb, mp 242-4°C (dec); sp act 29.65 μCi/mg or 9.52 mCi/mM; radiochemically pure by tlc (5% v/v MeOH in CH_2Cl_2).

Compound IV

A mixture of 302 mg (1.05 mmoles) of IIIa and 1.073 g (9.08 mmoles) of ethyl 2-methylcarbazate(9) was stirred under N_2 at 200°C for 85 min. The excess carbazate was removed at RT and 20 μm Hg. The residue was chromatographed on a column of 80 g of silica gel (70-230 mesh) eluted with 1.5 l. of 15% v/v Me_2CO in hexane. The eluate was collected in 15 ml fractions and the pooled residues from fractions 52 through 86 were recrystallized from a PhH-hexane mixture with slow cooling to give 242 mg (71% yield) of IV, mp 144-144.5°C; sp act 60.0 μCi/mg or 19.5 mCi/mM; radiochemically pure by tlc (10% v/v Me_2CO in CH_2Cl_2); λ_{max}^{EtOH} 215 nm (ε 38,950), λ_{sh}^{ETOH} 245 nm (ε 17,400), 300 (1,900); *anal.* ($C_{17}H_{13}ClN_4O$):C,H,N.

Compound V

A mixture of 294 mg (1.02 mmoles) of IIIa, 153 mg (1.30 mmoles) of dimethylaminoacetic acid hydrazide(10), and 3 ml of n-BuOH was refluxed with stirring under N_2 for 6 hrs. The solvent and excess hydrazide were removed at RT and 20 μm Hg. The residue was chromatographed on a column of 80 g of silica gel (70-230 mesh) eluted with 1.2 *l.* of 3% v/v MeOH in CH_2Cl_2. The eluate was collected in 15 ml fractions. The pooled residues from fractions 33 through 54 were recry-

stallized from a PhH-hexane mixture to give 230 mg (64.0% yield) of V, mp 168-9°C; sp act 55.5 μCi/mg or 19.5 mCi/mM; radiochemically pure by tlc (5% v/v MeOH in CH_2Cl_2); λ_{max}^{EtOH} 221 nm (ε 39,550), λ_{sh}^{EtOH} 245 nm (ε 16,400), 265 (6,750), 290 (3,050); *anal.* ($C_{19}H_{18}ClN_5$):C,H,N.

Compound VI

A mixture of 482 mg (1.50 mmole) of IIIb, 358 mg (3.30 mmoles) of allyloxyamine hydrochloride(11), 277 mg (3.30 mmoles) of $NaHCO_3$ and 15 ml of abs EtOH was refluxed with stirring for 16 hrs. The mixture was filtered and the inorganic salts were washed with 10 ml of EtOH. The combined filtrate and washing were concentrated and the residual green syrup was chromatographed on a 3 x 50 cm column of 150 g of silica gel eluted with 5% v/v Me_2CO and 7.5 ml of H_2O to give 458 mg (84.7% yield) of VI, mp 129-131°C; 26.45 μCi/mg or 9.52 mCi/mM, radiochemically pure by tlc (5% v/v Me_2CO in CH_2Cl_2); λ_{max}^{EtOH} 234 nm (ε 27,000), 349 (2,050), λ_{sh}^{EtOH} 209 nm (38,500), 275 (10,550); *anal.* ($C_{18}H_{15}Cl_2N_3O$):C,H,Cl,N.

ACKNOWLEDGEMENT

We gratefully acknowledge microanalyses by R. C. Anderson and A. W. Kuilema, and uv spectra by B. F. Zimmer and B. L. Story.

REFERENCES

1. a) Paper I: Hsi, R. S. P. - *J. Labelled Compds.* 9:435 (1973); b) Paper II: Hsi, R. S. P. - *J. Labelled Compds.* 10:389 (1974).
2. Archer, G. H. and Sternbach, L. H. - *J. Org. Chem.* 29:231 (1964).
3. Hester, J. B., Rudzik, A. D. and Kamdar, B. V. - *J. Med. Chem.* 14:1078 (1971).
4. Hester, J. B., Duchamp, D. J. and Chidester, C. G. - *Tetrahedron Lett.* 1609 (1971).
5. Hester, J. B. and Rudzik, A. D. - *J. Med. Chem.* 17:293 (1974).
6. Herberg, R. J. - *Anal. Chem.* 32:42 (1960).
7. Glycine-1-^{14}C supplied by New England Nuclear Corp., Boston, Ma.
8. Nefkens, G. H. L. - *Nature* 4709:309 (1960).

9. a) Pedersen, C. T. - *Acta Chem. Scand.* 18:2199 (1964); b) Wadsworth, W. S. - *J. Org. Chem.* 34:2994 (1969).

10. a) Pesson, M. and Dupin, S. - *Bull. Soc. Chim. France* 1962:250; b) Viscontini, M. and Meier, J. - *Helv. Chim. Acta* 33:1773 (1950).

11. Cope, A. C. and Towle, P. H. - *J. Am. Chem. Soc.* 71:3427 (1949).