The Synthesis of 4-(*o*-Fluorophenyl)-6,8-dihydro-3,8-dimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)one, A Metabolite of Zolazepam

Horace A. DeWald

Chemistry Department, Research and Development Division,
Parke, Davis and Company, Ann Arbor, Michigan 48106

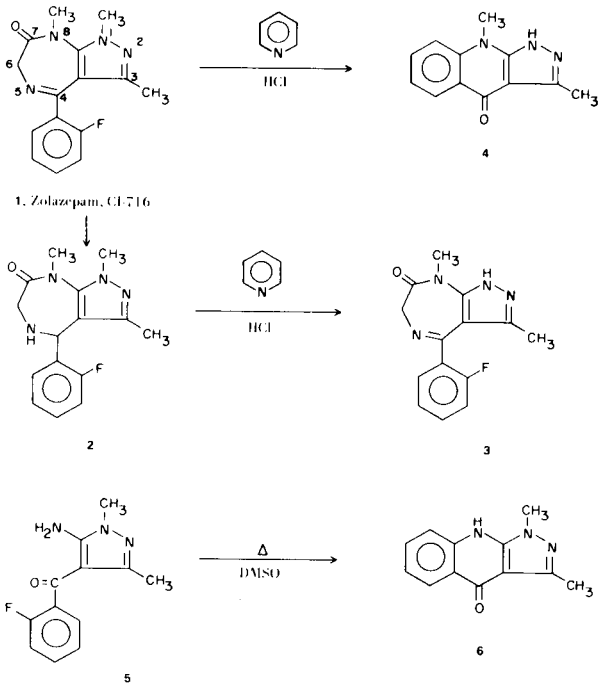
Received April 22, 1974

A metabolite of Zolazepam was prepared by a selective *N*-demethylation of a dihydro derivative of Zolazepam using pyridine hydrochloride.

The metabolism of 4-(*o*-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)one **1** (Zolazepam, CI-716) (1) has been studied in laboratory animals, and the major urinary metabolites were identified using combined gas chromatography-mass spectrometry (2). One of the observed metabolites was 4-(*o*-fluorophenyl)-6,8-dihydro-3,8-dimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)one **3**. This metabolite, which is 1-demethyl-**1**, represents a sex-related difference in rat metabolism, appearing in the urine of female rats only. It was prepared by selective *N*-dealkylation of a dihydro derivative of **1** using pyridine hydrochloride. This procedure was based on an earlier observation by Butler (3) who found that the reaction of 5-chloro-1,3-dimethylpyrazol-4-yl *o*-methoxyphenyl ketone with pyridine hydrochloride resulted in cleavage of the *N*-methyl group.

The desired metabolite **3** was not obtained directly from the reaction of **1** in refluxing pyridine hydrochloride (Scheme I). Although *N*-demethylation resulted, the reaction conditions employed were too vigorous for a pyrazolodiazepinone; the product which was obtained in good yield was the tricyclic system 1,9-dihydro-3,9-dimethyl-4*H*-pyrazolo[3,4-*b*]quinolin-4-one **4**, presumably as a result of cleavage of the diazepinone to an intermediate aminoketone which cyclized to **4**. This product **4** was shown to be different from its isomer 1,9-dihydro-1,3-dimethyl-4*H*-pyrazolo[3,4-*b*]quinolin-4-one **6**, which was synthesized by cyclization of the aminoketone 5-amino-1,3-dimethylpyrazol-4-yl-*o*-fluorophenyl ketone **5** (4) in dimethyl sulfoxide. This reaction indicated, however, that dealkylation of this pyrazolodiazepinone with pyridine hydrochloride was selective for the 1-methyl substituent. When the diazepinone system was stabilized by hydrogenation of the imine to **2**, the reaction of **2** with pyridine hydrochloride again was selective for the dealkylation of the 1-methyl substituent. Fortuitously, the benzylamine system was reoxidized to the imine by the reaction conditions, and moderate (25%) yields of

SCHEME I



the metabolite **3** were obtained directly from the reaction mixture.

The metabolite **3** exhibited tranquilizing activity as measured by milk consumption and antimetrazole screens (5), but of a lesser degree than the parent compound **1**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Ir spectra were determined in potassium bromide pellets.

Reaction of **1** with Pyridine Hydrochloride, 1,9-Dihydro-3,9-dimethyl-4*H*-pyrazolo[3,4-*b*]quinolin-4-one **4**.

A mixture of 85 g. (1 mole) of pyridine and 100 ml. of concentrated hydrochloric acid was distilled to a pot temperature

of 220°. To this solution of pyridine hydrochloride was added 10 g. (0.035 mole) of **1** and the mixture was stirred under reflux (210-215°) for 50 minutes. After cooling to 140°, the mixture was poured into 600 ml. of water. The resulting solution deposited 6.5 g. (74%) of a pale yellow solid **4**, m.p. 235°; mass spectrum m/e 212; ir 1620 cm^{-1} (C=O); nmr (d-DMSO) δ TMS 2.65 (s, 3H, C-CH_3), 3.75 (s, 3H, N-CH_3), 4.8-6.0 (broad 5H, $2H_2O$ + NH); 7.0-8.4 (m, 4H, aromatic).

Anal. Calcd. for $C_{12}H_{11}N_3O \cdot 2H_2O$: C, 57.83; H, 6.06; N, 16.85; H_2O, 14.4. Found: C, 57.74; H, 5.92; N, 16.63; H_2O, 14.0.

4-(*o*-Fluorophenyl)-4,5,6,8-tetrahydro-1,3,8-trimethylpyrazolo-[3,4-*e*][1,4]diazepin-7(1*H*)one **2**.

A solution of 99.5 g. (0.35 mole) of 4-(*o*-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)one **1** in one liter of methanol was hydrogenated in the presence of 2 g. of 10% Pt/C at an original hydrogen pressure of 50 psi. The hydrogenation was stopped when the calculated volume of hydrogen was consumed. The filtered solution was evaporated *in vacuo* to yield 100 g. of colorless oil **2**; mass spectrum m/e 288. A 7 g. sample of **2** was dissolved in 25 ml. of 2-propanol, treated with 5 ml. of 20% 2-propanolic hydrochloric acid and diluted with ethyl acetate to yield 7.5 g. of colorless solid as the hydrochloride salt of **2**, m.p. 218-220°; ir 1686 cm^{-1} (C=O); nmr (d-DMSO): δ TMS 1.8 (s, 3H, C-CH_3), 3.2 (s, 3H, N-CH_3), 3.72 (m, 5H, N-CH_3 and N-CH_2), 5.8 (s, 1H, benzylic CH), 7.0-7.7 (m, 4H aromatic), 12 (very broad, 1H).

Anal. Calcd. for $C_{15}H_{17}FN_4O \cdot HCl$: C, 55.51; H, 5.58; N, 17.25. Found: C, 55.76; H, 5.73; N, 17.12.

4-(*o*-Fluorophenyl)-6,8-dihydro-3,8-dimethylpyrazolo[3,4-*e*][1,4]-diazepin-7(1*H*)one, **3**.

Compound **2** (20 g., 0.07 mole) was added to pyridine hydrochloride which had been prepared by distilling a mixture of 175 g. of pyridine and 200 ml. of concentrated hydrochloric acid to a pot temperature of 225°. The mixture was stirred and heated at 220-228° with slow distillation for thirty minutes. After allowing the mixture to cool to *ca.* 160°, it was poured into 1.2 l. of cold water and the mixture was made basic with concentrated ammonium hydroxide and dichloromethane (800 ml.) was added. The organic layer was separated and evaporated to dryness *in vacuo*. The dark residue (14 g.) was pratitioned in 350 ml. of 3*N* hydrochloric acid and 150 ml. of ethyl acetate. The aqueous solution was separated, made basic with concentrated ammonium hydroxide and extracted with dichloromethane. The organic extracts were dried (magnesium sulfate), treated with Darco G-60 and evaporated *in vacuo*. The semi-solid residue was crystallized from 15 ml. of acetonitrile to yield 4.3 g. (23%) of **3** as a cream colored solid, m.p. 229-231°; mass spectrum m/e 272; ir 1682 cm^{-1} (C=O); nmr (d-DMSO): δ TMS 1.7 (s, 3H, C-CH_3), 3.28 (s, 3H, N-CH_3), 4.2 (s, 2H, N-CH_2-C=O), 7.0-7.6 (m, 4H, aromatic), 14 (broad, 1H, NH); identical to observed metabolite by GC-mass spec (2).

Anal. Calcd. for $C_{14}H_{13}FN_4O$: C, 61.76; H, 4.81; N, 20.57. Found: C, 61.82; H, 4.96; N, 20.70.

A small, second crop of **3** (2-3%) was obtained by retreating the combined residues of several runs with pyridine hydrochloride. In several runs, the crude demethylation product (14 g. of oil) was dissolved in 25 ml. of glacial acetic acid and treated with Jones reagent (4 ml.) at 25° for twenty minutes, but no improvement in yield of **3** was realized.

1,9-Dihydro-1,3-dimethyl-4*H*-pyrazolo[3,4-*b*]quinolin-4-one, **6**.

A solution of 4.8 g. (0.02 mole) of 5-amino-1,3-dimethylpyrazol-4-yl *o*-fluorophenyl ketone **5** (4) in 25 ml. of dimethyl sulfoxide was stirred at 150-160° for four hours and poured into 300 ml. of water. A cream colored solid separated upon cooling. The product **6** was collected by filtering and weighed 3.0 g. (70%), m.p. 335° dec.; ir 1646 cm^{-1} (C=O); nmr (d-DMSO): δ TMS 2.5 (s, 3H, C-CH_3), 3.8 (s, 3H, N-CH_3), 4.2-5.8 (very broad, 4H, H_2O), 7.0-8.4 (m, 4H, aromatic).

Anal. Calcd. for $C_{12}H_{11}N_3O \cdot 2H_2O$: C, 57.83; H, 6.06; N, 16.85. Found: C, 57.74; H, 6.05; N, 16.99.

Acknowledgment.

The author is grateful to Mr. W. Pearlman for the catalytic hydrogenation reactions, to Mr. C. Childs and co-workers for the microanalyses, and to Dr. J. Vandenbelt and staff for the determination of the spectral data.

REFERENCES

(1) H. A. DeWald and D. E. Butler, U. S. Patent 3,558,605 (1971).

(2) J. Baukema, R. A. Okerholm, and A. J. Glazko, *The Pharmacologist*, 15, 228 (1973). These authors used the name flupyrazopon to describe CI-716, however the USAN approved name is Zolazepam.

(3) D. Butler, private communication.

(4) H. A. DeWald and D. E. Butler, U. S. Patent 3,660,425 (1972).

(5) H. A. DeWald, I. C. Nordin, Y. J. L'Italien, and R. F. Parcell, *J. Med. Chem.*, **16**, 1346 (1973).