New Synthesis of 7-Bromo-1,3-dihydro-3-hydroxy-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one

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Received May 9, 1980

A new synthesis of 7-bromo-1,3-dihydro-3-hydroxy-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one (**5**) is described. Starting from bromazepam (**3**), C(3) acylation with lead tetraacetate/potassium iodide in acetic acid affords **4**, while its mild hydrolysis according to our recently described method (5) gives **5**. Improved hexamine cyclization of **1** into **3**, *via* quaternary hexaminium salt **2**, is discussed, and identification of the intermediates **7** and **8** is performed. Compound **5** undergoes on melting, or on brief heating in glacial acetic acid, the thermal rearrangement into quinazolin-2-aldehyde (**13**), the structure of which is confirmed by oxidation into the ester **14**, which in turn was hydrolyzed to the acid **15**. The same compound (**5**) rearranges on heating with manganese(III) acetate in acetic acid into the 3-amino-2-quinolone derivative **6**. On heating in glacial acetic acid in the presence of lead tetraacetate/potassium iodide (or iodine), compound **4**, in addition to giving the aldehyde **13**, ester **14** and acid **15** rearrangement products, affords 1,2-dihydroquinazolin-2-carboxylic acid **16**.

J. Heterocyclic Chem., **18**, 59 (1981).

Introduction.

Since our discovery of hexamine as a reagent of choice for the ring closure of 1,4-benzodiazepin-2-ones (1,2), it has been used for the cyclization of numerous 2-oxy, and 2-deoxy 1,4-benzodiazepines, as well as for the cyclization of other heterocycles (3). The method has subsequently been desclosed in the patent literature (4) for the cyclization of 2-(2′-bromoacetamido-5′-bromobenzoyl)pyridine (**1**) into 7-bromo-1,3-dihydro-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one (**3**, generic name bromazepam).

Herewith, we would like to report on our own findings pertinent to the ring closure of **3** with hexamine, as well as on the application of our *C*(3)-hydroxylation method (5) in the preparation of the *C*(3)-substituted derivatives **4** and **5**. A multistep preparation of **3**, based on separation of the *syn*-isomer of *ortho*-haloacetamidobenzophenone oximes, and the subsequent cyclization *via* 4,1,5-benzodiazocin-2-ones, is the only approach as yet described (9,10). It is important to note that existing general syntheses of *C*(3)-hydroxy-1,4-benzodiazepin-2-ones would require either intermediacy of the *N*(4)-oxide of **3** (6,7), or the formation of its *C*(3)-carbanion with strong bases in aprotic solvents (8). These procedures are not applicable for compound **3**, however, since the first one cannot be performed without concomitant *N*-oxidation of the pyridine nitrogen, while the second one is applicable only on *N*(1) alkylated derivatives of 1,4-benzodiazepin-2-ones, since *N*(1)-H compounds like **3** undergo decomposition readily.

Results and Discussion.

When 2-(2′-bromoacetamido-5′-bromobenzoyl)pyridine (**1**) was reacted with a 20% molar excess of hexamine in acetonitrile, nearly quantitative precipitation of crystalline quaternary salt **2** occured (Scheme 1). On heating in ethanol, the pure product **3** was obtained from **2** in 80-90% yield. Lower yields and less pure products were obtained when the cyclization was performed according to the desclosed procedure (4), *i.e.*, using a 200-250% molar excess of hexamine without isolation of the intermediary **2**. Our method avoids formation of quinolone **6**, as well as of the mono- and bis-imidazolidinone derivatives **7** and **8**, respectively; congeners of those have already been described for desmethyldiazepam (**9**) (2). Compounds **7** and **8** could only be identified on tlc as a trace impurities. The structure of compound **6** has been confirmed by its independent preparation from **3** *via* manganese(III) acetate induced rearrangement. On dissolution of **2** in water, and stirring at ambient temperature for 48 hours, the mono-imidazolidinone derivative **7** precipitated nearly quantitatively. It afforded **8** on brief heating with formaldehyde in aqueous solution; however, the best yields of pure **8** were obtained when started from hexaminium salt **2**. The mechanism of the formation of the related compounds during analogous synthesis of desmethyldiazepam **9** has already been discussed (2).

The 3-hydroxy derivative **5** has been obtained from **3** in 80% overall yield, whereby purification of the intermediate **4** could be avoided. The 3-acetoxy compound, however, could be isolated by crystallization from DMF-water (1:2) in 90% yield. Compound **5** underwent an interesting thermal rearrangement; on heating above

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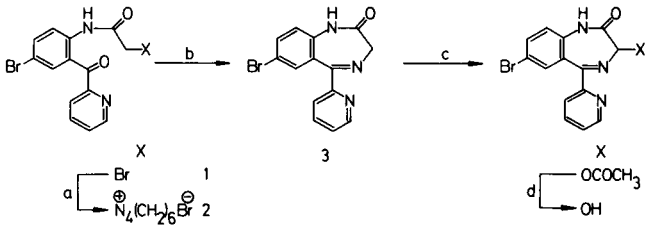
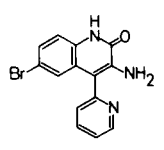
SCHEME I



a. $N_4(CH_2)_6/CH_3CN$, b. EtOH/Δ, c. Pb(IV)Ac/AcOH/KI, d. MeONa/MeOH/CH_2Cl_2

200° it melted, then solidified again. Crystallization from toluene afforded the aldehyde **13**. Among other characteristics, this compound exhibited a carbonyl frequence at 1720 cm^{-1} in the ir, and a singlet at 10.4 ppm for the C*H*O proton in the nmr. The same compound is formed on 10 minute heating under reflux in glacial acetic acid, or during 1 hour heating at 80°. On oxidation with lead tetraacetate in chloroform-acetic acid in the presence of ethanol it afforded ester **14**. It was hydrolized into the quinazoline-2-carboxylic acid **15**. Heating of **4** in glacial acetic acid afforded the compounds **13-15**, while on addition of potassium iodide/lead tetraacetate to the same solvent, and brief stirring at elevated temperatures, **4** rearranges into 1,2-dihydroquinazoline carboxylic acid **16**. Similar acid catalysed rearrangements have been described for **9** (11), as well as for the 3-methoxy derivatives of **9** and **10** (12,13).

Compound **5** has already been identified as the main *in vivo* metabolite of bromazepam (14,15). Thus, it stays in the same relation to bromazepam as the 3-hydroxy derivatives oxazepam (**11**) and temazepam (**12**) to their 3-deoxy congeners desmethyl diazepam (**9**) and diazepam (**10**), respectively.



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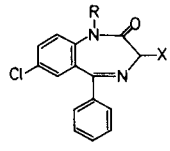
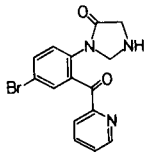


	R	X
9	H	H
10	CH_3	H
11	H	OH
12	CH_3	OH



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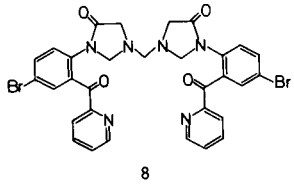

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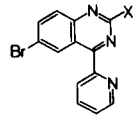
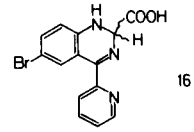


	X
13	CHO
14	$COOC_2H_5$
15	COOH



16

While the last two pairs of benzodiazepine derivatives are well known tranquilizers and anxiolyties in the clinical use (16), it was reported (17) that **5** possessed almost the same intrinsic activity as bromazepam **3**, however its uptake into the brain seemed to be less efficient. We have found that the more lipophylic 3-acetoxy compound **4** posses highly promising biological properties in the standard pharmacological tests (18). This is in accordance with the recent results of Maksay, *et al.* (19,20), who found that 3-acyloxy benzodiazepines pass the blood-brain barrier much easier then their 3-hydroxy congeners, and subsequently undergo rather fast enzymatic hydrolysis in the brain into the corresponding 3-hydroxy compounds, as well as with our finding which show that the 3-trichloroacetyl derivatives of **11** and **12** produced marked CNS activity, higher than the parent compounds (21).

Intensive *in vitro* and *in vivo* investigations of the 3-acetoxy derivative **4** are in progress.

EXPERIMENTAL

Melting points were determined on a Mettler FP 5, and are not corrected. Infrared spectra were obtained on a Perkin-Elmer M 297 spectrometer, and are for potassium bromide discs. Nmr spectra were run on a Perkin-Elmer R 12 instrument using TMS as internal standard. All reactions were monitored using tlc alumina plates precoated with Merck's silica gel 60F 254. Column chromatographic purifications were carried out with silica gel (0.05-0.2 mm) from Merck. Organic extracts were regularly dried over sodium sulfate and evaporated *in vacuo*.

2-(2′-Bromoacetylamino-5′-bromobenzoyl)pyridine (**1**) is described in the patent literature (22). We have found, however, that a simplified preparation in a two-phase system of toluene-water at 25° during 1 hour yielded over 90% of **1**, which can be used without further purification for preparation of **2**.

2-(2′-Hexaminiumacetyl)amino-5′-bromobenzoylpyridine Bromide (**2**).

2-(2′-Bromoacetylamino-5′-bromobenzoyl)pyridine **1**, (3.52 g., 10.0 mmoles) was dissolved in acetonitrile (200 ml.) and then hexamine (1.68 g., 12.0 mmoles) was added. Soon after from the clear solution precipitation began, while stirring was continued at room temperature for 4 hours. Then the precipitate was filtered, washed with acetonitrile (2 x 10 ml.), and dried *in vacuo*, affording 5.11 g. (95%) of pure **2**, m.p. 183-184° dec.; ir: 3400, 1673, 1570, 1525, 1480, 1310, 1285, 1270, 1250, 1235, 1000 cm^{-1}; nmr (DMSO-d_6): 3.73 (s, 2H), 4.62 (s, 6H), 5.30 (s, 6H), 7.5-8.8 (m, 7H), 11.0 (s, 1H).

Anal. Calcd. for $C_{20}H_{22}Br_2N_6O_2$ (538.26): C, 44.62; H, 4.11; N, 15.61. Found: C, 44.76; H, 4.10; N, 14.78.

7-Bromo-1,3-dihydro-3-acetoxy-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one (**4**).

Compound **3** (31.62 g., 0.10 mole) was dissolved in glacial acetic acid (400 ml.) and then immersed in an oil bath preheated at 60°; potassium iodide (24.9 g., 0.15 mole) was next added under vigorous stirring. After 15-20 minutes, lead tetraacetate (66.50 g., 0.15 mole stabilized with 12.5% acetic acid) was added at once, and stirring was continued for an additional 1 hour. The reaction mixture was then cooled to room temperature and methylene chloride (150 ml.) was added. After 15 minutes of stirring the inorganic precipitate was filtered, washed with methylene chloride, and the collected filtrate and washings were evaporated to dryness. The residue was slurried in chloroform (2000 ml.), followed by the addition of water (2000 ml.). Thereafter, sodium thiosulfate pentahydrate (10 g.), and the biphasic mixture was stirred for 3 hours at ambient temperature. On filtration, the aqueous layer was separated, and the organic phase was washed with water to *p*H 5. The organic extract was dried, evaporated, and crude **4** (35.1 g.) was triturated at 50° with 96% ethanol (200 ml.) affording pure product (33 g., 89.6%) with m.p. 232-233° dec. Recrystallization from DMF-water (1:2) afforded an analytically pure sample: ir: 3185, 3105, 3050, 2940, 1745, 1690, 1620, 1475, 1325, 1105, 1075, 810, 710, 625, 618 cm^{-1}; nmr (pyridine-d_5): 2.32 (s, 3H), 6.43 (s, 1H), 7.15-8.8 (m, 7H), 12.5 (broad s, 1H).

Anal. Calcd. for $C_{16}H_{12}BrN_3O_3$ (374.19): C, 51.35; H, 3.23; N, 11.23. Found: C, 51.45; H, 3.23; N, 11.24.

7-Bromo-1,3-dihydro-3-hydroxy-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one (**5**).

Compound **4** (32.0 g., 85.8 mmoles) was dissolved in a mixture of methylene chloride (1400 ml.) and methanol (260 ml.), and a solution of sodium methoxide (75.0 ml. 8.5% solution) was added dropwise. After 1 hour or stirring at room temperature, water (1500 ml.) was added and the *p*H was adjusted to 7 with 10% aqueous acetic acid. To the aqueous phase, sodium chloride (700 g.) was added and the mixture was stirred for 1 hour at ambient temperature. Following extraction with chloroform (2 x 350 ml.), the organic extracts were dried and evaporated. The crude product (26.4 g., 93%) was crystallized from DMF-water (1:3) affording 24.7 g. (87%) of pure **5**, m.p. 182-184°; ir: 3220, 3180, 1695, 1620, 1332, 1165, 1025, 830, 815, 750 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}BrN_3O_2$ (332.16): C, 50.62; H, 3.03; N, 12.65. Found: C, 50.36; H, 3.05; N, 12.47.

3-Amino-4-(2′-pyridyl)-6-bromoquinolin-2-one (**6**).

To the compound **3** (948 mg., 3.0 mmoles) dissolved in glacial acetic acid (12 ml.), manganese(III) acetate monohydrate (750 mg., 3.0 mmoles) was added, and the reaction mixture was stirred at 105° (bath temperature) for 6 hours. After evaporation to dryness, the residue was slurried in water (50 ml.), and extracted with methylene chloride (3 x 50 ml.). The organic extracts were washed with saturated aqueous bicarbonate, dried, evaporated, and the residue (1.04 g.) was purified on a 60 g. silica gel column. Using methylene chloride-acetone (3:1) as eluent, pure **6** (200 mg.) was isolated in fractions 76-95 (4 ml. pro fraction), on crystallization from diisopropyl ether it had m.p. 275-278° dec.; ir: 3460, 3340, 3160, 2980, 1660, 1570, 1468, 1385, 1190, 805, 670, 625 cm^{-1}; nmr (DMF-d_7): 5.75 (broad s, 2H), 7.3-8.95 (m, 7H), 12.1 (broad s, 1H).

Anal. Calcd. for $C_{14}H_{10}BrN_3O$ (316.16): C, 53.18; H, 3.18; N, 13.29. Found: C, 52.66; H, 3.22; N, 13.10.

3-(2′-Pyrido-2″-yl)-4′-bromophenyl-4-imidazolidinone (**7**).

The hexaminium salt **2** (5.0 g., 9.3 mmoles) was dissolved in water (300 ml.) at 25° and stirred for 48 hours. Slow precipitation of the product **7** took place. It was collected by filtration, thoroughly washed with water and dried affording 2.91 g. (90.6%) of the white powder, m.p. 138-141°; ir: 3300-3200, 1690 (broad), 1585, 1565, 1490, 1435, 1390, 1240, 1165, 990, 815, 750 cm^{-1}; nmr (deuteriochloroform): 3.10 (s, 2H), 4.60 (s, 2H), 7.1-8.8 (m, 7H).

Anal. Calcd. for $C_{15}H_{12}BrN_3O_2 \cdot 0.5H_2O$ (355.192): C, 50.72; H, 3.69; N, 11.83. Found: C, 50.03; H, 3.56; N, 12.44.

N,N′-Methylenebis-3-(2′-pyrido-2″-yl)-4′-bromo)phenyl-4-imidazolidinone (**8**).

The hexaminium salt **2** (8.77 g., 16.3 mmoles) was dissolved in water (560 ml.), to which 40 ml. of 40% aqueous formaldehyde was added, and heated at 50° (in the oil bath) for 48 hours. A white, crystalline precipitate was filtered off, washed with water and dried, affording 5.15 g. (90%) of the title compound **8**, m.p. 200-201° dec.; ir: 3420, 1715, 1675, 1583, 1480, 1435, 1400, 1300, 990, 955, 830, 795, 760, 680 cm^{-1}; nmr (DMF-d_7): 2.98 (s, 4H, 2 x CH_2), 3.08 (s, 2H, NCH_2), 4.70 (s, 2H, $COCH_2$), 7.4-8.8 (m, 14H).

Anal. Calcd. for $C_{31}H_{24}Br_2N_6O_4$ (704.38): C, 52.82; H, 3.43; N, 11.93. Found: C, 52.37; H, 3.33; N, 11.48.

7-Bromo-1,3-dihydro-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one (**3**).

Method A.

The hexaminium salt **2** (2.16 g., 4.0 mmoles), was dissolved in ethanol-water (4:1 v/v, 20 ml.), and stirred for 24 hours under reflux. Following evaporation of the solvent, the crystalline residue was slurried in water (40 ml.), stirred for 2 hours at ambient temperature, collected by filtration and dried. Thus, 1.05 g. (84.6%) of crude **3** was obtained, m.p. 233-234° dec. On recrystallization from ethanol-water, the m.p. rose to 246-247°.

Method B.

Compound **7**, prepared as the dihydrochloride from **8**, on brief dissolution in 30% methanolic hydrogen chloride, m.p. 155-160° (2.55 g., 6.08 mmoles), was dissolved in 15% ethanolic ammonia (15 ml.), and heated under reflux for 24 hours. Approximately one half of the solvent was evaporated, and water (25 ml.) was slowly added under stirring. On cooling, the product **3** precipitated, was collected by filtration, washed with water and dried yielding 1.51 g. (79%) of **3**, m.p. 241-242.

6-Bromo-4-(2′-pyridyl)quinazoline-2-carbaldehyde (**13**).

Method A.

Compound **5** (1.0 g.) was heated in an oil bath, preheated to 220-225° for 10 minutes. During this period, a clear fusion was formed. It was cooled and crystallized from toluene affording 0.78 g. (84%) of the aldehyde **13**, m.p. 214-216°; ir: 3110, 2875, 1720, 1600, 1580, 1550, 1530, 1480, 1380 cm^{-1}; nmr (deuteriochloroform): 7.5-9.7 (m, 7H), 10.4 (s, 1H).

Anal. Calcd. for $C_{14}H_8BrN_3O$ (314.10): C, 53.52; H, 2.57; N, 13.38. Found: C, 53.42; H, 2.55; N, 13.31.

Method B.

Compound **5** (332 mg., 1.0 mmole) was heated and stirred in 4 ml. of glacial acetic acid at 80° for 1 hour. After temporary dissolution, the product **13** began to crystallize. After cooling it was filtered and washed with toluene affording 235 mg. (70%) of the pure product.

6-Bromo-4-(2′-pyridyl)-2-carbethoxyquinazoline (**14**).

To the compound **13** (0.80 g.), dissolved in glacial acetic acid (8.0 ml.), chloroform (5.0 ml.), ethanol (0.5 ml.) and lead tetraacetate (2.9 g.) were added. The mixture was then stirred and heated at 100° for 4 hours. After evaporation of the solvent, the residue was applied on a 45 g. silica gel column eluted with methylene chloride-ethyl acetate (15:1). Thus, 0.64 g. of the product was obtained, which was crystallized from ethanol affording 0.50 g. (55%) of the pure ester **14**, m.p. 157-158°; ir: 3100, 3000, 1740, 1605, 1550, 1530, 1480, 1470, 1420, 1312, 1280, 1230 cm^{-1}; nmr (deuteriochloroform): 1.52 (t, 3H), 4.68 (q, 2H), 7.45-8.7 (m, 6H), 8.95 (d, 1H).

Anal. Calcd. for $C_{16}H_{12}BrN_3O_2$ (358.19): C, 53.65; H, 3.38; N, 11.73. Found: C, 53.41; H, 3.22; N, 11.80.

6-Bromo-4-(2′-pyridyl)quinazoline-2-carboxylic Acid (**15**).

The ester **14** (0.72 g., 2.0 mmoles) was hydrolyzed in a methanolic solution (15 ml.) of potassium hydroxide (0.5 g.). After 4 hours of stirring at ambient temperature, the *p*H was adjusted to neutral, the solvent was evaporated, and the residue was slurried in water. The undissolved crude product separated by filtration (0.43 g., 65%). On recrystallization from ethyl acetate, the pure acid **14** was obtained, m.p. 228-229.5°; ir: 3100, 3060, 1725, 1600, 1550, 1480, 1380, 1320, 1250, 890, 715 cm^{-1}; nmr (DMSO-d_6): 7.1-8.9 (m, 7H), 10.9 (broad s, 1H).

Anal. Calcd. for $C_{14}H_8BrN_3O_2$ (330.14): C, 50.93; H, 2.44; N, 12.73. Found: C, 50.95; H, 2.64; N, 12.46.

6-Bromo-4-(2′-pyridyl)-1,2-dihydroquinazoline-2-carboxylic Acid (**16**).

Compound **3** (3.16 g., 10.0 mmoles) was dissolved in glacial acetic acid (70 ml.) at 120° external temperature. To the resulting solution, potassium iodide (2.49 g., 15.0 mmoles) was added, and after 15 minutes of stirring, the heating bath was removed. Then lead tetraacetate (6.65 g., 15.0 mmoles, stabilized with 12.5% acetic acid) was added at once and heating at 120° was continued for another 2.5 hours. Chloroform (25 ml.) was added, and after brief stirring at ambient temperature the inorganic precipitate was filtered, washed with chloroform (25 ml.), and the combined filtrates were evaporated to dryness. The red-brown resin was dissolved in chloroform (200 ml.); water (250 ml.) was added and the mixture was vigorously stirred for 30 minutes. The organic layer was separated, dried and concentrated to 30 ml. Ether (30 ml.) was added, and the resulting slurry deposited for 30 minutes. Then, the precipitate was collected by filtration, washed with ether and dried affording the crude product (78%), which on trituration with hot dioxane, and subsequent recrystallization from methanol melted at 263-264° dec.; ir: 3270, 1690, 1660, 1590, 1475, 1428, 1190, 995, 825 cm^{-1}; nmr (DMSO-d_6): 5.82 (d, J = 8 Hz, 2H, on addition of deuterium oxide it collapses into s), 7.1-8.8 (m, 7H), 9.5 (broad d, J = 8 Hz, on addition of water it disappears), 10.8 (broad s, 1H).

Anal. Calcd. for $C_{14}H_{10}BrN_3O_2$ (332.16): C, 50.62; H, 3.03; N, 12.65. Found: C, 50.88; H, 3.08; N, 12.80.

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