Novel Heterocycles. I. Synthesis and Reactions of 6,7-Dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]-benzoxazine-1,3-dione

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6,7-Dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-1,3-dione (**1b**) was synthesized by a new route and its reactions with various nucleophiles are described.

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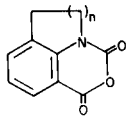
In the past decade, 2*H*-3,1-benzoxazine-2,4(1*H*)dione (isatoic anhydride) has proved to be a very versatile synthetic intermediate and its reactions with various nucleophiles are well documented in the literature (1,2,3).

The use of polycyclic anhydrides of type **1** in heterocyclic synthesis has not been described, therefore, this paper will describe the synthesis and chemistry of 6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-1,3-dione (**1b**).

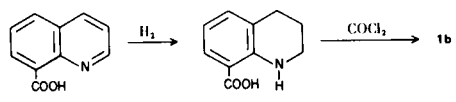


1 a) n = 1
b) n = 2

Since **1** is nothing more than an isatoic anhydride bridged from the heterocyclic ring to the benzene ring, treatment with various nucleophiles, as with the unbridged species, can lead to the formation of a variety of polycyclic heterocycles, almost all of which are new ring systems.

A search of the literature disclosed the synthesis of only one such anhydride, that of **1b**. Ziegler and Kappe (4) described its synthesis using a five step sequence starting from commercially available materials. The synthesis is fairly tedious and proceeds in an overall yield of only 25%. To provide large enough quantitites of **1b** for useful synthetic purposes this preparation was found to be inadequate and an alternate synthesis was devised (Scheme I).

Scheme I

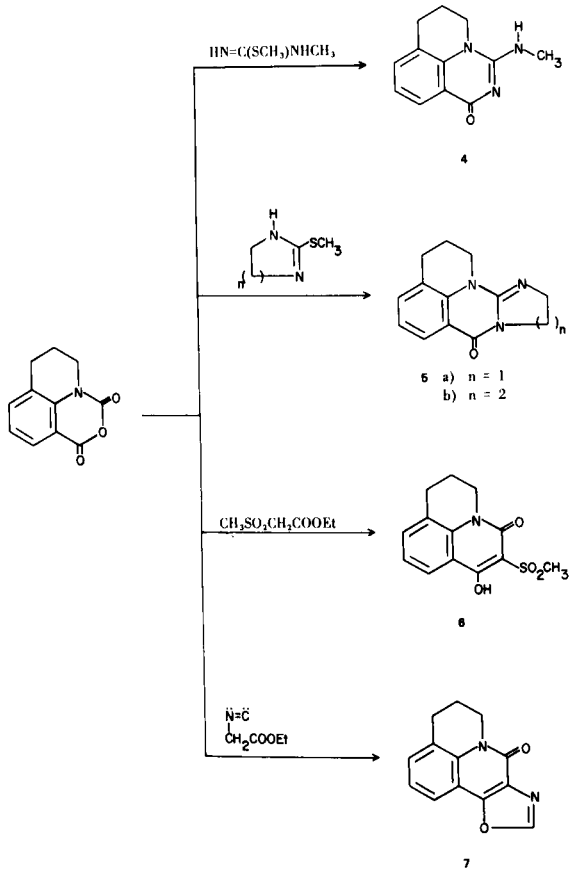


2 **3**

8-Quinolinecarboxylic acid (**2**), which can be obtained commercially or prepared by a known procedure (5), is readily hydrogenated at 3.5 atmospheres over platinum oxide to form the 1,2,3,4-tetrahydroquinoline (**3**) in 87% yield. The subsequent treatment of **3** with phosgene in the presence of base afforded **1b** in 95% yield.

Reactions of **1b** with various nucleophiles are shown in Scheme II. When **1b** was treated with 2,3-dimethyl-2-thiopseudourea in the presence of base, **4** was formed in 40% yield. Analogously, when cyclic *S*-methylthioureas were employed, **5a** and **5b** were isolated in respective yields of 58% and 25%.

Scheme II



4

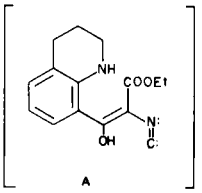
5 a) n = 1
b) n = 2

6

7

As in the case of isatoic anhydrides, **1b** reacts smoothly with the anion of active methylene compounds, accompanied by loss of carbon dioxide, to produce interesting polycyclic ring systems. Several pertinent reactions were attempted with the following results. When **1b** was allowed to react with a simple active methylene compound such as ethyl α-methylsulfonyl acetate in the presence of

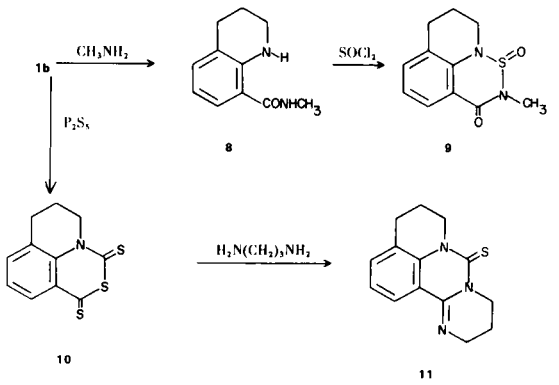
sodium hydride, **6** was isolated in 40% yield. The use of certain difunctional active methylene compounds leads to interesting tetracyclic ring systems. For example, treatment of **1b** with the anion of ethyl isocyanoacetate afforded **7** in 36% yield. The cyclization is believed to proceed, similar to that of the isatoic anhydride series (3), via intermediate **A**.



A

The heterocyclic anhydride ring in **1b** is easily opened by such bases as methylamine to yield the corresponding tetrahydroquinoline carboxamide (**8**). The treatment of such an amide with thionyl chloride furnishes the tricycle **9** in almost quantitative yield (Scheme III).

Scheme III



Compound **1b** additionally can be converted in moderate yield to the trithio intermediate **10** when allowed to react with phosphorus pentasulfide at an elevated temperature. This, in turn, can be condensed with 1,3-diaminopropane to form **11** which was only isolated in low yield.

Further studies on the synthesis of **1a** and additional tricyclic anhydrides and their reactions are in progress.

EXPERIMENTAL (6)

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer models 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass spectra were determined on an LKB 9000 spectrophotometer.

1,2,3,4-Tetrahydroquinoline-8-carboxylic Acid (**3**).

A solution of 270 g. of **2** in 2700 ml. of ethanol was hydrogenated in the presence of 27 g. of platinum oxide at 3.5 atmospheres for two hours. The catalyst was filtered from the reaction mixture and the solvent was removed under reduced pressure to yield 236 g. (87%) of **3**, m.p. 165-167° (Lit. (5) m.p. 161-163°).

6,7-Dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-1,3-dione (**1b**).

A mixture of 236 g. of **3** and 141 g. of anhydrous sodium carbonate in 4500 ml. of water was heated until a solution formed. The soluiton was cooled to room temperature then 3150 ml. of a phosgene solution (12.5% in benzene) was added dropwise and the mixture was stirred at room temperature for 24 hours. The benzene was removed from the reaction mixture under reduced pressure and the resulting precipitate was filtered, washed with water, dried, and recrystallized from methylene chloride/ether to yield 255 g. (95%) of **1b**, m.p. 188-190° (Lit. (4) m.p. 185-188°).

2,3-Dihydro-5-methylamino-1*H*,7*H*-pyrido[3,2,1-*ij*]quinazolin-7-one (**4**).

A mixture of 4.0 g. of **1b**, 4.6 g. of 2,3-dimethyl-2-thiopseudourea and 2.7 g. of anhydrous potassium carbonate in 75 ml. of dioxane was refluxed for 18 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a 10% solution of methanol/chloroform to elute the product. The solvent was removed under reduced pressure to yield 1.7 g. (40%) of **4**. An analytical sample was prepared by crystallization from methanol/ethyl acetate, m.p. 287-290°; ir (potassium bromide): 3270 cm^{-1}; nmr (deuteriochloroform/trifluoroacetic acid-d): δ 8.2 (m, 1), 7.5 (m, 2), 4.1 (t, 2), 3.3 (s, 3), 3.0 (t, 2), 2.3 (m, 2).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 67.0; H, 6.1; N, 19.5. Found: C, 66.9; H, 5.9; N, 19.6.

2,3,9,10-Tetrahydro-1*H*,7*H*-imidazo[2,1-*b*]pyrido[3,2,1-*ij*]quinazolin-7-one (**5a**).

A mixture of 8.0 g. of **1b**, 4.6 g. of 2-methylthio-2-imidazoline, and two sodium hydroxide pellets in 150 ml. of dioxane was refluxed for 4.5 hours. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride and extracted into 1*N* hydrochloric acid. The aqueous phase was washed with methylene chloride, then made basic by addition of 10% aqueous sodium bicarbonate solution. The resulting precipitate was filtered, washed with water and dried to yield 5.2 g. (58%) of **5a**. An analytical sample was prepared by crystallizaiton from methylene chloride/ether, m.p. 233-235°; ir (chloroform): 1675, 1630, 1310 cm^{-1}; nmr (deuteriochloroform): δ 7.95 (m, 1), 7.1 (m, 2), 4.1 (m, 6), 2.9 (t, 2), 2.2 (m, 2).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.7; H, 5.8; N, 18.5. Found: C, 68.7; H, 6.2; N, 18.4.

2,3,10,11-Tetrahydro-1*H*,7*H*,9*H*-pyrido[3,2,1-*ij*]pyrimido[2,1-*b*]-quinazolin-7-one (**5b**).

Using the procedure for **5a**, 7.0 g. of **1b** and 4.5 g. of 2-methylthio-3,4,5,6-tetrahydro-2-pyrimidine yielded 2.1 g. (25%) of **5b**, m.p. 159-162°; ir (chloroform): 1680, 1630, 1505, 1420, 1320 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.0 (m, 2), 3.95 (m, 4), 3.6 (t, 2), 2.85 (t, 2), 2.0 (m, 4).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 70.0; H, 6.3; N, 17.4. Found: C, 69.7; H, 6.5; N, 17.3.

2,3-Dihydro-7-hydroxy-6-methylsulfonyl-1*H*-5*H*-benzo[*ij*]quinolizin-5-one (**6**).

To a solution of 5.8 g. of ethyl α-methylsulfonyl acetate in 75 ml. of *N*,*N*-dimethylacetamide was added 1.7 g. of sodium

hydride (50% in mineral oil, pentane washed) in portions. After the evolution of hydrogen ceased, a solution of 7.0 g. of **1b** in 75 ml. of *N,N*-dimethylacetamide was added all at once and the mixture was heated at 120° for 90 minutes (evolution of carbon dioxide occurs). The solvent was removed under reduced pressure, water was added to the residue, and the aqueous phase was washed with methylene chloride, then acidified with 2*N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and was crystallized from ethanol to yield 3.8 g. (40%) of **6**, m.p. 201-203°; ir (chloroform): 1635, 1275, 1105 cm^{-1}; nmr (deuteriochloroform): δ 13.4 (s,1), 7.95 (m, 1), 7.5-7.1 (m, 2), 4.1 (m, 2), 3.45 (s, 3), 2.95 (t, 2), 2.1 (m, 2).

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.9; H, 4.7; N, 5.0; S, 11.5. Found: C, 55.7; H, 5.0; N, 5.2; S, 11.5.

5,6-Dihydro-4*H*,8*H*-benz[*ij*]oxazolo[5,4-*b*]quinolizin-8-one (**7**).

To a solution of 3.2 g. of ethyl isocyanoacetate in 40 ml. of *N,N*-dimethylacetamide was added 1.4 g. of sodium hydride (50%, pentane washed) in portions. When the evolution of hydrogen ceased a solution of 5.6 g. of **1b** in 60 ml. of *N,N*-dimethylacetamide was added all at once. The mixture was then placed in an oil bath at 50°, and the temperature was raised slowly to 120° over a period of 30 minutes and then kept there for 4.5 hours (carbon dioxide evolves at approximately 70-80°). The solvent was removed under reduced pressure and water was added to the residue. The resulting precipitate was filtered, dissolved in a minimum amount of chloroform and chromatographed on a column of silica gel using 10% methanol/chloroform to elute the product, which was then crystallized from methylene chloride/ethanol to yield 2.3 g. (36%) of **7**, m.p. 295-298°; ir (Nujol): 1680 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (s, 1), 7.85 (m, 1), 7.35 (m, 2), 4.4 (m, 2), 3.1 (t, 2), 2.2 (m, 2).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.0; H, 4.5; N, 12.4. Found: C, 68.7; H, 5.0; N, 12.2.

N-Methyl-1,2,3,4-tetrahydroquinoline-8-carboxamide (**8**).

Gaseous methylamine was bubbled through a suspension of 15.0 g. of **1b** in 250 ml. of dioxane for one hour. The solvent was removed under reduced pressure and the resulting solid was dissolved in methylene chloride and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished the product which was recrystallized from ether/pentane to yield 11.8 g. (82%) of **8**, m.p. 100-102°; ir (chloroform): 3480, 3360, 1640 cm^{-1}; nmr (deuteriochloroform): δ 7.5 (m, 1), 7.0 (m, 2), 6.35 (m, 2), 3.3 (t, 2), 2.9 (d, 3), 2.7 (t, 2), 1.9 (m, 2).

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.4; H, 7.4; N, 14.7. Found: C, 69.2; H, 7.4; N, 14.3.

8,9-Dihydro-2-methyl-7*H*-pyrido[3,2,1-*ij*][1,2,3]benzothiadiazin-3(2*H*)one 1-Oxide (**9**).

To a solution of 3.3 g. of **8** in 50 ml. of benzene was added 2.1 g. of thionyl chloride in 10 ml. of benzene. The resulting suspension was refluxed for one hour. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using chloroform to elute the product. Removal of the solvent under reduced pressure yielded 3.8 g. (97%) of **9**. An analytical sample was prepared by crystallization from ether, m.p. 95-98°; ir (chloroform): 1665, 1140 cm^{-1}; nmr (deuteriochloroform): δ 8.0 (m, 1), 7.1 (m, 2), 3.75 (m, 2), 3.4 (s, 3), 2.85 (t, 2), 2.1 (m, 2).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.9; H, 5.1; N, 11.9; S, 13.6. Found: C, 56.3; H, 5.3; N, 11.8; S, 13.8.

6,7-Dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzothiazine-1,3-dithione (**10**).

A suspension of 6.0 g. of **1b** and 7.0 g. of phosphorus pentasulfide in 150 ml. of pseudocumene was refluxed for 1.5 hours. While hot, the solvent was decanted from any gum that formed and the supernatant was allowed to cool slowly. The resulting precipitate was filtered, washed with ethanol, and recrystallized from methylene chloride/ethanol to yield 3.8 g. (51%) of **10**, m.p. 193-195° (additional product can be obtained by concentration of the solvent from the reaction mixture), nmr (deuteriochloroform): δ 8.5 (m, 1), 7.4 (m, 2), 4.7 (m, 2), 3.1 (m, 2), 2.25 (m, 2); ms: molecular ion at m/e 251.

Anal. Calcd. for $C_{11}H_9NS_3$: C, 52.6; H, 3.6; N, 5.6. Found: C, 52.5; H, 3.6; N, 5.6.

5,6,11,12-Tetrahydro-4*H*,8*H*,10*H*-pyrido[3,2,1-*ij*]pyrimido[1,2-*c*]-quinazoline-8-thione (**11**).

A suspension of 4.0 g. of **10** and 1.5 g. of 1,3-diaminopropane in 100 ml. of water was refluxed for one hour. An additional 0.5 g. of the diamine was added and the mixture was refluxed an additional 2 hours. The reaction mixture was cooled and then extracted with methylene chloride. The organic phase was extracted with 3*N* hydrochloric acid, washed with methylene chloride, basicified with 25% sodium hydroxide and extracted into methylene chloride. The organic phase was dried over sodium sulfate and chromatographed on a column of silica gel using chloroform to elute the product which was then crystallized from methylene chloride/ethanol to yield 0.3 g. (7.3%) of **11**, m.p. 220-222°; nmr (deuteriochloroform): δ 8.0 (m, 1), 7.2 (m, 2), 4.4 (m, 4), 3.65 (t, 2), 2.85 (t, 2), 2.1 (m, 4).

Anal. Calcd. for $C_{14}H_{15}N_3S$: C, 65.3; H, 5.9; N, 16.3. Found: C, 65.0; H, 6.1; N, 16.5.

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(6) No attempt has been made to optimize the yields of the described reactions.