Quinazolines and 1,4-Benzodiazepines. XLIII (1). Oxidations with Ruthenium Tetroxide

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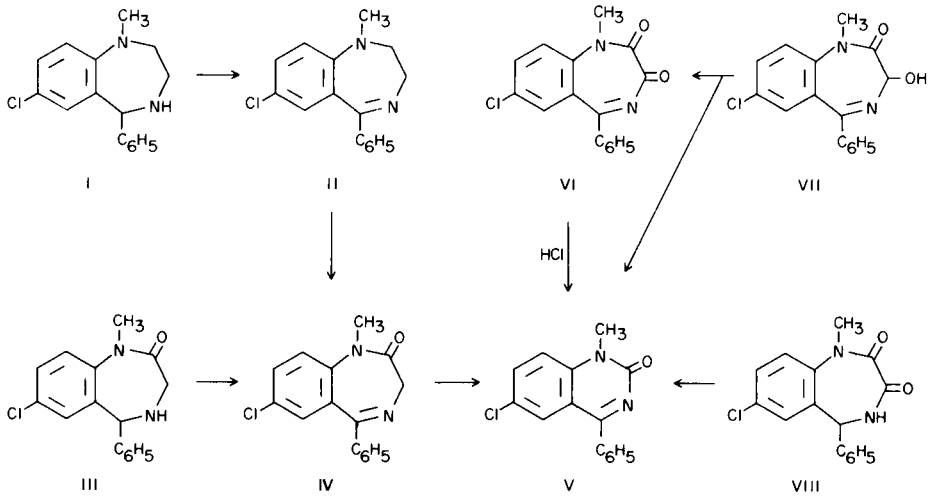
Although ruthenium tetroxide was first discovered more than a century ago (2), relatively few reactions with this reagent have been examined by the organic chemist. Berkowitz and Rylander (3) showed that ruthenium tetroxide can be used as a multi-purpose oxidant. These and other authors reported on the oxidation of aldehydes to acids, alcohols to aldehydes or ketones (3,4a-d), ethers to esters (3,5a-b) and olefins to aldehydes, ketones and compounds containing hydroxyl groups (3, 5b 6a-e). Oxidations of sulfides to sulfones have also been reported (6e). Little work has been carried out in the area of ruthenium tetroxide oxidations of organic compounds containing nitrogen. It is known however that ruthenium tetroxide converts amides to imides (3, 5b, 7) but there is only one literature reference to the oxidation of amines with ruthenium tetroxide and this reports the formation of mixtures and intractable residues (3).

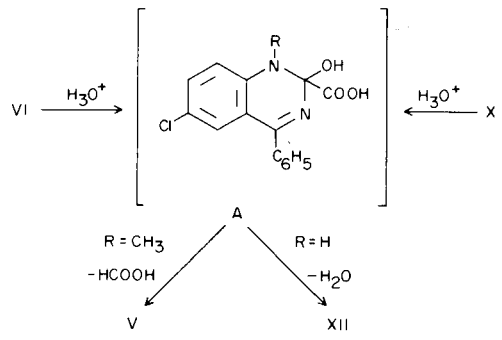
We have extended the scope of ruthenium tetroxide oxidations to include a number of 1,4-benzodiazepines. Thus the tetrahydro-1,4-benzodiazepine (I) was smoothly oxidized in chloroform solution to the corresponding dihydro derivative, compound II, in 43% yield (8). The amine (II) and the amide (III) were also readily converted to the dihydro-1,4-benzodiazepin-2-one (IV). In the case of III the quinazoline (V) was also isolated.

The formation of the quinazolone can probably be best explained by the oxidation of IV to the dione (VI). Hydrolysis of the 3,4-bond and recyclization with ring contraction would lead to an intermediate of type A. Loss of formic acid from the α-hydroxy acid would then lead to the observed quinazolone V. The oxidation of the 3-hydroxybenzodiazepinone (VII) led to the isolation of both the postulated intermediary dione (VI) and the quinazolone (V). Acid catalyzed rearrangement of the dione then gave V in good yield as did oxidation of the 4,5-dihydrodione (VIII). In all of these oxidations varying amounts of the unstable dione (VI) were detected by thin layer chromatography. In most cases the mixtures of

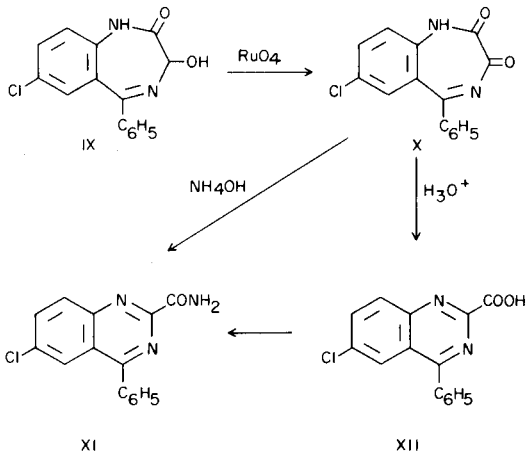


I II VI VII

III IV V VIII



products in the mother liquors were not separated, but converted by acid treatment to the more stable end product, compound V.



Oxidation of the 1-unsubstituted 3-hydroxy derivative (IX) with ruthenium tetroxide led to the isolation of the corresponding dione (X) in 57% yield. Treatment of the mother liquors with ammonia afforded the known quinazolinecarboxamide (XI) (9) in 7% yield. Again rearrangement of the unstable dione would account for the formation of the quinazoline, and in this case the intermediate A (R=H) would dehydrate to form the quinazoline carboxylic acid (XII) (9). The acid (XII) was readily obtained by treatment of X with mineral acid.

EXPERIMENTAL (10)

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (II).

A stirred solution of 1.37 g. (0.005 mole) of 7-chloro-1-methyl-5-phenyl-1,2,4,5-tetrahydro-3*H*-1,4-benzodiazepine (I) (11) in 25 ml. of carbon tetrachloride in an ice bath was treated by the dropwise addition (45 minutes) of 87 ml. (0.005 mole) of a 0.064 molar solution of ruthenium tetroxide in chloroform (4a). The reaction mixture was stirred for an additional 0.5 hour when excess reagent was decomposed by the addition of 10 ml. of 2-propanol. The solution was filtered through Celite, which was washed first with 100 ml. of water and then with 50 ml. of methylene chloride. The filtrates were separated and the organic layers were washed with 75 ml. of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness.

The residual oil was dissolved in 25 ml. of benzene and chromatographed over 75 g. of neutral Grade I alumina ("Woelm"). Using 200 ml. of benzene as the eluent, 100 mg. of an oil was obtained which was discarded. By changing to ether (750 ml.) and then ethyl acetate (750 ml.), 0.6 g. (43%) of II (m.p. and m.m.p. with an authentic sample (11) 101-103°) was obtained after removal of solvents and crystallization of the combined residue from a mixture of ether and petroleum ether, (b.p. 30-60°).

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IV).

(a) From 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (II).

A solution of 732 mg. (2.7 mmoles) of II in 10 ml. of chloroform was treated at 0° with 180 ml. (9.7 mmoles) of a 0.054 molar solution of ruthenium tetroxide in chloroform (addition time 0.5 hour). The mixture was then stirred for 0.5 hour when 5 ml. of 2-propanol and 200 ml. of water was added. The mixture was filtered through Celite. The layers were separated and the aqueous layer was washed with chloroform (3 x 25 ml.). The combined chloroform layers were dried over magnesium sulfate, filtered and evaporated to a small volume. Hexane was added and the solution was set aside for crystallization. Filtration afforded 426 mg. (55%) of IV as white prisms, m.p. and m.m.p. with an authentic sample (12) 128-132°.

(b) From 7-Chloro-1,3,4,5-tetrahydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (III).

A solution of 1 g. (0.0035 mole) of III in 25 ml. of chloroform was stirred in an ice bath and was treated with 108 ml. (0.007 mole) of a 0.065 molar solution of ruthenium tetroxide in chloroform over a 10 minute period. After standing 18 hours at room temperature an additional 75 ml. (0.005 mole) of ruthenium tetroxide was added and the reaction was allowed to stand for an additional 18 hours. Water (50 ml.) was added and the mixture was filtered through Celite. The chloroform layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from ether to give 0.6 g. (60%) of IV as white prisms, m.p. and m.m.p. with an authentic sample 128-132°.

6-Chloro-1,2-dihydro-1-methyl-4-phenylquinazolin-2-one (V).

(a) From the Oxidation of III.

An examination of the mother liquors obtained from the oxidation of III by thin layer chromatography showed the presence of considerable amounts of the dione (VI) which was converted directly to V without isolation.

The mother liquors were evaporated to dryness and heated on the steam bath for 1 hour with 30 ml. of concentrated hydrochloric acid. The solution was then made basic with ammonium hydroxide and extracted with 100 ml. of dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residual oil was treated with boiling hexane to remove aminobenzophenone and the insoluble residue was crystallized from a mixture of ether and hexane to give 0.1 g. (11%) of V as pale yellow rods, m.p. and m.m.p. with an authentic sample (13) 221-226°.

(b) From 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzo-

diazepin-2-one (IV).

A solution of 1 g. (0.0035 mole) of IV in 25 ml. of chloroform cooled in an ice bath was treated with 109 ml. (0.007 mole) of a 0.065 molar solution of ruthenium tetroxide. After standing overnight at room temperature an additional 75 ml. (0.005 mole) of ruthenium tetroxide was added and the reaction was again allowed to stand for 18 hours. Water (10 ml.) was added and the reaction was filtered through Celite. The chloroform layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The residual oil was crystallized from methanol to give 0.2 g. (21%) of V as pale yellow rods, m.p. and m.m.p. 221-225°. A visual estimation of a thin layer chromatogram of the mother liquors indicated the presence of some starting material together with considerable amounts of compounds V and VI.

(c) From 7-Chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine-2,3-dione (VI).

A solution of 50 mg. (0.167 mmole) of VI in 25 ml. of dichloromethane was acidified with several drops of 1 *N* hydrochloric acid and after 30 minutes, the dichloromethane was evaporated to dryness. The residue was made basic with ammonium hydroxide and the mixture was filtered. The precipitate was washed with water and dried to give 30 mg. (66%) of V as pale yellow rods, m.p. and m.m.p. 220-226°.

(d) From 7-Chloro-4,5-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine-2,3-dione (VIII).

A solution of 1 g. (0.003 mole) of VIII (14) in 25 ml. of chloroform, cooled in an ice bath, was treated with 109 ml. (0.007 mole) of a 0.065 molar ruthenium tetroxide solution. The mixture was allowed to stand for 18 hours at room temperature when an additional 75 ml. (0.005 mole) of ruthenium tetroxide solution was added. After standing for another 18 hours, 10 ml. of water was added and the reaction mixture was filtered through Celite. The chloroform layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness.

The oil was crystallized from methanol and the precipitate was then recrystallized from a mixture of dichloromethane and hexane to give 0.4 g. of starting material.

The filtrates were evaporated to dryness and the residue was heated on the steam bath for 2 hours in 25 ml. of 6 *N* hydrochloric acid. The solution was next made basic with ammonium hydroxide and extracted with 75 ml. of dichloromethane. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness. The oil was treated with boiling hexane and the insoluble residue was crystallized from ether and recrystallized from methanol to give 0.13 g. (25%) of V as pale yellow rods, m.p. 220-223°.

7-Chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine-2,3-dione (VI).

A stirred solution of 0.5 g. (0.002 mole) of 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (VII) (14) in 12 ml. of chloroform cooled in an ice bath was treated with the dropwise addition of 51 ml. (0.003 mole) of a 0.065 molar ruthenium tetroxide solution. After 18 hours, 15 ml. of water was added and the mixture was filtered through Celite. The chloroform layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The oil was recrystallized twice from a mixture of dichloromethane and hexane to give 0.15 g. (33%) of V as pale yellow rods, m.p. 224-226°. The mother liquors were then crystallized from ether and the product recrystallized from a mixture of dichloromethane and hexane to give 0.2 g. (45%) VI as white prisms, m.p. 169-174° dec.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.52; H, 4.07; N, 9.24.

7-Chloro-5-phenyl-1*H*-1,4-benzodiazepine-2,3-dione (X) and 6-Chloro-4-phenylquinazoline-2-carboxamide (XI).

A stirred suspension of 3 g. (0.0105 mole) of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IX) (14) in 10 ml. of chloroform, cooled in an ice bath, was treated with 200 ml. (0.013 mole) of a 0.065 molar solution of ruthenium tetroxide in chloroform. After 18 hours at room temperature, 25 ml. of water was added and the solution was filtered through Celite. A precipitate which then formed in the filtrates was removed by filtration and recrystallized first from ethyl acetate and then from a mixture of dichloromethane and petroleum ether to give 1.7 g. (57%) of X as pale yellow plates, melting at 248-251° dec.

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: C, 63.28; H, 3.19; N, 9.84; Found: C, 63.02; H, 3.14; N, 9.54.

The chloroform-soluble fraction from the original Celite filtration was washed with 100 ml. of dilute ammonium hydroxide, 75 ml. of a saturated brine solution, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized twice from methanol to give 0.2 g. (7%) of XI as white rods, m.p. and m.m.p. with an authentic sample (9) 265-269°.

6-Chloro-4-phenylquinazoline-2-carboxylic acid (XII).

A mixture of 0.5 g. (0.0018 mole) of X, 25 ml. of dichloromethane and 25 ml. of a 10% aqueous solution of potassium carbonate was shaken for 10 minutes and then allowed to stand overnight. The precipitate was removed by filtration, stirred with 25 ml. of dilute acetic acid for 1 hour, and then filtered and washed with water. The product was recrystallized from methanol to give 0.2 g. (40%) of XII as white rods, m.p. and m.m.p. with an authentic sample (9), 210-214°.

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(1965)] we reported that using chromic trioxide in acid, compounds of types I and III could not be oxidized to compounds to types II and IV. We have recently repeated this work and found that the oxidation proceeds smoothly, if the rate of addition of the oxidant is carefully controlled. Apparently, protonation of the benzylamine function hinders the oxidation process and therefore an excess of the base has to be present.

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