Studies in Alkylation. I. Synthesis and Reactions of Spiro[oxirane-2,4′-piperidines]

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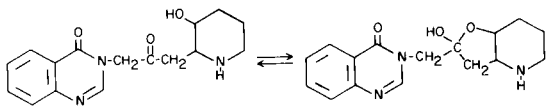
Spiro[oxirane-2,4′-piperidines] have been prepared by the action of dimethyloxosulfonium methylide on 4-piperidones. The spiro[oxirane-2,4′-piperidines] act as alkylating agents to introduce (4-hydroxy-4-piperidyl) methyl moieties onto heteroaromatic compounds such as 4(3*H*)-quinazolone.

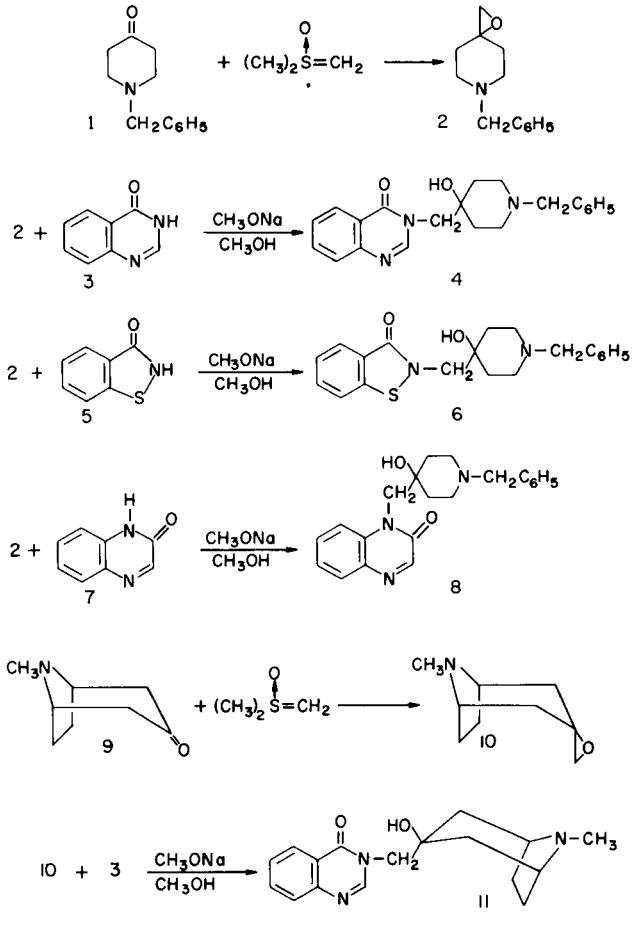
A convenient synthesis of spiro[oxirane-2,4′-piperidine] derivatives has been demonstrated utilizing 4-piperidones and dimethyloxosulfonium methylide. To our knowledge this is the first time that the oxirane synthesis of Corey and Chaykovsky (1) has been used with amino ketones. The reaction affords a simple and direct route to amino epoxides of a type that cannot easily be prepared by other methods.

The spiro[oxirane-2,4′-piperidines] were required as convenient reagents for introducing a (4-hydroxy-4-piperidyl)methyl moiety. Compounds containing this moiety were desired as part of our program to prepare new substances for testing as antimalarial agents. Hydroxyl and amino groups are found in the side chains of a number of potent antimalarial drugs such as quinine and other quinolylcarbinol amines. Our objectives were to prepare compounds with a hydroxy group β- and an amino group δ- to a heteroaromatic nucleus such as 4(3*H*)-quinazolone. These structural features were derived from the cyclic hemiketal form of the antimalarial alkaloid febrifugine:



The reaction of 1-benzyl-4-piperidone (**1**) with dimethyloxosulfonium methylide gave the corresponding epoxide 6-benzyl-1-oxa-6-azaspiro[2.5]octane (**2**) in moderate yield (2). This compound had been isolated previously by Morosawa (3) as a by-product in the ring homologization of **1** with *N*-nitrosomethylurethane. The ring system also has been reported with a variety of substituents; the compounds were obtained by reactions such as the Darzens glycidic ester condensation (4), by dehydration of a pinacol (5), and by the action of sodium methoxide on α-haloketones (6).

Tropinone (**9**) reacted with dimethyloxosulfonium methylide to give spiro[oxirane-2,3′-tropane] (**10**). This ring system was previously reported with a 3-carbethoxy group (7), prepared by a Darzens glycidic ester condensation with **9**.



The infrared spectra of **2** and **10** were devoid of carbonyl absorption. The nmr spectra showed singlets at 2.58 and 2.38 ppm respectively, assigned to the protons of the oxirane ring.

Reaction of 4(3*H*)-quinazolone (**3**) with **2** in methanolic sodium methoxide gave 3-[(1-benzyl-4-hydroxy-4-piperidyl)methyl]-4-quinazolone (**4**). The infrared spectrum of **4** showed the expected sharp hydroxyl absorption at 3450 cm^{-1}, and quinazolone absorption at 1610 and 1660 cm^{-1}. Proton nmr spectrometry showed a singlet at δ4.09 ppm ascribed to the 3-quinazolonyl-CH_2-protons.

Condensation of **2** with benzisothiazolone (**5**) and with quinoxalone (**7**) gave, respectively, 2-[(1-benzyl-4-hydroxy-4-piperidyl)methyl]benzisothiazolone (**6**) and 1-[(1-benzyl-4-hydroxy-4-piperidyl)methyl]quinoxalone (**8**).

The reaction between **3** and **10** in methanolic sodium methoxide gave [(3-hydroxy-3-tropanyl)methyl]-4-quinazolone (**11**). The infrared spectrum of **11** showed the expected sharp hydroxyl absorption at 3300 cm^{-1}, and quinazolone absorption at 1610 and 1660 cm^{-1}; the nmr spectrum contained a singlet at δ4.05 ppm from the 3-quinazolonyl-CH_2-protons.

EXPERIMENTAL

6-Benzyl-1-oxa-6-azaspiro[2.5]octane (2).

A solution of dimethyloxosulfonium methylide (1) was prepared under dry nitrogen from sodium hydride (10.5 g. of a 50% dispersion in mineral oil, 0.225 mole) and trimethyloxosulfonium iodide (49.5 g., 0.225 mole) in 150 ml. of anhydrous dimethyl sulfoxide. 1-Benzyl-4-piperidone (28.4 g., 0.150 mole) was added in 20 minutes at room temperature to the stirred dimethyloxosulfonium methylide solution, and stirring was continued at room temperature for 18 hours. The reaction mixture was poured into 400 ml. of cold water and the solution extracted several times with ether. The combined ether extracts were washed once with 50 ml. of water, dried (magnesium sulfate), concentrated, and distilled under reduced pressure yielding 11.0 g. 33%) of **2**, b.p. 93° (0.06 mm), reported (3) 114° (0.43 mm); nmr (deuteriochloroform) δ2.58 (S, 2H, oxirane CH_2), 3.54 (S, 2H, N-CH_2-C_6H_5) and 7.29 ppm (S, 5H, N-CH_2-C_6H_5); mass spectrum *m/e* 203 ($C_{13}H_{17}NO$).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.65; H, 8.45; N, 6.81.

Spiro[oxirane-2,3′-tropane] (10).

Reaction of 17.3 g. (0.124 mole) of tropinone (**9**) with dimethyloxosulfonium methylide generated from 45.8 g. (0.203 mole) of trimethyloxosulfonium iodide and 9.75 g. (0.203 mole) of sodium hydride (50% mineral oil dispersion) in 139 ml. of anhydrous dimethylsulfoxide in the manner described for the preparation of **2** afforded 7.51 g. (40%) of **10**, b.p. 30° (0.07 mm); nmr (deuteriochloroform) δ2.33 (S, 3H, N-CH_3) and 2.38 ppm (S, 2H, oxirane CH_2); mass spectrum *m/e* 153 ($C_9H_{15}NO$).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.65; H, 9.86; N, 9.04.

3-[(1-Benzyl-4-hydroxy-4-piperidyl)methyl]-4-quinazolone (4).

To a solution of 1.00 g. (0.007 mole) of 4(3*H*)-quinazolone in 7.5 ml. of 1*N* methanolic sodium methoxide (stirred for 20 minutes at room temperature) was added 5.14 g. (0.025 mole) of 6-benzyl-1-oxa-6-azaspiro[2.5]octane (**2**). The solution was refluxed overnight, cooled, diluted with water, and concentrated *in vacuo* to remove the methanol. The resulting aqueous solution was extracted three times with chloroform; the combined organic phase was washed once with 10% sodium hydroxide, dried (magnesium sulfate), and freed of solvent *in vacuo* yielding a viscous liquid. Crystallization from benzene gave 675 mg. (28%) of white crystals, m.p. 145.5-147.5°; nmr (deuteriochloroform) δ3.52 (S, 2H, N-CH_2-C_6H_5), 4.09 (S, 2H, 3-quinazolonyl-CH_2-) and 7.29 ppm (S, 5H, N-CH_2-C_6H_5).

Anal. Calcd. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.15; H, 6.52; N, 11.86.

2-[(1-Benzyl-4-hydroxy-4-piperidyl)methyl]-benzisothiazolone (6).

Condensation of 1.00 g. (0.007 mole) of benzisothiazolone (8), 7.5 ml. of 1*N* methanolic sodium methoxide and 4.11 g. (0.02 mole) of 6-benzyl-1-oxa-6-azaspiro[2.5]octane (**2**) in the manner described for the preparation of **4** led to 561 mg. (24%) of white crystals, m.p. 168°; ir (potassium bromide) 3400 (OH) and 1670 cm^{-1} (N-C=O); nmr (deuteriochloroform) δ3.76 (S, 2H, N-CH_2-C_6H_5), 3.93 (S, 2H, 2-benzisothiazolonyl-CH_2) and 7.38 ppm (S, 5H, N-CH_2-C_6H_5); mass spectrum *m/e* 354 ($C_{20}H_{22}N_2O_2S$).

Anal. Calcd. for $C_{20}H_{22}N_2O_2S$: C. 67.70; H, 6.21; N, 7.91. Found: C, 67.30; H, 6.28; N, 7.80.

1-[(1-Benzyl-4-hydroxy-4-piperidyl)methyl]-quinoxalone (8).

Condensation of 1.00 g. (0.007 mole) of quinoxalone, 7.5 ml. of 1*N* methanolic sodium methoxide and 4.11 g. (0.02 mole) of 6-benzyl-1-oxa-6-azaspiro[2.5]octane (**2**) in the manner described for the preparation of **4** afforded 500 mg. (21%) of orange crystals, m.p. 166.5-167°; ir (potassium bromide), 3450 (OH), 1660 (N-C=O) and 1610 cm^{-1} (C=N); nmr (deuteriochloroform) δ3.65 (S, 2H, N-CH_2-C_6H_5), 4.36 (S, 2H, 2-quinoxalonyl-CH_2-) and 7.35 ppm (S, 5H, N-CH_2-C_6H_5); mass spectrum *m/e* 349 ($C_{21}H_{23}N_3O_2$).

Anal. Calcd. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.84; H, 6.74; N, 11.70.

[(3-Hydroxy-3-tropanyl)methyl]-4-quinazolone Hemihydrate (11).

To a solution of 1.50 g. (0.01 mole) of 4(3*H*)-quinazolone in 11.5 ml. of 1*N* methanolic sodium methoxide (stirred for 20 minutes at room temperature) was added 5.78 g. (0.038 mole) of spiro[oxirane-2,3′-tropane] (**10**). After stirring at room temperature overnight, the solution was diluted with 150 ml. of water and 65 ml. of a 10% sodium hydroxide solution. The methanol was evaporated under reduced pressure and the aqueous solution was extracted three times with chloroform. The combined chloroform layers were dried (magnesium sulfate) and concentrated *in vacuo* leaving an oily material. High vacuum distillation afforded some recovered oxirane **10**. Addition of ether to the pot residue gave 1.05 g. (32%) of crystalline **11**, m.p. 104-115°; nmr (deuteriochloroform) δ2.31 (S, 3H, N-CH_3) and 4.05 ppm (S, 2H, 3-quinazolonyl-CH_2).

Anal. Calcd. for $C_{17}H_{21}N_3O_2 \cdot \frac{1}{2}H_2O$: C, 66.23; H, 7.14; N, 13.64. Found: C, 66.36; H, 7.14; N, 13.40.

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