DERIVATIVES OF THE sym-OCTAHYDROACRIDINE SERIES

V. Syntheses from sym-Octahydroacridin-4-ol N-Oxide*

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4, 5-Dihydroxy-, 4, 5-diacetoxy-, 4, 5-dichloro-, and 4-hydroxy-5-oxo-sym-octahydroacridines and the N-oxides of 1, 2, 3, 4, 7, 8-hexahydroacridine and of 4, 5-dihydroxy-sym-octahydroacridine have been synthesized. The dehydration of 4, 5-dihydroxy-sym-octahydroacridine has led to 1, 2, 7, 8-tetrahydroacridine. The latter adds two molecules of hydrogen to the double bonds and also one molecule of acetoacetic ester with the formation of, respectively, sym-octahydroacridine and 3-[acetyl(ethoxycarbonyl)methyl]-1, 2, 3, 4, 7, 8-hexahydroacridine.

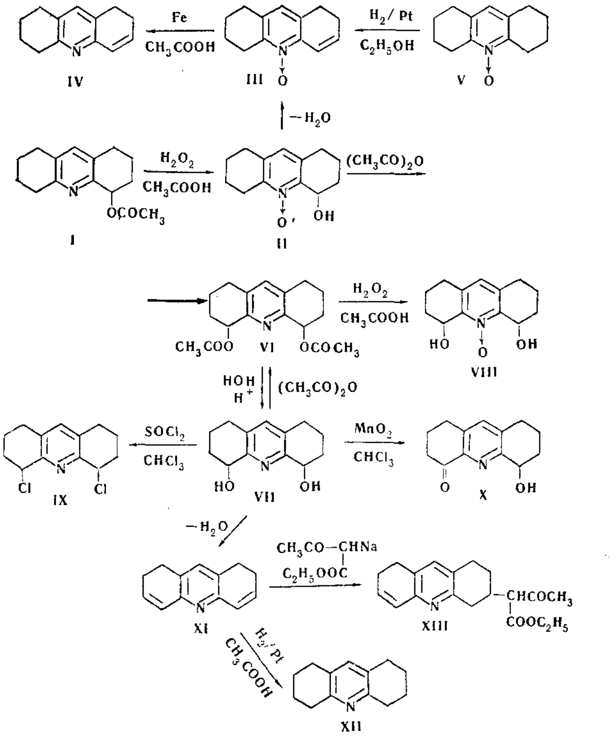
It has been reported previously [1] that sym-octahydroacridin-4-ol N-oxide (II) is formed by the oxidation of the corresponding aminoalcohol—sym-octahydroacridin-4-ol—with hydrogen peroxide in acetic acid. We have found [2] that the same compound II can be obtained directly from 4-acetoxy-sym-octahydroacridine (I) in higher yield. Such N-oxidation accompanied by hydrolysis has been reported previously in the oxidation of pyrid-4-ylmethyl acetate [3].

The dehydration of the oxide II by heating with polyphosphoric acid led to 1, 2, 3, 4, 7, 8-hexahydroacridine N-oxide (III) which, in contrast to the corresponding base IV [4], is a crystalline substance. The hydrogenation of the N-oxide III with hydrogen over platinum over ethanol led to the known sym-octahydroacridine N-oxide (V) [5]; hydrogenation in acetic acid gives mainly compound V and, judging from a chromatogram, traces of sym-octahydroacridine (XII). The removal of the N-oxide oxygen is readily achieved by reducing the oxide III with iron in acetic acid under the conditions that we have described previously [5].

The reaction of the oxide II with acetic anhydride led to 4, 5-diacetoxy-sym-octahydroacridine (VI), which is completely characteristic for α, α'-dialkylpyridines [6]. The oxidation of the diacetate VI with peracetic acid led to sym-octahydroacridine-4, 5-diol N-oxide (VIII). The acid hydrolysis of the diacetate VI led to sym-octahydroacridine-4, 5-diol (VII). Treatment of the latter with thionyl chloride in chloroform gave 4, 5-dichloro-sym-octahydroacridine (IX); the reaction takes place with a fairly good yield only when a considerable excess of the chlorinating agent is used. The acetylation of the glycol VII with acetic anhydride led to the diacetate VI which, as shown above, is also formed by the reaction of the oxide II with this reagent.

The dehydration of the glycol VII by heating in polyphosphoric acid led to 1, 2, 7, 8-tetrahydroacridine (XI), which, in contrast to 1, 2, 3, 4-tetrahydroacridine [7] is a liquid. Compound XI is a peculiar analog of 2, 6-divinylpyridine. It readily adds two molecules of hydrogen, with the formation of XII, and one molecule of acetoacetic ester to give 3-[acetyl(ethoxycarbonyl)methyl]-1, 2, 3, 4, 7, 8-hexahydroacridine (XIII).

The action of active manganese dioxide on the glycol VII led to the oxidation of one alcohol group. The IR spectrum of the 4-hydroxy-sym-octahydroacridin-5-one (X) obtained shows absorption bands characteristic for the carbonyl and hydroxy groups.



EXPERIMENTAL

The IR spectra were obtained on a UR-10 spectrophotometer with NaCl and LiF prisms. The UV spectra were obtained on an SF-4 spectrophotometer in absolute ethanol. Alumina of activity II was used for the thin-layer chromatograms. The picrates were prepared by mixing alcoholic solutions of the substances and picric acid; in the case of compound VII the mixture was diluted with water. The hydrochlorides were obtained by passing dry HCl into solutions of the substances into absolute ethanol (in the case of compound VII, in a mixture of benzene and ether).

sym-Octahydroacridin-4-ol N-oxide (II). A mixture of 8.6 g of I, 28 ml of glacial acetic acid, and 7 ml of 28% H_2O_2 was heated at 75° C for 9 hr, and then 6 ml of H_2O_2 was added, and it was heated for another 12 hr. After cooling, the mixture was made alkaline with an aqueous solution of potassium carbonate and extracted with chloroform (3 x 30 ml). Evaporation of the solvent left 6.8 g (88%) of crystals of the oxide II with mp 117° C, identical with the compound obtained previously [1]. UV spectrum, λ_{max}: 265 nm (log ε 3.48). IR spectrum (in CCl_4): ν_{OH} 3300–3500 cm^{-1} (broad band).

For part IV, see [12].

1,2,3,4,7,8-Hexahydroacridine N-oxide (III). With stirring, 10.1 g of the oxide II in 60 g of polyphosphoric acid was gradually heated to 180° C over 2 hr and was then poured onto 120 g of ice and made alkaline with 40% NaOH solution. The oil that separated out was extracted with benzene (3 x 70 ml). Evaporation of the solvent yielded 8.8 g (94%) of crystals of the oxide III. Light yellow needles, readily soluble in polar solvents and less readily in petroleum ether. Mp 99–99.5° C (from heptane). Found, %: C 77.91, 77.69; H 7.58, 7.59; N 7.06, 7.00. Calculated for $C_{13}H_{15}NO$, %: C 77.52; H 7.52; N 6.97. IR spectrum (in CCl_4): ν_{NO} 1350 and 1320 cm^{-1} (split band). UV spectrum, λ_{max}: 290 and 250 nm (log ε 3.26 and 3.51). Picrate—yellow-green needles with mp 137° C (from methanol). Found, %: N 12.94, 12.92. Calculated for $C_{13}H_{15}NO \cdot C_6H_3N_3O_7$, %: N 13.01. Hydrochloride—light yellow prisms readily soluble in water, with mp 152–153° C (from dioxane). Found, %: Cl 14.65. Calculated for $C_{13}H_{15}NO \cdot HCl$, %: Cl 14.92.

Reduction of the oxide III. A mixture of 0.6 g of the hydrochloride of III, 6 ml of 98% acetic acid and 0.7 g of reduced iron was boiled for 2 hr. The cooled mixture was filtered and neutralized with saturated potassium carbonate solution, and the base IV was extracted with benzene and was identified in the form of the picrate [1]. Yield 77%.

Hydrogenation of the oxide III. A 0.3114 g quantity of the oxide III in 20 ml of ethanol was hydrogenated over 0.0592 g of PtO_2 prepared by a published method [8]. After 25 min, the theoretical amount of hydrogen had been absorbed. Hydrogen number: found 113.2; calculated for one double bond 111.2. The catalyst was filtered off, the ethanol was evaporated off, and the residue was recrystallized from heptane to give the oxide V with mp 142–143° C. According to the literature, mp 144–145° C [9]; 140–142° C [10]. A mixture with a reference sample of the oxide V had mp 142–143° C. R_f 0.73 (ethyl acetate); for the reference sample, R_f 0.73 (ethyl acetate).

4,5-Diacetoxy-sym-octahydroacridine (VI). a) A suspension of 22 g of the oxide II in 120 ml of acetic anhydride was added over half an hour to 20 ml of boiling acetic anhydride, and the mixture was boiled for another 1 hr 30 min. The solvent was distilled off, and the residue was made alkaline with potassium carbonate; the precipitate that deposited was washed with water and dried. Yield was 30 g (~100%).

b) A mixture of 5.1 g of the glycol VII and 25 ml of acetic anhydride was boiled for 3 hr. After the mixture had been made alkaline with potassium carbonate, 6.4 g (91%) of the diacetate VI was obtained. Colorless rods with mp 127.5–128.5° C (from hexane). Found, %: C 67.22; 67.32; H 7.35, 7.33; N 4.45, 4.53. Calculated for $C_{17}H_{21}NO_4$, %: C 67.30; H 6.99; N 4.62. IR spectrum (in CCl_4): 1760 and 1260 cm^{-1} (ester bonds). Picrate—lemon yellow plates with mp 180–180.5° C (decomp., from methanol). Found, %: N 10.44, 10.41. Calculated for $C_{17}H_{21}NO_4 \cdot C_6H_3N_3O_7$, %: N 10.52. Hydrochloride—colorless rods, insoluble in water, with mp 179–179.5° C (from dioxane). Found, %: Cl 9.96, 10.52. Calculated for $C_{17}H_{21}NO_4 \cdot \cdot HCl$, %: Cl 10.43.

sym-Octahydroacridine-4,5-diol (VII). a) A solution of 9 g of the diacetate VI in 60 ml of HCl (1 : 3) was heated at ~100° C for 2 hr. After alkalinization with potassium carbonate, 5.9 g (90%) of the diol VII was obtained.

b) A mixture of 8.2 g of the ester I, 20 ml of 98% CH_3COOH and 5 ml of 28% H_2O_2 was heated at 70–80° C for 10 hr, and then 4 ml of H_2O_2 was added and the mixture heated for another 13 hr. The solvent was evaporated off, and the residue was dissolved in 15 ml of acetic anhydride; the resulting solution was added dropwise to 10 ml of boiling acetic anhydride over 1 hr 30 min, and the mixture was boiled for another half hour. The solvent was distilled off under reduced pressure; the residue was dissolved in 40 ml of 10% HCl, and the solution was heated in the boiling water bath for 2 hr. Then it was made alkaline with 10% K_2CO_3, and 6 g (83%) of crystals of the glycol VII identical with the material obtained by method (a) was filtered off. Long needles very sparingly soluble in petroleum ether and ether, readily soluble in polar solvents. Mp 156.5–158° C (from a mixture of benzene and heptane, 1 : 2). Found, %: C 71.76, 71.53; H 7.85, 7.89; N 6.69, 6.51. Calculated for $C_{13}H_{17}NO_2$, %: C 71.22; H 7.81; N 6.39%. IR spectrum (in CCl_4): ν_{OH} 3600–3500 cm^{-1} (broad band). UV spectrum, λ_{max}: 276 nm (log ε 4.33). Picrate—yellow plates with mp 135–136° C (from water). Found, %: N 12.23, 12.39. Calculated for $C_{13}H_{17}NO_2 \cdot C_6H_3N_3O_7$, %: N 12.50. Hydrochloride—pale yellow rods, soluble in water, with mp 202–203° C (decomp., from dioxane). Found, %: Cl 13.60, 13.82. Calculated for $C_{13}H_{17}NO_2 \cdot HCl$, %: Cl 13.88. The dibenzoate was obtained by the Schotten-Baumann benzoylation of the glycol VII with benzoyl chloride. Pointed rods with mp 163–165° C (from a mixture of heptane and benzene, 3 : 1). Found, %: C 75.15; 75.06; H 6.21, 6.30. Calculated for $C_{27}H_{25}NO_4$, %: C 75.84; H 5.89. IR spectrum (in KBr): 1740 and 1290 cm^{-1} (ester bonds).

sym-Octahydroacridine-4,5-diol N-oxide (VIII). A mixture of 6 g of the diacetate VI, 15 ml of 98% of CH_3COOH, and 3 ml of 30% H_2O_2 was heated at 70–80° C for 9 hr, and then 2 ml of H_2O_2 was added and the mixture heated for another 13 hr. After being made alkaline with potassium carbonate, the mixture was extracted with benzene. Evaporation of the dried benzene extract gave a vitreous mass, the treatment of which with absolute ethanol yielded 1.3 g (28%) of the oxide VIII. Pointed rods with mp 172–173° C (from a mixture of heptane and benzene, 5 : 2). Found, %: C 65.66, 65.57, H 7.35, 7.39; N 5.64, 5.83. Calculated for $C_{13}H_{17}NO_3$, %: C 66.36, H 7.29; N 5.96. IR spectrum (in CCl_4): ν_{OH} 3520–3400 cm^{-1} (broad band); ν_{NO} 1320 and 1300 cm^{-1} (split band).

4,5-Dichloro-sym-octahydroacridine (IX). With stirring, 15 ml of thionyl chloride in 15 ml of dry $CHCl_3$ was added dropwise to 6.6 g of the diol VII in 25 ml of dry chloroform, and the mixture was stirred at room temperature for 7 hr and boiled for 1 hr, after which the solvent was evaporated off and the residue was treated with dry ether. The solid residue was treated with potassium carbonate and chloroform. After evaporation of the solvent, 4.2 g (55%) of the base IX was obtained. Yellow rods with mp 147–149° C (from heptane). Found, %: C 61.09, 61.16; H 6.59, 6.45; Cl 27.52, 27.55. Calculated for $C_{13}H_{15}Cl_2N$, %: C 60.95; H 5.91; Cl 27.68. IR spectrum (in KBr): ν_{C-Cl} 700 and 675 cm^{-1}.

4-Hydroxy-sym-octahydroacridin-5-one (X). A mixture of 3.3 g of the glycol VII, 11 g of active manganese dioxide [11], and 250 ml of dry benzene was stirred at room temperature for 15 hr. The MnO_2 was filtered off and washed with C_6H_6; after evaporation in vacuum, 1.9 g (58%) of the ketoalcohol X was obtained. Orange yellow pointed plates with mp 143–144° C (from a mixture of heptane and benzene, 2 : 1). Found, %: C 72.46, 72.30; H 7.47, 7.37. Calculated for $C_{13}H_{15}NO_2$, %: C 71.86; H 6.97. IR spectrum (in KBr): ν_{CO} 1720 cm^{-1}; ν_{OH} 3340 cm^{-1}.

1,2,7,8-Tetrahydroacridine (XI). This was obtained in a similar manner to the oxide III by heating 15.3 g of the glycol VII in 153 g of polyphosphoric acid to 180° C. Yield was 8.7 g (68%). Almost odorless colorless mobile liquid; bp 86–87° C (0.01 mm); n_D^{20} 1.635; d_4^{20} 1.086. Found, %: C 85.35, 85.23; H 7.44, 7.43; N 8.04, 8.03. Calculated for $C_{13}H_{13}N$, %: C 85.19; H 7.15; N 7.64. IR spectrum (in CCl_4): 3060 and 3030 cm^{-1} (ethylene bonds). Picrate—yellow rods with mp 198° C (decomp., from a mixture of n-propanol and dioxane, 1 : 1). Found, %: N 13.52, 13.54. Calculated for $C_{13}H_{13}N \cdot C_6H_3N_3O_7$, %: N 13.53. Hydrochloride—cream-colored water-soluble rods with mp 202–203° C (decomp., from dioxane). Found, %: Cl 16.21, 15.79. Calculated for $C_{13}H_{13}N \cdot HCl$, %: Cl 16.14.

The hydrogenation of the base XI was carried out under the conditions described for the oxide III; the solvent was acetic acid. Hydrogen number: found 252.3, 245.0. Calculated for two double bonds 244.5. After the evaporation of the solvent and alkalinization, compound XII was obtained. Yield 93%. Mp 67° C. A mixture with a reference sample of sym-octahydroacridine had mp 66° C.

3-[Acetyl(ethoxycarbonyl)methyl]-1,2,3,4,7,8-hexahydroacridine (XIII). In portions, 0.3 g of Na and then 4.1 g of the tetrahydroacridine XI were added to 25 ml of acetoacetic ester. The reaction mixture was boiled for 5 hr 30 min, evaporated under reduced pressure, acidified with 20 ml of HCl (1 : 2), and extracted with ether (2 x 20 ml); the aqueous layer was made alkaline with dilute KOH solution and extracted with $CHCl_3$ (2 x 20 ml). The residue after the evaporation of the solvent was distilled in vacuum to give 4.4 g (58%) of a fraction boiling at 160–180° C (0.04–0.08 mm); n_D^{20} 1.559. Found, %: C 72.52, 72.38; H 7.43, 7.44; N 4.11, 4.08. Calculated for $C_{19}H_{23}NO_3$,

%: C 72.80; H 7.40; N 4.47. IR spectrum (in CCl_4): 1750 and 1250 cm^{-1} (ester bonds); 3060 and 3020 cm^{-1} (ethylene bond).

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