INVESTIGATION OF THE PRODUCTS OF THE REACTION OF EPICHLOROHYDRIN WITH AROMATIC AMINES

XVII.* 2-HALOMETHYL-2,3-DIHYDRO-1H-BENZ[g]INDOLES, 3-HALO-1,2,3,4-TETRAHYDROBENZO[h]QUINOLINES, AND THEIR DERIVATIVES

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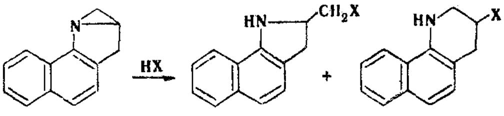
The action of hydrogen halides on 7a,8-dihydro-7H-azirino[1,2-*a*]benz[g]indole gives 2-halomethyl-2,3-dihydro-1H-benz[g]indoles and 3-halo-1,2,3,4-tetrahydrobenzo[h]quinolines, which were converted to the corresponding N-nitroso derivatives and then to the isonitroso derivatives. 2-(Benzoxymethyl)-2,3-dihydro-1H-benz[g]indole hydrohalides were obtained by heating 1-benzoyl-2-halomethyl-2,3-dihydro-1H-benz[g]indoles. The reaction of 3-halo-1,2,3,4-tetrahydrobenzo[h]quinolines with thionyl chloride at room temperature gives 3-halo-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinolines, while refluxing with thionyl chloride gives 6-chlorobenzo[h]quinoline.

In developing our previously published research [2], we have studied the reaction of 7a,8-dihydro-7H-azirino[1,2-*a*]benz[g]indole (I) with hydrogen halides. As in the case of hydrogen chloride [2], the action of hydrogen bromide or iodide on I brings about cleavage of the aziridine ring at both the $N-C_2$ and the $N-C_3$ bonds to give a mixture of 2-halomethyl-2,3-dihydro-1H-benz[g]indole (II, IV) and 3-halo-1,2,3,4-tetrahydrobenzo[h]quinoline (III, V).



I II,IV III,V

II,III X = Br; IV,V X = I

It is known that rearrangement to 6-isonitroso derivatives is peculiar to N-nitroso derivatives of the 1,2,3,4-tetrahydroquinoline series [3, 4]. In order to expand the range of application of this reaction, we nitrosated the resulting 3-halo-1,2,3,4-tetrahydrobenzo[h]quinolines and then converted the resulting 1-nitroso derivatives (VIII-X) to 3-halo-6-oximino-2,3,4,6-tetrahydrobenzo[h]quinolines (XI-XIII) by treatment with hydrochloric acid. 3-Chloro-6-(benzoximino)-2,3,4,6-tetrahydrobenzo[h]quinoline (XIV) is formed by the action of benzoyl chloride on XI. The corresponding benzoyl derivatives could not be obtained from XII or XIII under similar conditions; this can apparently be explained by the increase in the lability of the halogen atom. Thus XIII is dehalogenated even on heating in alcohol.

A previously described [5] compound that does not contain halogen – apparently 1-benzoyl-1,2(or 1,4)-dihydrobenzo[h]quinoline (XV) – was obtained by the action of alkalis on N-benzoyl derivatives of III and V.

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*See [1] for communication XVI.

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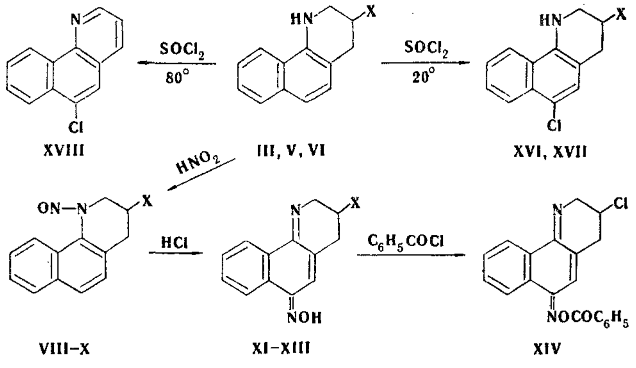
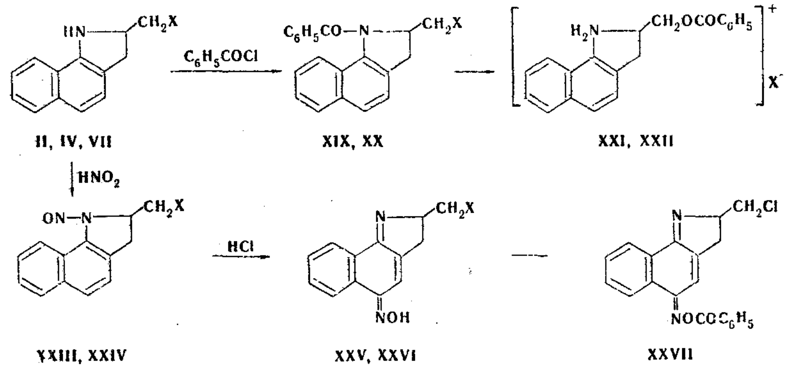
6-Chloro-1,2,3,4-tetrahydrobenzo[h]quinolines are formed by the reaction of 1,2,3,4-tetrahydrobenzo[h]quinoline derivatives with thionyl chloride [6, 7]. At the boiling point of thionyl chloride, chlorination is accompanied by aromatization of the tetrahydropyridine ring [8]. Replacement of the bromine atom by a chlorine atom also occurs in the case of 3-hydroxy-6-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline [7].



VI, VIII, XI X=Cl; III, IX, XII, XVI X=Br; V, X, XIII, XVII X=I

3-Bromo(iodo)-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XVI, XVII) is formed in the reaction of III or V with thionyl chloride at room temperature, while 6-chlorobenzo[h]quinoline (XVIII) is obtained in each case when these compounds are refluxed with thionyl chloride.

2-Halomethyl-2,3-dihydro-1H-benz[g]indoles are conveniently isolated from mixtures with 3-halo-1,2,3,4-tetrahydrobenzo[h]quinolines in the form of N-acyl derivatives. The corresponding 2-(benzoxymethyl)-2,3-dihydro-1H-benz[g]indole hydrohalides (XXI, XXII) are formed smoothly when 1-benzoyl-2-halomethyl-2,3-dihydro-1H-benz[g]indoles (XIX, XX) are heated in alcohol.



VII, XXIII, XXV X=Cl; XIX, XXI X=Br; XX, XXII, XXIV, XXVI X=I

The action of nitrous acid on IV or VII gave 1-nitroso-2-halomethyl-2,3-dihydro-1H-benz[g]indoles (XXIII, XXIV), for which rearrangement to C-nitroso derivatives is also characteristic. In analogy with 1-nitroso-1,2,3,4-tetrahydrobenzo[h]quinolines, it can be assumed that the nitroso group in this case is also shifted to the para position relative to the nitrogen atom to give 2-halomethyl-5-oximino-3,6-dihydro-2H-benz[g]indoles (XXV, XXVI). 2-Chloromethyl-5-(benzoximino)-3,6-dihydro-2H-benz[g]indole (XXVII) was obtained by the action of benzoyl chloride on XXV. Thus the method for the production of p-substituted (relative to the nitrogen atom) derivatives by isomerization of N-nitroso compounds is also extended to 5-substituted dihydrobenz[g]indoles.

EXPERIMENTAL

Mixture of Hydrobromides of 2-Bromomethyl-2,3-dihydro-1H-benz[g]indole (II) and 3-Bromo-1,2,3,4-tetrahydrobenzo[h]quinoline (III). A 100-ml sample of 30% hydrobromic acid was added with cooling and stirring to a solution of 15.7 g (0.09 mmole) of 7a,8-dihydro-7H-azirino[1,2-*a*]benz[g]indole (I) in 70 ml of ether, and the resulting precipitate was removed by filtration and washed with water and ether to give 24.0 g (81%) of a product with mp 198° (dec.). Found: Br 46.1; 46.5; N 4.1; 4.0%. $C_{13}H_{12}BrN \cdot HBr$. Calculated: Br 46.6; N 4.1%.

TABLE 1. Derivatives of 3-Halotetrahydrobenzo[h]quinolines and 2-(Halomethyl)dihydrobenzo[g]indoles

Compound	Decomp. point, °C*	Empirical formula	Found, %		Calc., %		Yield, %
			halogen	N	halogen	N	
VIII	94	$C_{13}H_{11}ClN_2O$	14,4; 14,1	11,0; 11,1	14,4	11,4	77
IX	95	$C_{13}H_{11}BrN_2O$	27,1; 27,2	9,5; 9,3	27,4	9,6	76
X	94	$C_{13}H_{11}IN_2O$	—	8,1; 8,1		8,3	53
XXIII	91	$C_{13}H_{11}ClN_2O$	14,4; 14,2	11,4; 11,2	14,4	11,4	53
XXIV	107	$C_{13}H_{11}IN_2O$	—	8,1; 8,0		8,3	53
XI	134	$C_{13}H_{11}ClN_2O$	14,1; 14,1	11,7; 11,4	14,4	11,4	75
XII	130†	$C_{13}H_{11}BrN_2O$	27,3; 27,1	9,6; 9,7	27,4	9,6	75
XIII	119	$C_{13}H_{11}IN_2O$	—	8,6; 8,7		8,3	59
XXV	182	$C_{13}H_{11}ClN_2O$	14,2; 14,4	11,3; 11,3	14,4	11,4	50
XXVI	171,5	$C_{13}H_{11}IN_2O$	—	8,1; 8,4		8,3	52

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* Heating rate 15 deg/min.

† Heating rate 30 deg/min.

Base III. This compound was obtained by shaking a mixture of the isomeric hydrobromides with distilled water in the presence of ether. The ether was removed, and the resulting crystals were removed by filtration and washed with ether to give III (38-45%) with mp 84.5-85.5° (from petroleum ether). Found: Br 30.7; 30.8; N 5.3; 5.2%. $C_{13}H_{12}BrN$. Calculated: Br 30.5; N 5.3%.

1-Benzoyl-3-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline. A mixture of 2.1 g (8 mmole) of III, 1.4 g (0.01 mole) of benzoyl chloride, 2.0 g of potassium carbonate, and 50 ml of dry ether was refluxed for 40 h. The precipitate was removed by filtration and washed with ether and water to give 2.0 g (69%) of a product with mp 184.5-185.5° (from alcohol). Found: Br 21.8; 21.8; N 3.8; 3.9%. $C_{20}H_{16}BrNO$. Calculated: Br 21.8; N 3.8%.

Mixture of Hydriodides of 2-Iodomethyl-2,3-dihydro-1H-benz[g]indole (IV) and 3-Iodo-1,2,3,4-tetrahydrobenzo[h]quinoline (V). A method similar to that used to obtain a mixture of hydrobromides of II and III was used to obtain a mixture of hydriodides of IV and V [mp 172° (dec.)] from I and hydriodic acid in 83% yield. Found: I 58.0; 59.4; N 3.4; 3.4%. $C_{13}H_{12}IN \cdot HI$. Calculated: I 58.0; N 3.2%.

2-Iodomethyl-2,3-dihydro-1H-benz[g]indole (IV). A 17.5-g (0.04 mole) sample of a mixture of hydriodides of IV and V was shaken with water in the presence of ether. The ether solution was diluted with n-hexane, and the ether was partially removed. The solution was decanted from the oily substance and held at 0° for several days (it is best to do this with crystallization centers present). The resulting crystals of IV were removed by filtration to give 4.4 g (36%) of a product with mp 49-51° (from hexane). Found: N 4.8; 4.7%. $C_{13}H_{12}IN$. Calculated: N 4.5%.

3-Iodo-1,2,3,4-tetrahydrobenzo[h]quinoline (V). After the isolation of IV, the solvents were removed, and the oily residue was treated with ether. The resulting crystals were removed by filtration and washed with a small amount of ether to give 5.5 g (44%) of a product with mp 99-100° (from petroleum ether). Found: N 4.6; 4.5%. $C_{13}N_{12}IN$. Calculated: N 4.5%.

1-Benzoyl-3-iodo-1,2,3,4-tetrahydrobenzo[h]quinoline. A mixture of 1.6 g (5 mmole) of V, 1.4 g (0.01 mole) of benzoyl chloride, 2.8 g (0.02 mole) of potassium carbonate, and 50 ml of dry ether was refluxed for 60 h to give 1.8 g (85%) of a product with mp 175-175.5° (from alcohol). Found: N 3.4; 3.5%. $C_{20}H_{16}INO$. Calculated: N 3.4%.

1-Nitroso-3-halo-1,2,3,4-tetrahydrobenzo[h]quinolines (VIII-X) and 1-Nitroso-2-halomethyl-2,3-dihydro-1H-benz[g]indoles (XXIII, XXIV) (Table 1). A solution of 0.01 mole of III (or IV-VII) in 100 ml of glacial acetic acid was diluted with 25 ml of water and cooled to −2°, and 50 ml of 0.2 M sodium nitrite cooled to 0° was added with stirring. The precipitate was removed by filtration, washed with water, and recrystallized from alcohol.

3-Halo-6-oximino-2,3,4,6-tetrahydrobenzo[h]quinolines (XI-XIII) and 2-Halomethyl-5-oximino-3,6-dihydro-2H-benz[g]indoles (XXV, XXVI) (Table 1). A solution of 1.3 ml of concentrated hydrochloric acid in 12.5 ml of alcohol was added to a solution of 5 mmole of N-nitroso derivative VIII-X, XXIII, or XXIV in 15 ml of ether−toluene (1 : 2), and the mixture was held at room temperature for 24 h. The precipitated hydrochloride of the isonitroso derivative was removed by filtration and treated in alcohol with sodium acetate. The resulting crystals were washed with alcohol and water and recrystallized from alcohol (except for XIII).

3-Chloro-6-benzoximino-2,3,4,6-tetrahydrobenzo[h]quinoline (XIV). A mixture of 1.2 g (5 mmole) of XI, 0.7 g (5 mmole) of benzoyl chloride, and 20 ml of pyridine was held at room temperature for 5 min, and the resulting precipitate was removed by filtration and washed with water and alcohol to give 1.6 g (91%) of a product with mp 130° (dec., from alcohol). Found: Cl 10.1; 9.9; N 8.2; 8.1%. $C_{20}H_{15}ClN_2O_2$. Calculated: Cl 10.1; N 8.0%.

1-Benzoyl-1,2(or 1,4)-dihydrobenzo[h]quinoline (XV). A solution of 0.7 g (2 mmole) of 1-benzoyl-3-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline and 0.1 g (2 mmole) of potassium hydroxide in 50 ml of alcohol was refluxed for 1.5 h, after which it was cooled, and the resulting crystals were removed by filtration and washed with water and alcohol to give 0.5 g (88%) of a product with mp 198-199°. No melting-point depression was observed for a mixture of this product with an authentic sample [5].

Compound XV was similarly obtained in 54% yield from 1-benzoyl-3-iodo-1,2,3,4-tetrahydrobenzo[h]quinoline.

3-Bromo-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XVI). A mixture of 0.5 g (2 mmole) of III and 2 ml of thionyl chloride was held at room temperature for 15 min, after which it was treated with ice, and the precipitate was removed by filtration and shaken with aqueous sodium carbonate solution in the presence of ether. The ether was then removed to give 0.3 g (46%) of XVI with mp 111.7-113° (from petroleum ether). Found: halogen 39.2; 39.2; N 4.5; 4.7%. $C_{13}H_{11}BrClN$. Calculated: halogen 38.9; N 4.7%.

3-Iodo-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XVII). This compound was similarly obtained in 37% yield from V and had mp 119.5-120.5° (from petroleum ether). Found: halogen 47.2; 47.2; N 4.1; 4.2%. $C_{13}H_{11}ClIN$. Calculated: halogen 47.3; N 4.1%.

6-Chlorobenzo[h]quinoline (XVIII). A mixture of 1.6 g (6 mmole) of III and 6 ml of thionyl chloride was refluxed for 1.5 h, after which it was decomposed with ice, and the precipitate was removed by filtration and washed with water. Compound XVIII was treated with sodium carbonate and recrystallized from alcohol to give 0.5 g (37%) of a product with mp 98-99°. No melting-point depression was observed for a mixture of this product with an authentic sample [8].

Compound XVIII was similarly obtained in 27% yield by refluxing V with thionyl chloride.

1-Benzoyl-2-bromomethyl-2,3-dihydro-1H-benz[g]indole (XIX). A 13.7-g (0.04 mole) sample of a mixture of hydrobromides of II and III, which was obtained by reaction of I with hydrobromic acid, was shaken with water in the presence of ether. The ether solution was washed with water and dried with magnesium sulfate. A 4.2-g (0.03 mole) sample of benzoyl chloride and 5.6 g (0.04 mole) of potassium carbonate were added to the dry ether solution, and the mixture was shaken at room temperature for 10 h. The solid was removed by filtration and washed with ether and water to give 4.8 g (33%) of a product with mp 162.5-163.5° [from chloroform–alcohol (1 : 1)]. Found: Br 22.1; 22.2; N 3.9; 3.8%. $C_{20}H_{16}BrNO$. Calculated: Br 21.8; N 3.8%.

1-Benzoyl-2-iodomethyl-2,3-dihydro-1H-benz[g]indoline (XX). This compound [mp 150.5-151.5° from chloroform–alcohol (1 : 1)] was obtained in 39% yield as in the preceding experiment by treatment of a mixture of IV and V with benzoyl chloride at room temperature for 40 h. Found: N 3.4; 3.4%. $C_{20}H_{16}INO$. Calculated: N 3.4%.

2-(Benzoxymethyl)-2,3-dihydro-1H-benz[g]indole Hydrobromide (XXI). A solution of 2.2 g (6 mmole) of XIX in 30 ml of alcohol was refluxed for 5-10 min, after which it was cooled, and the resulting crystals were removed by filtration to give 2.1 g (91%) of a product with mp 212-213.5° (from alcohol). Found: N 3.8; 3.8%. $C_{20}H_{17}NO_2 \cdot HBr$. Calculated: N 3.6%. Treatment with sodium acetate gave 2-(benzoxymethyl)-benz[g]indoline, which did not depress the melting point of an authentic sample [2].

2-(Benzoxymethyl)-2,3-dihydro-1H-benz[g]indole Hydriodide (XXII). This compound was similarly obtained from XX in 90% yield and had mp 213.5-214.5° (from alcohol). Found: C 55.7; 55.9; H 4.2; 4.4; N 2.9; 3.0%. $C_{20}H_{17}NO_2 \cdot HI$. Calculated: C 55.7; H 4.2; N 3.3%.

2-Chloromethyl-5-(benzoylisonitrosooximino)-3,6-dihydro-2H-benz[g]indole (XXVII). A mixture of 0.5 g (2 mmole) of XXV, 0.3 g (2 mmole) of benzoyl chloride, and 20 ml of pyridine was held at room temperature for 12 h, and XXVII was isolated by a known method to give 0.6 g (86%) of a product with mp 151° (dec., from alcohol). Found: Cl 10.1; 10.2; N 8.1; 8.0%. $C_{20}H_{15}ClN_2O_2$. Calculated: Cl 10.1; N 8.0%.

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