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1,9,8-CYCLIZATION OF 1,8-DISUBSTITUTED ANTHRAQUINONES. 12H-BENZO[m,n]CHROMENO[2,3,4-k,l]ACRIDINE DERIVATIVES

S. V. Reznichenko, V. P. Shapkin, and S. I. Popov

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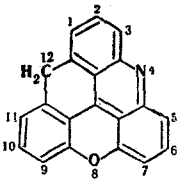
The cyclization of 1-(2,5-dihalophenylamino)-8-hydroxyanthraquinones or the corresponding 8-methoxycompounds in concentrated sulfuric acid has given derivatives of a new hexanuclear heterocyclic system — 12H-benzo[m,n]chromeno[2,3,4-k,l]acridine. It has been shown that the double cyclization takes place initially through the closure of the pyridine ring with the formation of 9H-napth[3,2,1-k,l]acridine, the product of 1,9-cyclization. Under the reaction conditions the latter undergoes intramolecular aroxylation with the formation of a pyran ring under atypical conditions.

In preceding papers we have described some 1,9,8-cyclization reactions of 1,8-disubstituted anthraquinones as a result of which various new heterocycles have been obtained: anthranaphthyridine [1], and pyrano-, pyrrolo-, and furanopyridoanthrone [2, 3]. In the majority of cases it was impossible to isolate monocyclized derivatives because of the spatial propinquity of the substituents that arose after the formation of the first ring.

Developing these investigations we have made an attempt to synthesize derivatives of a new hexanuclear heterocyclic system of pyranokeramidonine (12H-benzo[m,n]chromeno[2,3,4-k,l]-acridine) (I).



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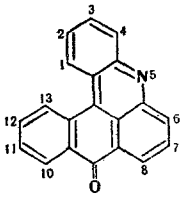
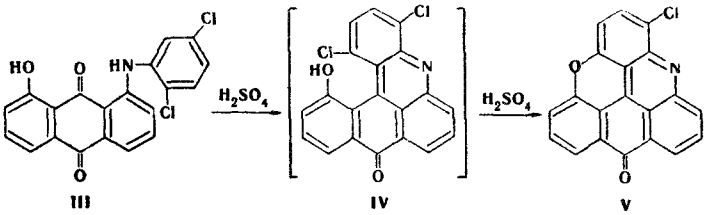


II

For this purpose we synthesized 1-(2,5-dichloroanilino)-8-hydroxyanthraquinone (III). It is known that 1-phenylaminoanthraquinone and its derivatives cyclize in sulfuric acid with the formation of keramidonine (9H-napth[3,2,1-k,l]acridin-9-one) (II) [4, 5]. The cyclization of the hydroxy derivative (III) should give 1,4-dichloro-13-hydroxykeramidonine (IV), the dehydrochlorination of which could lead to the pyranokeramidonine derivative (V). The chlorine atom in the ortho position to the nitrogen atom in compound (III) ensures the unambiguous direction of cyclization at the only free ortho position.

When compound (III) was heated in 87% H_2SO_4 the pyranokeramidonine (V) was formed directly. No intermediate formation of the hydroxykeramidonine (IV) was observed.



III IV V

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 519-523, April, 1980. Original article submitted June 7, 1979.

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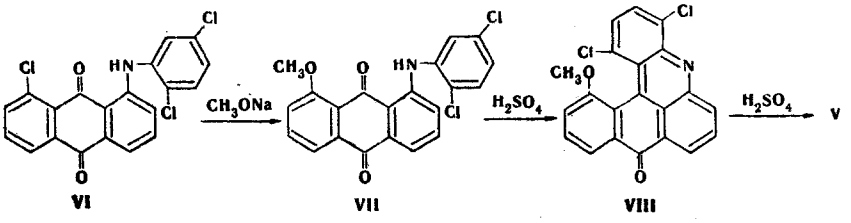
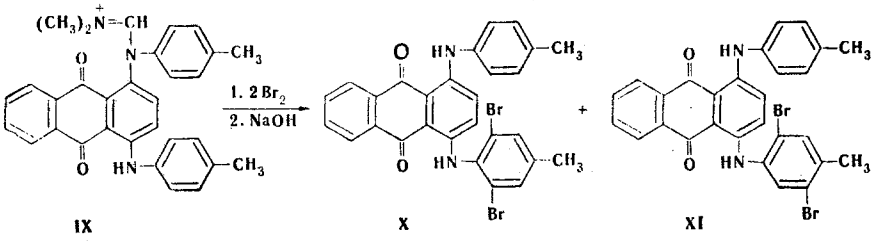
It is obvious that the favorable steric factors arising in the intermediate compound (IV) lead to intramolecular aroxylation under atypical conditions. It was possible to isolate the keramidonine formed as an intermediate when 1-(2,5-dichloroanilino)-8-methoxyanthraquinone (VII), which was obtained from 1-(2,5-dichloroanilino)-8-chloroanthraquinone (VI), was used. The cyclization of the methoxy derivative (VII) in 70% H_2SO_4 at a temperature not exceeding 150°C formed the dichloro-13-methoxykeramidonine (VIII), which, in its turn, when the methoxy group was saponified under more severe conditions cyclized to the pyranokeramidonine (V).



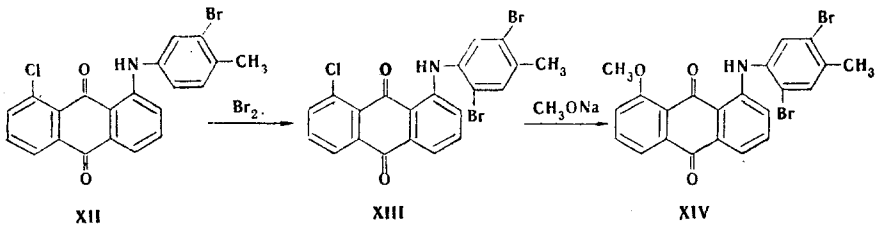
We have shown previously [6] that the bromination of the dimethylformamidinium salt of 1,4-di(4-methylanilino)anthraquinone (IX) in 87% H_2SO_4 followed by hydrolysis of the amidinium group forms exclusively 1-(2,6-dibromo-4-methylanilino)-4-(4-methylanilino)anthraquinone (X) — the 2,6- isomer.



However, if bromination is performed in 94% H_2SO_4, a decrease in the rate of introduction of the second bromine atom is observed and, together with the 2,6-isomer (X), the dibromo derivative (XI) is formed in approximately equal amount. The change in the orientation of the bromine atom takes place in the second stage of the reaction, since bromination by the first mole of bromine leads only to a monobromo derivative with the bromine in the ortho position to the nitrogen atom.

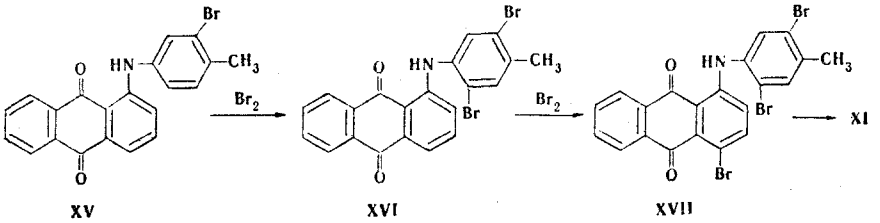
The formation of the 2,5-isomer (XI) appeared the most probable, although the possibility of obtaining the 2,3-isomer does not contradict the rules of orientation. Since the independent synthesis of the isomer (XI) was found to be difficult, the detection of the pyranokeramidonine forming reaction could prove to be convenient for the establishment of its structure since only in the case of the 2,5-isomer should it take place with the closure of the pyran ring and in the case of the 2,3-isomer it should stop at the dibromokeramidonine stage.

With this aim we synthesized the presumable 1-(2,5-dibromo-4-methylanilino)-8-methoxyanthraquinone (XIV) by the successive bromination of 1-(3-bromo-4-methylanilino)-8-chloroanthraquinone (XII) to 1-(2,5-dibromo-4-methylanilino)-8-chloroanthraquinone (XIII) and the replacement of the chlorine atom by a methoxy group.

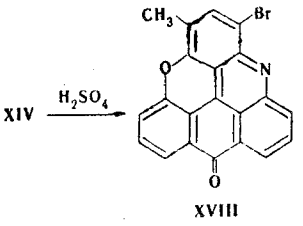


To confirm that the bromine atoms in compound (XIV) were present in the totyl residue precisely in the same positions as in the isomer (XI) under investigation, we obtained 1-(2,5-dibromo-4-methylanilino)anthraquinone (XVI) by the bromination of 1-(3-bromo-4-methyl-

anilino)anthraquinone (XV). On further bromination, compound (XVI) formed the tribromo derivative (XVII). On reaction with p-toluidine, compound (XVII) gave the isomer (XI).



When the methoxydibromo derivative (XIV) was heated in 87% H_2SO_4 the corresponding pyranokeramidonine (XVIII) was obtained as the sole reaction product, which confirms the presence of the bromine atoms in compound (XI) in the 2,5 positions.



The derivatives (V) and (XVIII) of the new heterocyclic compound pyranokeranidonine that were obtained are high-melting blue substances (in the crystalline state) sparingly soluble in the usual solvents. As compared with the keramidonines (460-480 nm) the maximum of the main absorption band of their solutions are shifted bathochromically to 570 and 580 nm, respectively.

EXPERIMENTAL

UV spectra were taken on a Specord UV-Vis spectrometer (GDR) in DMFA. The substances were separated by column chromatography on silica gel L 40/100. The course of the reactions was monitored and the purity of the compounds was checked on Solufol UV-254 plates. Melting points were determined on a Boetius heated microstage (GDR).

1-Chloro-8-(2,5-dichloroanilino)anthraquinone (VI). A mixture of 8.31 g (30 mmole) of 1,8-dichloroanthraquinone, 20 g (120 mmole) of 2,5-dichloroaniline, 0.01 g (0.055 mmole) of $(AcO)_2Cu$, and 2 g (20 mmole) of anhydrous AcOK was stirred at 140°C. The reaction was complete after 4 h, when the formation of the disubstituted derivative began. The mixture was cooled to 70°C and poured into 100 ml of isopropanol, and the resulting precipitate was filtered off and was washed with 40% ethanol, with 1% HCl, and with water. The substance was chromatographed in toluene. The red zone was collected and this yielded 2.07 g (17.15%) of compound (VI) with mp 202-203°C (from toluene). Found: Cl 26.2%. $C_{20}H_{10}Cl_3NO_2$. Calculated Cl 26.4%. The amount of unchanged 1,8-dichloroanthraquinone recovered was 5 g.

1-(2,5-Dichloroanilino)-8-methoxyanthraquinone (VII). At 55°C, 5 ml of a solution of sodium methanolate in methanol (5 g of metallic sodium in 50 ml of methanol) was added to a solution of 0.4 g (1 mmole) of compound (VI) in 25 ml of toluene, the mixture was stirred at 83-85°C for 40 min, the solvents were distilled off under vacuum, 50 ml of 5% HCl was added, and the solid was filtered off and washed with water. This gave 0.36 g (94.7%) of compound (VII) with mp 214-215°C (from toluene). Found: Cl 18.0%. $C_{21}H_{13}Cl_2NO_3$. Calculated: Cl 17.8%.

1-(2,5-Dichloroanilino)-8-hydroxyanthraquinone (III). A mixture of 0.5 g (1.3 mmole) of compound (VII), 50 ml of AcOH, and 12 ml of HBr (d_4^{20} 1.49) was boiled at 110-112°C for 3 h, after which it was cooled and 10 ml of water was added. The resulting suspension was filtered and the residue was washed with water. This gave 0.47 g (97.9%) of compound (III) with mp 247-248°C (from $CHCl_3$). Found: C 62.4; H 3.0; Cl 18.5; N 3.6%. $C_{20}H_{11}Cl_2NO_3$. Calculated: C 62.5; H 2.9; Cl 18.5; N 3.7%.

1,4-Dichloro-13-methoxynaphth[3,2,1-k,l]acridin-9-one (VIII). A solution of 0.79 g (2 mmole) of compound (VII) in 80 ml of 70% H_2SO_4 was stirred at 130°C for 1 h and at 140°C for

1 h 30 min, and was then cooled and poured into 250 ml of ice water, and the resulting precipitate was filtered off and washed with water. Then it was chromatographed in chloroform. First the red zone was collected, giving 0.07 g (9.2%) of the hydroxy derivative (III). Then the main orange zone was eluted, giving 0.57 g (76%) of compound (VIII) with mp 221-223°C from ($CHCl_3$). Found: C 66.4; H 2.9; Cl 18.8; N 3.6%. $C_{21}H_{11}Cl_2NO_2$. Calculated: C 66.3; H 2.9; Cl 18.7; N 3.7%.

5-Chloro-12-H-benzo[m,n]chromeno[2,3,4-k,l]acridin-12-one (V). A. A mixture of 0.4 g (1 mmole) of compound (III) and 5 ml of 87% H_2SO_4 was stirred at 150°C for 2 h and was then cooled and poured into 50 ml of ice water, and the precipitate was filtered off and washed with water. This gave 0.3 g (88.2%) of compound (V) with mp >360°C (from DMFA). UV spectrum, λ_{max}, nm (log ε): 371 (3.53), 392 (3.38), 541 (3.85), 571 (381). Found: C 72.6; H 2.6; Cl 10.5; N 4.6%. $C_{20}H_8ClNO_2$. Calculated: C 72.8; H 2.5; Cl 10.7; N 4.3%.

B. A mixture of 0.4 g (1.1 mmole) of compound (VIII) and 4 ml of 87% H_2SO_4 was stirred at 180°C for 2 h and was then cooled and the product was isolated as in A. This gave 0.32 g (91.4%) of compound (V) with mp >360°C (from DMFA).

C. A mixture of 0.35 g (0.88 mmole) of compound (VII) and 5 ml of 87% H_2SO_4 was stirred at 180°C for 2 h and was then cooled and the product was isolated as in A. This gave 0.23 g (78%) of compound (V), mp >360°C (from DMFA). The compounds obtained by methods A, B, and C had identical IR and UV spectra.

1-(2,5-Dibromo-4-methylanilino)-4-(4-methylanilino)anthraquinone (XI). A. A mixture of 1.02 g (2 mmole) of N,N-dimethyl-N'-[4-(4-methylanilino)anthraquinon-1-yl]-N'-(4-methylphenyl)amidinium chloride [7] (IX), 10 ml of 94% H_2SO_4, and 0.21 ml (8 mmole) of Br_2 was stirred at 20°C for 2 weeks and it was then poured into 75 ml of ice water and the resulting precipitate was filtered off, washed with 50 ml of 5% HCl, and dried. The salt was hydrolyzed by boiling in 20 ml of 2% ethanolic NaOH and, after cooling, the solid matter was filtered off and washed with water. Then it was chromatographed in CCl_4, the first green zone being collected and yielding 0.59 g (51.4%) of compound (XI) with mp 247-248.5°C (from CCl_4). Found: C 58.3; H 3.5; Br 27.7; N 4.7%. $C_{28}H_{20}Br_2N_2O_2$. Calculated: C 58.4; H 3.5; Br 27.7; N 4.9%. The second, less mobile, blue-green zone yielded 0.56 g (48.6%) of compound (X) with mp 258-259°C (from isopropanol). Found: C 58.3; H 3.5; Br 27.8; N 4.82%. $C_{28}H_{20}Br_2N_2O_2$.

B. A mixture of 0.4 g (0.73 mmole) of compound (XVII), 4 g (37 mmole) of 4-methylaniline, 0.3 g (3.1 mmole) of anhydrous AcOK, and 0.01 g (0.055 mmole) of $(AcO)_2Cu$ was stirred at 120°C for 1 h and then at 150°C for 40 min, after which it was cooled to 50°C, treated with 20 ml of methanol, and filtered, and the residue was washed with 1% HCl and with water. Then it was chromatographed in CCl_4 and the main green zone was collected to give 0.15 g (35.7%) of compound (XI) with mp 247-249°C (from CCl_4).

The substances obtained by methods A and B melted with no depression of the melting point, and their IR spectra were identical.

1-(3-Bromo-4-methylanilino)-8-chloroanthraquinone (XII). A mixture of 1.39 g (5 mmole) of 1,8-dichloroanthraquinone, 10 g (54 mmole) of 3-bromo-p-toluidine, 0.3 g (3.1 mmole) of anhydrous AcOK, and 0.01 g (0.055 mmole) of $(AcO)_2Cu$ was stirred at 150°C for 4 h, cooled to 70°C, and treated with 50 ml of isopropanol, and the solid matter was filtered off and was washed with 50% ethanol acidified with concentrated HCl and with water. Then it was chromatographed from toluene, the main red zone being collected to give 1.22 g (57%) of compound (XII) with mp 168-170°C (from toluene). Found: Br 18.7; Cl 8.5%. $C_{21}H_{13}BrClNO_2$. Calculated: Br 18.7; Cl 8.3%.

1-(2,5-Dibromo-4-methylaniline)-8-chloroanthraquinone (XIII). A mixture of 1.6 g (3.8 mmole) of compound (XII), 20 ml of $CHCl_3$, and 0.02 ml (0.78 mmole) of Br_2 was stirred at 20°C for 48 h. Then the solvent was evaporated under vacuum to dryness and the residue was chromatographed in toluene, the red zone being collected and yielding 1.53 g (80.5%) of compound (XIII) with mp 243-245°C (from $CHCl_3$). Found: Br 31.4; Cl 7.0%. $C_{21}H_{12}Br_2ClNO_2$. Calculated: Br 31.6; Cl 7.0%.

1-(2,5-Dibromo-4-methylanilino)-8-methoxyanthroquinone (XIV). A yield of 0.34 g (89.5%) of compound (XIV) was obtained from 0.38 g (0.75 mmole) of 1-(2,5-dibromo-4-methylanilino)-8-chloroanthraquinone (XIII) in the same way as for compound (VII). mp 242-243°C (from $CHCl_3$) Found: C 53.0; H 3.1; Br 31.9; N 2.6%. $C_{22}H_{15}Br_2NO_3$. Calculated: C 52.7; H 3.0; Br 31.9; N 2.8%.

5-Bromo-7-methyl-12H-benzo[m,n]chromeno[2,3,4-k,l]acridin-12-one (XVIII). A yield of 0.2 g (75.6%) of compound (XVIII) was obtained from 0.34 g (0.68 mmole) of 1-(2,5-dibromo-4-methylanilino)-8-methoxyanthraquinone (XIV) in a similar manner to compound (V) by method C. mp >360°C (from DMFA). UV spectrum, λ_{max}, nm: 381, 402, 551, 581 nm. Found: C 64.9; H 2.6; Br 20.5; N 3.6%. $C_{21}H_{10}BrNO_2$. Calculated: C 65.0; H 2.6; Br 20.6; N 3.6%.

1-(3-Bromo-4-methylanilino)anthraquinone (XV). A mixture of 2.43 g (10 mmole) of 1-chloroanthraquinone, 10 mg (540 mmole) of 3-bromo-p-toluidine, 0.25 g (2.5 mmole) of anhydrous AcOK, and 0.02 g (0.11 mmole) of $(AcO)_2Cu$ was stirred at 150°C for 3 h and it was then cooled, and the product was isolated and chromatographed in a similar manner to compound (XII). This gave 2.44 g (62.1%) of compound (XV) with mp 217-218°C (from isopropanol). Found: Br 20.5%. $C_{21}H_{14}BrNO_2$. Calculated: Br 20.4%.

1-(2,5-Dibromo-4-methylanilino)anthraquinone (XVI). A mixture of 0.08 g (0.2 mmole) of compound (XV) and 50 ml of AcOH was heated to 80°C and then a solution of 0.015 ml (0.6 mmole) of Br_2 in 2 ml of AcOH was added and the reaction mixture was stirred for 30 min, cooled, diluted with 10 ml of water, and treated with 0.1 g of Na_2SO_3, and the precipitate was filtered off and washed with water. Then it was chromatographed in toluene, the second red zone being collected and yielding 0.05 g (52.1%) of compound (XVI) with mp 237-239°C (from toluene). Found: Br 34.0%. $C_{21}H_{13}Br_2NO_2$. Calculated: Br 33.9%. The substance isolated from the first orange-red zone was identical with compound (XVII).

1-Bromo-4-(2,5-dibromo-4-methylanilino)anthraquinone (XVII). A mixture of 0.39 g (1 mmole) of compound (XV), 60 ml of AcOH, 0.75 g (7.6 mmole) of anhydrous AcOK, and 0.15 ml (6.8 mmole) of Br_2 was boiled for 2 h, after which it was cooled, diluted with 50 ml of water, and treated with 0.2 g of Na_2SO_3, and the precipitate was filtered off and was washed with 20 ml of 80% AcOH and with water. After chromatography in toluene, 0.3 g (54.54%) of compound (XVII) was obtained with mp 222-224°C (from toluene). Found: Br 43.4%. $C_{21}H_{12}Br_3NO_2$. Calculated: Br 43.6%.

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