QUINONES

L.* CONDENSATION OF 2,3-DICHLORO-p-BENZOQUINONE WITH N-ALKYL(ARYL)-β-AMINOCROTONIC ACID ESTERS

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UDC 547.756'728.1:542.953

It is shown that the condensation of 2,3-dichloro-p-benzoquinone with N-alkyl(aryl)-β-aminocrotonic acid esters leads, depending on the conditions and the nature of the substituent attached to the nitrogen of the aminocrotonic ester, either to substituted dichlorohydroquinones or to 5-hydroxy-6,7-dichloroindole derivatives. The latter are oxidized by nitric acid to the corresponding o-quinones.

Continuing our investigations of the condensation of 2,3-dichloro-p-benzoquinone with aminocrotonic ester and substituted β-aminocrotonic esters [1, 2], we have found that, depending on the conditions and particularly the nature of the substituent attached to the nitrogen of the aminocrotonic ester, this reaction leads either to indole derivatives I-VII or to substituted dichlorohydroquinones VIII-XI, which are not intermediates in the synthesis of 5-hydroxyindole derivatives.

According to our observations, they are converted in almost quantitative yields, apparently via adduct C, to 5-hydroxybenzofuran derivative XII on brief heating in acetic acid or alcohol. The formation of 5-hydroxyindole derivatives can be explained only by splitting out of water from adduct B. The other mechanism for the formation of 5-hydroxyindoles, which consists in the cyclization of substituted dichlorohydroquinones with the evolution of water under mild conditions and without a catalyst, does not have analogies. Thus, the occurrence of the Nenitzescu reaction in the direction of the synthesis of indole derivatives or substituted dichlorohydroquinones depends on the tendency of adducts A for isomerization. 5-Hydroxyindole derivatives are obtained when the process for conversion of adducts A to adducts B competes with the isomerization of adducts A to substituted dichlorohydroquinones. A confirmation of the mechanism that we have proposed for the Nenitzescu reaction is the fact of the isolation of adducts during the reaction of p-quinones with enamines [3-5].

The major products of the condensation of 2,3-dichloro-p-benzoquinone with N-alkylaminocrotonic esters are substituted dichlorohydroquinones VIII-XI rather than adducts C. This is confirmed by the presence in the PMR spectra of a signal at 1.7 ppm from the protons of the CH_3 group attached to the double bond and by the absence of a singlet at 4.0-5.0 ppm, which was previously observed for compounds of the type of adduct C; an absorption band at 1640 cm^{-1}, which indicates conjugation of the carbonyl group with the vinylamine residue, is observed in the IR spectra of the derivatives obtained. 1-Alkyl-5-hydroxyindoles I-IV could be obtained in the mixture with corresponding dichlorohydroquinones VIII-XI only by the addition of N-alkylaminocrotonic esters to excess 2,3-dichloro-p-benzoquinone.

The reaction of 2,3-dichloro-p-benzoquinone with N-aryl-β-aminocrotonic esters yielded 1-aryl-5-hydroxyindoles V-VII along with substituted dichlorohydroquinones. The latter could not be isolated in pure form. However, their formation is confirmed by the fact that the action of acetic acid on the mother liquors

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*See [8] for communication XLIX.

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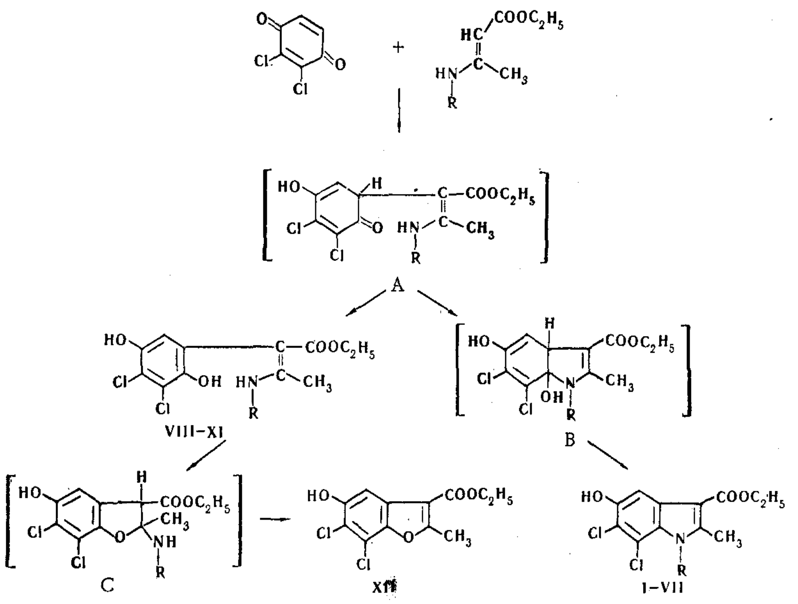
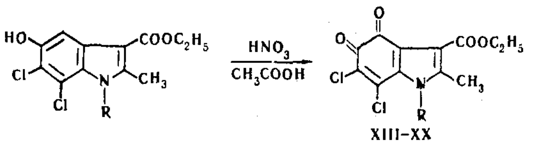
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 335-338, March, 1971. Original article submitted September 29, 1969.



I $R=CH_3$; II C_3H_7; III C_4H_9; IV $CH_2C_6H_5$; V C_6H_5; VI $p\text{-}CH_3C_6H_4$; VII $p\text{-}CH_3OC_6H_4$; VIII CH_3;
IX C_3H_7; X C_4H_9 XI $CH_2C_6H_5$

obtained after isolation of 1-arylindole derivatives V-VII leads to the formation of the corresponding 5-hydroxybenzofuran (XII). The structures of 5-hydroxyindoles I-VII were proved by the presence in the IR spectra of absorption bands at 1650 cm^{-1} (C=O) and 3280 cm^{-1} (OH) and two fundamental absorption bands with λ_{max} 245-247 and 290-293 nm in the UV spectra; the structure of 5-hydroxybenzofuran derivative XII was proved by comparing it with a sample obtained by another method [6].

A study of the transformations of the derivatives that we obtained is of definite interest. o-Quinones XIII-XX are formed in high yields by oxidation of 5-hydroxy-6,7-dichloroindoles I-VII and 2-methyl-3-carbethoxy-5-hydroxy-6,7-dichloroindole [2] with nitric acid according to the method in [7]:



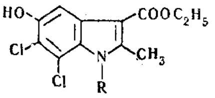
XIII R=H; XIV CH_3; XV C_3H_7; XVI C_4H_9; XVII $CH_2C_6H_5$;
XVIII C_6H_5; XIX $p\text{-}CH_3C_6H_4$; XX $p\text{-}CH_3OC_6H_4$

The fact that XIII-XX belong to the o-quinone class is confirmed by the absence of an absorption band with λ_{max} 290-293 nm, which is present in the starting 5-hydroxyindoles, and by the appearance of new absorption bands with λ_{max} 347-350 nm and 528-550 nm in the UV spectra as well as by the absence of an absorption band at 3200-3700 cm^{-1} in the IR spectra.

EXPERIMENTAL

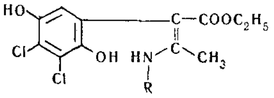
1,2-Dimethyl-3-carbethoxy-5-hydroxy-6,7-dichloroindole (I). A solution of 4.2 g (0.03 mole) of N-methylaminocrotonic ester in 50 ml of dichloroethane was added in the course of 15 min to a refluxing solution of 5.4 g (0.03 mole) of 2,3-dichloro-p-benzoquinone in 50 ml of dichloroethane with simultaneous distillation of the azeotrope (80-90 ml). The reaction mixture was allowed to stand overnight in a refrigerator, and the resulting precipitate was filtered, washed on the filter with carbon tetrachloride, and treated with 100 ml of methanol at 18-20°. The precipitate was then filtered and air dried to give 0.65 g (7.1%) of a product with mp 240-241.5° (from dioxane). Found %: C 51.5; H 4.4; Cl 23.1; N 4.7. $C_{13}H_{13}Cl_2NO_3$. Calculated %: C 51.7; H 4.3; Cl 23.5; N 4.6. Data on 5-hydroxyindoles II and III, similarly obtained, are presented in Table 1. The methanol mother liquor was vacuum evaporated to give 6.15 g (63%) of ethyl β-methylamino-α-(2,5-dihydroxy-3,4-dichlorophenyl)crotonate with mp 142-144° (decomp., from toluene). Found %: C 49.1; H 5.0; Cl 21.9; N 4.3. $C_{13}H_{15}Cl_2NO_4$. Calculated %: C 48.8; H 4.7; Cl 22.2; N 4.4.

TABLE 1



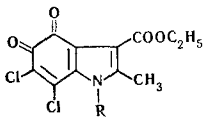
Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
II	206—207	$C_{15}H_{17}Cl_2NO_3$	54,4	5,3	21,3	4,5	54,6	5,2	21,5	4,3	7,0
III	169—170	$C_{16}H_{19}Cl_2NO_3$	55,7	5,6	20,9	4,1	55,8	5,6	20,6	4,1	4,7
IV	203—204	$C_{19}H_{17}Cl_2NO_3$	60,6	4,7	18,8	3,7	60,3	4,5	18,8	3,7	8,5
V	191,5—192,5	$C_{18}H_{15}Cl_2NO_3$	59,4	4,2	19,3	3,8	59,4	4,2	19,5	3,8	12,5
VII	213—214	$C_{19}H_{17}Cl_2NO_4$	58,0	4,3	18,0	3,5	57,9	4,3	18,0	3,6	11,5

TABLE 2



Compound	mp, °C (decomp.)	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
IX	136—137	$C_{15}H_{19}Cl_2NO_4$	51,7	5,6	20,8	4,1	51,8	5,5	20,4	4,0	57
X	119—120	$C_{16}H_{21}Cl_2NO_4$	53,1	5,9	19,9	4,0	53,1	5,9	19,6	3,9	71
XI	114—115	$C_{19}H_{19}Cl_2NO_4$	57,7	4,9	17,9	3,7	57,6	4,8	17,9	3,5	50

TABLE 3



Compound	mp, °C (decomp.)	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
XIII	248—250	$C_{12}H_9Cl_2NO_4$	47,5	3.0	23,2	4,9	47,7	3,0	23,5	4,6	88
XV	130—132	$C_{15}H_{15}Cl_2NO_4$	52,2	4,5	20,7	4,2	52,4	4,4	20,6	4,1	92
XVI	128—129,5	$C_{16}H_{17}Cl_2NO_4$	53,9	4,6	19,8	4,0	53,7	4,8	19,8	3,9	97
XVII	139—140	$C_{19}H_{15}Cl_2NO_4$	58,1	3,7	17,9	3,5	58,2	3,9	18,1	3,6	90
XVIII	209,5—211	$C_{18}H_{13}Cl_2NO_4$	57,8	3,6	18,7	3,6	57,4	3,5	18,8	3,7	94
XIX	236—237	$C_{19}H_{15}Cl_2NO_4$	57,8	3,8	18,0	3,9	58,2	3,9	18,1	3,6	90
XX	215—216	$C_{19}H_{15}Cl_2NO_5$	55,7	3,5	17,1	3,4	55,9	3,7	17,4	3,4	84

1-(p-Tolyl)-2-methyl-3-carbethoxy-5-hydroxy-6,7-dichloroindole (VI). This experiment was carried out under conditions which were similar to those used to obtain I, but the order of addition of the reagents was changed. N-(p-Tolylamino)crotonic ester, obtained from 3.4 g (0.03 mole) of p-toluidine and 4.4 g (0.03 mole) of acetoacetic ester in 60 ml of dichloroethane, and a solution of 5.4 g (0.03 mole) of 2,3-dichloro-p-benzoquinone in 50 ml of dichloroethane were used for the reaction. The reaction product was filtered, washed with carbon tetrachloride, and air dried to give 1.9 g (16.5%) of a product with mp 233.5-234.5° (from methanol–dioxane). Found %: C 60.2; H 4.6; Cl 18.8; N 3.9. $C_{19}H_{17}Cl_2NO_3$. Calculated %: C 60.3; H 4.5; Cl 18.8; N 3.7. Data on 5-hydroxyindoles V and VII, similarly obtained, are presented in Table 1. The mother liquor after isolation of VI was refluxed for 1 h with 20 ml of acetic acid, the mixture was allowed to stand overnight in the refrigerator, and the resulting precipitate was filtered, washed with carbon tetrachloride, and air dried to give 1.05 g of XII with mp 203.5-205° (from methanol) (mp 202.5° [6]). A sample of this product did not depress the melting point of a sample of XII obtained via the method in [6].

Ethyl β-Methylamino-α-(2,5-dihydroxy-3,4-dichlorophenyl)crotonate (VIII). This experiment was carried out under the conditions used to obtain VI using 8.4 g (0.06 mole) of N-methylaminocrotonic ester in 15 ml of dichloroethane and 10.8 g (0.06 mole) of 2,3-dichloro-p-benzoquinone in 100 ml of dichloroethane to give 15.3 g (77%) of VIII with mp 142-144° (decomp., from toluene). Found %: C 49.1; H 4.7; Cl 22.1; N 4.3. $C_{13}H_{15}Cl_2NO_4$. Calculated %: C 48.8; H 4.7; Cl 22.2; N 4.4. Data on substituted dichlorohydroquinones IX-XI, similarly obtained, are presented in Table 2.

2-Methyl-3-carbethoxy-5-hydroxy-6,7-dichlorobenzofuran (XII). A mixture of 3.2 g (0.01 mole) of VIII was refluxed for 5 min with 20 ml of acetic acid. The mixture was cooled, and the resulting precipitate was filtered, washed with acetic acid and water, and air dried to give 2.7 g (94%) of XII with mp 205-206° (from methanol). Found %: C 49.9; H 3.3; Cl 24.4. $C_{12}H_{10}Cl_2O_4$. Calculated %: C 49.8; H 3.5; Cl 24.5. A sample of this product did not depress the melting point of a sample of XII obtained via the method in [6].

1,2-Dimethyl-2-carbethoxy-4,5-dioxo-6,7-dichloroindole (XIV). A solution of 0.4 ml [0.54 g (0.009 mole)] of nitric acid (sp. gr. 1.35) in 5 ml of acetic acid was added dropwise in the course of 30 min to a suspension of 1.0 g (0.003 mole) of I in 20 ml of acetic acid. The reaction mixture was held at 15-20° with stirring for 1.5 h. The resulting precipitate was filtered. The mother liquor was diluted with three volumes of water, and the resulting precipitate was filtered and added to the major mass to give 1 g (95%) of XIV with mp 181.5-183° (decomp., from ethyl acetate). Found %: C 49.7; H 3.5; Cl 22.7; N 4.6. $C_{13}H_{11}Cl_2NO_4$. Calculated %: C 49.4; H 3.5; Cl 22.5; N 4.4. Data on o-quinones XIII and XV-XX, similarly obtained, are presented in Table 3.

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