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REACTION OF 4H-1,3-BENZOXAZINE-4-ONIUM SALTS WITH C-NUCLEOPHILIC AROMATIC COMPOUNDS

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A method is proposed for the synthesis of 2-(4-dialkylaminophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-ones and diindolylcyaninemethanes by reaction of 4H-1,3-benzoxazin-4-onium salts with N,N-dialkylanilines and indole.

It follows from the results of a quantum-mechanical calculation of the oxazinium cation* that the positive charge in salts I is localized on the $C_{(2)}$, $C_{(4)}$, and $C_{(6)}$ atoms of the heteroring and that the highest charge is concentrated on the meso-carbon atom. According to the calculation, attack by nucleophilic reagents should be directed to the 2 position of the heteroring; this is actually observed in the reactions of benzoxazinonium salts with activated homo- and heteroaromatic compounds.

It has been shown that, depending on the conditions, benzoxazinonium salts react with dialkylanilines in different ways. For example, dimethylaniline reacts like a tertiary amine at room temperature, and equilibrium $I \rightleftharpoons III$, which, however, is shifted to the left when the mixture is refluxed, since under these conditions dimethylanilines acts as a C-nucleophilic arylating agent, is established in the reaction mixture as a consequence of this. The previously unknown 2-(4-dialkylaminophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-ones (IIa-f, see Table 1) were obtained by this method by refluxing 4H-1,3-benzoxazin-4-onium perchlorates (I) [1] with N,N-dialkylaniline in acetic acid or nitromethane. The dihydrobenzoxazinone salts formed in some cases can be isolated.

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* The quantum-mechanical calculation was performed by V. I. Minkin and R. M. Minyaev.

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TABLE 1. 2,3-Dihydro-4H-1,3-benzoxazin-4-ones (II) and Diindolylcyaninemethanes (IV)

Compound	R	R′	R″	mp, °C	Recrystallization solvent	Empirical formula	Found, %			Calc., %			IR spectra,[a] cm^{-1}	Yield, %
							C	H	N	C	H	N		
IIa	CH_3	H	CH_3	201—202	Ethanol	$C_{17}H_{18}N_2O_2$	72,3	6,4	9,9	72,3	6,3	9,5	3170, 3040, 1680, 1616, 1588, 1568, 1530, 1255	66
IIb	C_6H_5	H		177	Aqueous ethanol	$C_{22}H_{20}N_2O_2$	76,7	6,2	7,8	76,7	5,8	8,1	3190, 3060, 1678, 1616, 1590, 1571, 1528, 1247	55
IIc	CH_3	C_6H_5		196	Isopropyl alcohol	$C_{23}H_{22}N_2O_2$	77,3	6,6	7,9	77,1	6,2	7,8	1673, 1612, 1590, 1567, 1526, 1249	80
IId		CH_3		141—142	Reprecipitated from isopropyl alcohol by addition of water	$C_{18}H_{20}N_2O_2$	73,1	7,2	9,1	73,0	6,8	9,5	1667, 1618, 1592 (sh), 1571, 1533, 1238	44
IIe		H	C_2H_5	177—178	Isopropyl alcohol	$C_{19}H_{22}N_2O_2$	73,0	7,2	9,0	73,5	7,1	9,0	3185, 3055, 1680, 1617, 1584, 1567, 1526	44
IIf		H	C_3H_7	163—165	Isopropyl alcohol	$C_{21}H_{26}N_2O_2$	74,0	7,7	8,3	74,6	7,7	8,3		41
IVa	CH_3			198—200	Glacial acetic acid	$C_{18}H_{15}N_2ClO_4$[b]	60,4	4,3	8,0	60,7	4,2	7,9	3260, 1586, 1530, 1489, 1100	77
IVb	C_6H_5			277	Nitromethane	$C_{23}H_{16}N_2ClO_4$[c]	65,7	4,2	6,8	65,9	3,8	6,7	3250, 1587, 1520, 1126	74

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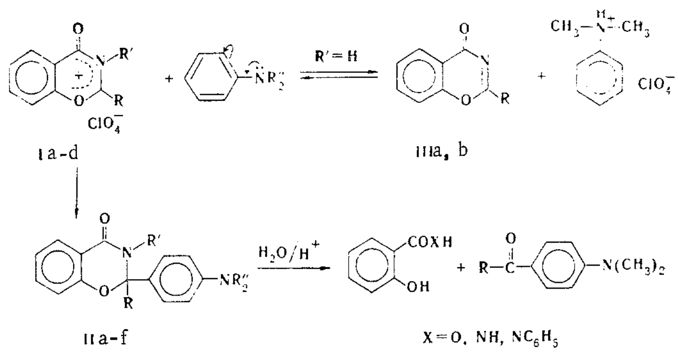
[a] The IR spectra of the diindolylcyanines were not characteristic because of the low intensities of the absorption bands.

[b] Found: Cl 10.4%. Calculated: Cl 10.0%.

[c] Found: Cl 8.3%. Calculated: Cl 8.5%.

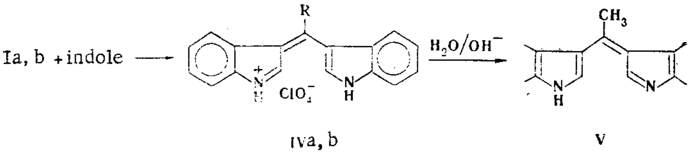


II a R=CH$_3$, R'=H; b R=C$_6$H$_5$, R'=H; c R=CH$_3$, R'=C$_6$H$_5$; d R=R'=CH$_3$

Two high-intensity absorption bands at 1680 and 1618 cm^{-1}, corresponding to the absorption of 2,3-dihydrobenzoxazinone [2], are present in the IR spectra of synthesized II. The appearance of absorption bands of stretching vibrations of an NH bond at 3170-3190 and 3040-3060 cm^{-1} in the spectra of IIa, b, e, f is characteristic for NH-dihydrobenzoxazinones.

Quantitative cleavage of the heteroring to give p-dimethylaminoaceto(benzo)phenones and salicylamide (or salicylic acid) occurs in the acid hydrolysis of dihydrobenzoxazinones. Similar decomposition of the dihydrooxazinone ring is observed during prolonged arylation in acetic acid, and this may be a convenient method for the synthesis of some ketones.

The reaction of salts I with indole cannot be stopped at the step involving the formation of the corresponding dihydrobenzoxazinones. Diindolylcyanines IV, the structure of which was confirmed by alternative synthesis, were obtained regardless of the reaction conditions and the component ratio. Thus 1-(3-indolyl)-1-(3-indolidene)ethane perchlorate, identical to IVa, which is converted to the previously known V [4] on treatment with a weakly alkaline (NaHCO$_3$) solution, was similar obtained [3] by acylation of indole with acetic anhydride in the presence of half-molar amounts of perchloric acid.



Attempts were also made to subject other compounds (anisole, veratrole, dimethylaminotoluidine, phenol, fluorene, and resorcinol and its dimethyl ether) to C-nucleophilic addition, but the yields of dihydrobenzoxazinones were low (2-6%).

EXPERIMENTAL

The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with a Tesla BC 487C spectrometer (80 MHz) at 50°C with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

2-Methyl-2-(4-dimethylaminophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (IIa). A mixture of 7.86 g (0.03 mole) of perchlorate Ia and 3.45 g (0.03 mole) of dimethylaniline in 30 ml of glacial acetic acid was refluxed for 1 h, after which it was cooled, made alkaline with sodium hydroxide solution, and extracted with chloroform. Evaporation of the solvent yielded 5.58 g (66%) of IIa with mp 201-202°C (from isopropyl alcohol).

Acidification of the aqueous layer gave 0.38 g (21%) of N-acetylsalicylamide with mp 143° [5].

Compounds IIc-f were similarly obtained (see Table 1).

The synthesized dihydrobenzoxazinones were obtained as colorless crystalline substances that were only slightly soluble in most organic solvents; they did not give any coloration with an alcohol solution of ferric chloride.

The reaction mixture was diluted with ether to obtain the perchlorate of IIa. The liberated oil began to crystallize when it was allowed to stand in a refrigerator. Workup gave 1.99 g (52%) of a product with mp 191° (dec., from glacial acetic acid). IR spectrum: 3250 and 3040 (NH$_2$); 1674 (C=O); 1619, 1587, 1511, 1253 (=C-O-); 1100 cm^{-1} (ClO$_4^-$). Found: C 54.0; H 5.5; Cl 9.6; N 7.3%. $C_{17}H_{18}NO_2 \cdot HClO_4$. Calculated: C 53.3; H 5.0; Cl 9.3; N 7.3%. Base IIa was isolated from the perchlorate by treatment with an alkaline solution.

More prolonged (up to 2 h) refluxing and a twofold excess of dimethylaniline were necessary for the preparation of dihydrobenzoxazinone IIb, since otherwise the salt if deprotonated under the influence of the amine.

2-Phenyl-4H-1,3-benzoxazin-4-one (IIIb). A mixture of 3.24 g (0.01 mole) of perchlorate Ib and 1.15 g (0.01 mole) of dimethylaniline in nitromethane or glacial acetic acid was refluxed for 1 h, after which it was made alkaline and extracted with chloroform. Evaporation of the solvent yielded 1.5 g (67%) of IIIb with mp 102° (from cyclohexane) (mp 102° [6]).

N,N-Dimethylaniline perchlorate (identified by a mixed-melting-point determination with an authentic sample), with mp 82° (from glacial acetic acid), was isolated by dilution of the reaction mixture with ether.

Reaction of Perchlorate Ia with Dimethylaniline in the Cold. An equimolar amount of dimethylaniline was added to a suspension of perchlorate Ia in glacial acetic acid, and the mixture was stirred thoroughly. The resulting crystalline precipitate was removed by filtration, washed three to four times with ether, and dried. PMR spectra (ppm): perchlorate Ia [1], 2.75 (s, CH_3) and 7.25-7.95 (m, phenylene); dimethylaniline perchlorate, 3.05 (d, CH_3NCH_3, J = 3 Hz) and 7.22 (s, phenyl). The relative intensities of the signals indicate that perchlorate Ia and dimethylaniline perchlorate are present in the investigated sample in a ratio of 1 : 1.5.

Dimethylaniline and 2-methylbenzoxazinone IIIa, with mp 217° (from benzene) [7], were isolated from the filtrate.

Hydrolysis of 2,3-Dihydrobenzoxazinones. A) A 2.82-g (0.01 mole) sample of IIa was refluxed in 20 ml of 5% hydrochloric acid for 30 min, after which the mixture was cooled and filtered to give 0.93 g (68%) of salicylamide with mp 137° (from water). Alkalization of the filtrate yielded 1.52 g (93%) of p-dimethylaminoacetophenone with mp 106-108° (from water) (mp 103, 105.5, and 110.5° [5]). IR spectrum: 1661 (C=O); 1616, 1594, and 1556 cm^{-1}. Found: C 73.2; H 7.9; N 8.5%. $C_{10}H_{13}NO$. Calculated: C 73.6; H 8.0; N 8.59%.

p-Dimethylaminobenzo- and acetophenones were similarly isolated in 80 and 95% yields, respectively, in the hydrolysis of IIb, c.

When the compounds were refluxed in 15% hydrochloric acid, hydrolysis gave salicylic acid. Dihydrobenzoxazinones are resistant to weakly alkaline hydrolysis.

B) p-Dimethylaminoacetophenone was obtained directly by refluxing (4 h) perchlorate Ic and dimethylaniline (1 : 2) in glacial acetic acid with subsequent alkalization of the mixture and extraction of the product with benzene. Workup of the extract gave a product with mp 106-108° in 91% yield.

1-(3-Indolyl)-1-(3-indolidene)ethane Perchlorate (IVa). A) A 1.17-g (0.01 mole) sample of indole was added to a solution of 1.31 g (0.005 mole) of perchlorate Ia in 5 ml of nitromethane or acetonitrile, and the mixture was refluxed for 1.5-2 min. It was then cooled and diluted with a small amount of ether, and the resulting brick-red precipitate was removed by filtration and washed with ether to give 1.37 g (77%) of a product with mp 198-200° (dec., from glacial acetic acid).

Perchlorate IV b was similarly obtained (see Table 1).

B) A 0.5-ml (0.005 mole) sample of 70% perchloric acid was added dropwise to a solution of 1.17 g (0.01 mole) of indole in 7 ml of acetic anhydride, and the mixture was cooled and diluted with a small amount of ether. Workup gave 1.12 g (63%) of the salt with mp 198-200°.

1-(3-Indolyl)-1-(3-indolidene)ethane (V). This compound, with mp 223° (reprecipitated from alcohol by the addition of water) (mp 223° [4]), was obtained by refluxing (3-4 min) perchlorate IV a in 10% sodium bicarbonate solution.

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