INVESTIGATIONS OF IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

IV.* REACTION OF IMIDAZO[1,2-a]BENZIMIDAZOLES WITH ALDEHYDES

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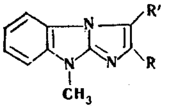
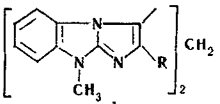
The conversion of 2-phenyl(methyl)-9-methylimidazo[1,2-a]benzimidazole to 3-hydroxymethyl derivatives, Mannich bases, and cyanine dyes is described.

As found previously, the 3-position in the imidazo[1,2-a]benzimidazole molecule is highly active with respect to electrophilic reagents (nitrous acid, diazonium salts, etc.) [1]. In this communication it is shown that these compounds also react readily with aldehydes.

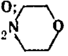


I-VIII



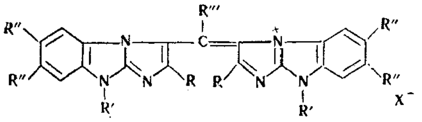
IX a,b

IX a R = C_6H_5
b R = CH_3

I R = C_6H_5, R' = H;
III R = C_6H_5, R' = CH_2OH;
V R = C_6H_5, R' = CHO;
VII R = C_6H_5, R' = CH_2N  ;

II R = CH_3, R' = H;
IV R = CH_3, R' = CH_2OH;
VI R = CH_3, R' = CHO;
VIII R = CH_3, R' = $CH_2N(C_2H_5)_2$

3-Hydroxymethyl derivatives (III and IV) are formed smoothly at 20° by the action of aqueous formaldehyde on 2-phenyl- and 2-methylimidazo[1,2-a]benzimidazoles (I and II). The position of the hydroxymethyl group in these compounds was proved by oxidizing them with active manganese dioxide to aldehydes V and VI, which were previously described in [2]. The hydroxyl group is replaced by an amine residue in the reaction of III and IV with secondary amines, and dialkylaminomethyl derivatives (VII and VIII) are formed; they were also obtained directly from I and II via the Mannich reaction. The reaction is accompanied by the formation of bis(imidazo[1,2-a]benzimidazolyl)methane derivatives (IX), which can also be synthesized in quantitative yield by heating I and II with formaldehyde.



X a R = R' = CH_3, R'' = R''' = H;
b R = C_6H_5, R' = CH_3, R'' = R''' = H;
c R = C_6H_5, R' = $CH_2C_6H_5$, R'' = R''' = H;
d R = C_6H_4Br-p, R' = CH_3, R'' = R''' = H;
e R = CH_3, R' = C_2H_5, R'' = CH_3, R''' = H;
f R = C_6H_5, R' = C_2H_5, R'' = CH_3, R''' = H;
g R = C_6H_5, R' = CH_3, R'' = H, R''' = $C_6H_4NO_2$-p;
h R = CH_3, R' = CH_3, R'' = H, R''' = $C_6H_4NO_2$-p;
i R = C_6H_5, R' = C_2H_5, R'' = CH_3, R''' $C_6H_4NO_2$-p;
X a-f X = Br^-; X g-i X = CH_3COO^-

Compounds V and VI react with starting I and II to form symmetrical methinylcyanine dyes (Table 1). The reaction is carried out in boiling glacial acetic acid, which protonates the N_1 atom and thereby increases the activity of the CH group in the 3-position. The yields, however, are low (about 10%). Dyes Xa-f are ob-

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[*] See [1] for communication III.

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TABLE 1. Cyanine Dyes – Imidazo[1,2-a]benzimidazole Derivatives

Comp.	Crystal color (alcohol solution color)	mp	Empirical formula	Found, %	Calc., %	Yield, %
X a	Violet crystals (dark-raspberry)	>330°	$C_{23}H_{21}BrN_6$	N 18,3	N 18,2	70
X b	Black plates with a violet luster (dark-turquoise)	291–292	$C_{33}H_{25}BrN_6$	N 14,3	N 14,4	85
Xc	Black shiny crystals with a green tint (turquoise)	187–189	$C_{45}H_{33}BrN_6$	C 73,0; H 4,7; Br 10,3; N 11,4	C 73,3; H 4,5; Br 10,8; N 11,4	87
Xd	Dark-violet needles (dark-turquoise)	260–261	$C_{33}H_{23}Br_3N_6$	N 11,1	N 11,3	92
Xe	Dark-cherry powder (lilac-colored)	>350	$C_{29}H_{33}BrN_6$	N 15,5	N 15,4	72
Xf	Dark-blue crystals (blue)	294	$C_{39}H_{37}BrN_6$	C 69,7; H 5,6; Br 11,5; N 12,7	C 69,9; H 5,6; Br 11,9; N 12,6	89
X g	Dark-violet needles (blue)	272–274	$C_{41}H_{31}N_7O_4$	N 14,4	N 14,3	88,5
Xh	Dark-claret crystals (dark-raspberry)	>350	$C_{31}H_{27}N_7O_4$	C 66,2; N 17,41; H 5,0	C 66,3; N 17,46; H 4,9	Quantit.
Xi	Dark-blue powder (blue)	212–215	$C_{47}H_{43}N_7O_4$	C 73,5; H 5,8	C 73,3; H 5,6	Quantit.

TABLE 2. Absorption Maxima of Symmetrical Methinylcyanine Dyes*

Dye	λ^1_{max}, nm	lg ε	λ^2_{max}, nm	lg ε
X a	367	3,398	540	3,844
X b	446	3,819	616	4,339
X c	448	3,649	620	4,062
X d	464	3,870	622	4,387
X e	367†	3,934	560	4,064
X f	484	3,796	630	4,301

*The UV absorption spectra of methanol solutions with concentrations of the order of 10^{-4} mole/liter were obtained with an SF-4A spectrophotometer.

†Inflection.

tained considerably more readily in good yields by the reaction of I and II with ethyl orthoformate under the same conditions. Similarly constructed, deeply colored dyes (Xg-i) are formed by the condensation of imidazo[1,2-*a*]benzimidazoles with aromatic aldehydes, for example, p-nitrobenzaldehyde [2].

The UV spectral data for Xa-f (Table 2) indicate that replacement of the methyl group in the 2-position of imidazo[1,2-*a*]benzimidazole by an aryl radical causes a bathochromic shift of the absorption maxima. The introduction of a benzyl or ethyl group into the 9-position of the ring and the introduction of two methyl groups into the 6- and 7-positions have virtually no effect on the color index of the compounds. The presence of an aryl radical in the methine group is weakly reflected in the color of the compounds.

EXPERIMENTAL

9-Methyl-3-hydroxymethyl-2-phenylimidazo[1,2-*a*]benzimidazole (III). A total of 0.25 g (1 mmole) of I was thoroughly triturated with excess 40% formalin, during which an oily lump formed. The next day, the formalin was decanted, and the residue was triturated with water. The resulting crystals were filtered, washed with water, and dried in a vacuum desiccator over P_2O_5 to give 0.27 g (96%) of a substance which sintered on heating and then melted at 85-87°. It was quite readily soluble in most organic solvents. It could not be recrystallized since it is converted to IXa on attempts to do so. Similar decomposition with the formation of formalin and water also occurs on storage and on heating to 110-120°. Found %: C 73.80;

H 5.33; N 15.48. $C_{17}H_{15}N_3O$. Calculated %: C 73.63; H 5.45; N 15.15. IR spectrum: ν_{OH} appears at 3000-3100 cm^{-1}, while δ_{OH} appears at 1030 cm^{-1}.

2,9-Dimethyl-3-hydroxymethylimidazo[1,2-*a*]benzimidazole (IV). Compound II (0.1 g) was dissolved in the cold in 1.5 ml of 40% formalin. A quantitative yield (0.12 g) of a white precipitate formed immediately. The silky needles (from alcohol) did not have a sharp melting point because of gradual conversion to IXb. Found %: C 66.71; H 6.29; N 19.65. $C_{12}H_{13}N_3O$. Calculated %: C 66.96; H 6.09; N 19.52. IR spectrum: ν_{OH} appears as a broad band with a peak at 3140 cm^{-1}, while δ_{OH} appears at 1020 cm^{-1}. The hydrochloride of IV was obtained by triturating IV with a small amount of concentrated HCl to give snow-white needles (from absolute alcohol with ether) which melted at 252° with gradual decomposition. Found %: C 53.57; H 6.12; N 15.86; Cl 13.46. $C_{12}H_{13}N_3O \cdot HCl \cdot H_2O$. Calculated %: C 53.43; H 5.98; N 15.58; Cl 13.15.

2-Imino-5,6-dimethyl-3-phenacyl-1-ethylbenzimidazoline. A solution of 5.67 g (0.03 mole) of 2-amino-5,6-dimethyl-1-ethylbenzimidazole and 5.97 g (0.03 mole) of phenacyl bromide in 50 ml of ethanol was refluxed for 2 h. The next day, the precipitate was filtered and washed with ether to give 10.6 g (82%) of the hydrobromide as colorless, fibrous needles with mp 297-298° (from alcohol). Found %: C 58.65; H 5.83; Br 20.29; N 10.83. $C_{19}H_{21}N_3O \cdot HBr$. Calculated %: C 58.77; H 5.71; Br 20.58; N 10.82. Treatment of a hot alcohol solution of the hydrobromide with 40% alkali yielded the imine as fine, snow-white needles with mp 180-181° (from aqueous alcohol). Found %: C 74.18; H 6.77; N 14.00. $C_{19}H_{21}N_3O$. Calculated %: C 74.24; H 6.89; N 13.67.

6,7-Dimethyl-2-phenyl-9-ethylimidazo[1,2-*a*]benzimidazole. 2-Imino-5,6-dimethyl-3-phenacyl-1-ethylbenzimidazoline hydrobromide (5 g) was refluxed for 5 h in 200 ml of concentrated HCl and 5 ml of $POCl_3$. The mixture was cooled, and the resulting precipitate was filtered and washed with water to give 4.5 g of the hydrobromide. Treatment of a hot aqueous alcoholic solution of the hydrobromide with excess ammonia yielded 3.6 g (quantitative) of the base with mp 189-190° (from alcohol). Found %: C 78.75; H 6.86; N 14.78. $C_{19}H_{19}N_3$. Calculated %: C 78.86; H 6.62; N 14.52.

6,7-Dimethyl-3-hydroxymethyl-2-phenyl-9-ethylimidazo[1,2-*a*]benzimidazole. A total of 0.5 g of 6,7-dimethyl-2-phenyl-9-ethylimidazo[1,2-*a*]benzimidazole in 6 ml of formalin was refluxed for 30 min to give 0.55 g (quantitative) of shiny colorless crystals with mp 257° (from alcohol). Found %: C 75.00; H 6.90; N 12.94. $C_{20}H_{21}N_3O$. Calculated %: C 75.21; H 6.63; N 13.15. IR spectrum: ν_{OH} appears as a broad band with a peak at 3185 cm^{-1}, while δ_{OH} appears at 1030 cm^{-1}.

Oxidation of III with Active Manganese Dioxide. Freshly prepared active manganese dioxide (2.5 g) [3] was added to a solution of 0.56 g (2 mmole) of III in 30 ml of dry chloroform. The mixture was allowed to stand, and the course of the reaction was monitored by means of thin-layer chromatography (Al_2O_3, chloroform eluant, development by iodine). The reaction was complete in 30 min. The precipitate of MnO_2 was filtered and washed on the filter with chloroform. The chloroform was removed by distillation to give snow-white needles with mp 146-147° (from dioxane) which were identical to the genuine aldehyde V. The yield was quantitative. The 2,4-dinitrophenylhydrazone of V had mp 303-304°.

9-Methyl-3-morpholinomethyl-2-phenylimidazo[1,2-*a*]benzimidazole (VII). A solution of 1.05 g (4.25 mmole) of I, 0.4 ml (5 mmole) of 40% formalin, and 0.44 ml (5 mmole) of morpholine in 10 ml of ethanol was refluxed for 3 h on a water bath. The alcohol was removed in vacuo, and the residue was triturated with water and allowed to stand in a refrigerator. The next day the precipitate was filtered and washed with ether to give 1.28 g (89.5%) of a product with mp 129-130° which was soluble in alcohol but insoluble in ether, hexane, and water. It decomposed on heating with water (the odor of formalin was detected, and the melting point was lowered). Found %: C 72.77; H 6.56; N 16.19. $C_{21}H_{22}N_4O$. Calculated %: C 72.80; H 6.40; N 16.17. The dipicrate of VII was obtained as bright-yellow needles with mp 233° (from alcohol). Found %: N 17.45. $C_{21}H_{22}N_4O \cdot C_{12}H_6N_6O_{14}$. Calculated %: N 17.41. The dihydrochloride of VII was formed as an oil on passage of dry HCl (2 wt. equivalents) into a benzene solution of VII. Trituration of the resulting oil with acetone gave crystals of the monohydrate as snow-white needles with mp 162° (decomp., from alcohol–acetone) which were quite soluble in water in the cold. Found %: C 57.75; H 6.14; N 13.17; Cl 16.02. $C_{21}H_{22}N_4O \cdot 2HCl \cdot H_2O$. Calculated %: C 57.67; H 5.99; N 12.81; Cl 16.21.

2,9-Dimethyl-3-diethylaminomethylimidazo[1,2-*a*]benzimidazole (VIII). A. This was similarly obtained in quantitative yield by refluxing an alcohol solution of 0.46 g (2.5 mmole) of II, 0.25 ml (3 mmole) of formalin, and 0.31 ml (3 mmole) of diethylamine for 1.5 h and had mp 77-78° (from petroleum ether). Found %: C 71.00; H 7.80; N 20.60. $C_{16}H_{22}N_4$. Calculated %: C 71.08; H 8.20; N 20.72.

If the mixture of starting materials is refluxed for a longer period, for example 7 h, colorless bis(2,9-dimethylimidazo[1,2-*a*]-3-benzimidazolyl)methane (IXb) gradually precipitates in 33% yield from the hot solution. This compound was obtained as snow-white needles with mp 322° (from dimethylformamide) which were insoluble on heating in water, alcohol, and dioxane. Found %: C 72.34; H 5.85; N 21.92. $C_{23}H_{22}N_6$. Calculated %: C 72.22; H 5.79; N 21.97.

B. An alcohol solution of 0.2 g of IV and 0.2 ml of diethylamine was refluxed for 1 h. The fine needles of IXb (40% yield with mp 332°) that precipitated on cooling were filtered and washed with alcohol; the alcoholic mother liquor was evaporated, and the residue was triturated with water to give 0.15 g (60%) of a substance with mp 77-78°. This product did not depress the melting point of the product of part A. The dihydrochloride of VIII was obtained by treatment of VIII with a small excess of HCl with subsequent trituration of the resulting oily substance with acetone to give a product with mp 163° (from alcohol–acetone). Found %: C 52.94; H 7.44; N 15.66; Cl 19.58. $C_{16}H_{22}N_4 \cdot 2HCl \cdot H_2O$. Calculated %: C 53.19; H 7.25; N 15.50; Cl 19.63.

Bis(9-methyl-2-phenylimidazo[1,2-a]-3-benzimidazolyl)methane (IXa). A total of 0.3 g of I was refluxed with 3 ml of 40% formalin for 30 min. The initially formed oil gradually crystallized to give 0.32 g (quantitative) of snow-white crystals with mp 267-268° (from alcohol). Found %: C 78.37; H 5.30; N 16.38. $C_{33}H_{26}N_6$. Calculated %: C 78.23; H 5.17; N 16.60.

Cyanine Dyes (Xa-f). A. A solution of 0.4 g of I (or another starting imidazo[1,2-*a*]benzimidazole) and 1 ml of ethyl orthoformate in 2 ml of glacial acetic acid was refluxed for 6-10 h. The solution was cooled, and 2-3 ml of saturated aqueous KBr was added. The resulting precipitate was filtered, air dried, and treated with acetone. The dyes were soluble in acetone and were separated from the inorganic salts in this way. The acetone solution was evaporated, and the residue was purified by reprecipitation from alcohol with ether.

The dyes were soluble in alcohol, chloroform, and acetone, slightly soluble in benzene and dioxane; only dyes with a methyl group in the 2-position were moderately soluble in water.

B. The same dyes were formed by prolonged refluxing of equimolecular amounts of the 3-formyl derivatives (V and VI) with the starting I and II in glacial acetic acid. However, the yields in this case were low (8-10%).

Dyes Xg-i. These were formed by refluxing 2 mmole of imidazo[1,2-*a*]benzimidazole with 1 mmole of nitrobenzaldehyde in acetic acid for 30-120 min. The brightly colored solution was evaporated, and the residue was triturated with petroleum ether and filtered. The crystals were purified by reprecipitation from alcohol with ether. The resulting dyes were quite soluble in alcohol, chloroform, benzene, and acetone, and insoluble in petroleum ether and diethyl ether.

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