

## SYNTHESIS OF SOME 2-ARYL-2,3,4,6-TETRAHYDRO-1,2,4-BENZOTRIAZINE-3,6-DIONES\*

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A series of 2-ethoxycarbonylamino-4-hydroxyazobenzenes *Ia* to *Ih* have been prepared by coupling of diazonium salts with ethyl *m*-hydroxyphenylcarbamate in alkaline medium. The compounds have been transformed to the corresponding 2-aryl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-diones *IIa* to *IIIh* by both alkali and acid catalyzed cyclization. Structure of the compounds *I* and *II* has been proved by IR and <sup>1</sup>H-NMR spectroscopy and comparison of the electronic spectrum of the derivative *IIa* with that of 2-phenyl-4-methyl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-dione (*IIIa*) prepared by methylation of benzotriazine *IIa*.

2,3,4,6-Tetrahydro-1,2,4-benzotriazine-3,6-dione and its derivatives attracted our attention for their close relationship to 6-azauracil, as they can be considered its vinylogues. This report deals with synthesis of some 2-aryl derivatives of the mentioned type.

Coupling of diazonium salts with ethyl *m*-hydroxyphenylcarbamate in strongly alkaline medium gave the respective 2-ethoxycarbonylamino-4-hydroxyazobenzenes *Ia* to *Ih* in high yields; very small amounts of position isomers were removed by recrystallization from ethanol. The almost uniform coupling at the *para* position to OH group agrees with the previous finding<sup>1</sup> concerning the coupling of benzene-diazonium chloride with *m*-acetylaminophenol.

Structure of the compounds *I* follows from their ability of ring closure to the corresponding 2-aryl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-diones *IIa* to *IIIh* and from results of <sup>1</sup>H-NMR and IR spectroscopy. In the IR spectrum of the compound *Ia* a lowering in  $\nu(\text{NH})$  of carbamate N—H bond by 46 cm<sup>-1</sup> can be seen as compared with the starting ethyl 3-hydroxyphenylcarbamate, which is due to intramolecular hydrogen bond between N—H and azo groups. Simultaneous decrease of  $\nu(\text{OH})$  from 3612 cm<sup>-1</sup> (for the starting phenol) to 3600 cm<sup>-1</sup> (azo-compound *Ia*)

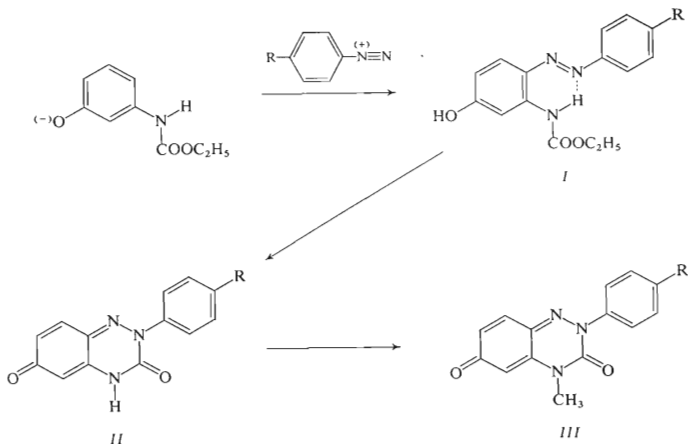
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can be ascribed only to the strong polar effect of azo group. Also the comparison of  $^1\text{H-NMR}$  spectra of the azo compound *Ia* and the starting ethyl 3-hydroxyphenylcarbamate indicates that the azo group is *ortho* to carbamate group. Spectrum of the starting phenol contains besides  $\text{CH}_3$  (1.25 ppm) and  $\text{CH}_2$  (4.10 ppm) signals those of aromatic protons in the region 6.1 to 7.2 ppm. The doublet at 6.38 ppm, the both components of which are further split into triplets by 2 protons from *meta* position, can be assigned to the H atom standing *ortho* to phenolic hydroxyl and *para* to ethoxycarbonylamino group. This signal is maintained also in the spectrum of the azo compound *Ia*, but here the both components of the doublet are further split to doublets only, as there is no proton present at *ortho* position with respect to ethoxycarbonylamino group and at *para* position with respect to phenolic hydroxyl group. A weak downfield shift (by 0.4 ppm) of this signal is due to polar effect of azo group.

Cyclization of azo compounds *I* to the corresponding derivatives of 1,2,4-benzotriazine *II* is achieved by heating in both alkaline and strongly acid media, whereas thermal cyclization does not occur. This finding can be explained by that in neutral media the compounds *I* exist only in their azo form which is unfavourable for cyclization. The same conclusion can be drawn also from IR spectroscopic study of the compound *Ia*, where marked bands of valence vibration of OH ( $3600\text{ cm}^{-1}$ ) and NH ( $3405\text{ cm}^{-1}$ ) bonds are observable, the NH band position remaining unchanged after  $^{14}\text{N}$ — $^{15}\text{N}$  substitution of the phenyl-bound azo nitrogen atom. IR spectra of the compound *Ia* ( $10^{-3}\text{ M}$  in tetrachloromethane) showed that intermolecular hydrogen bonds are formed between CO group of the carbamate residue and phenolic hydroxyl group, which is manifested by a broad band at  $3320\text{ cm}^{-1}$  ( $\nu(\text{OH})$ ) and a band at  $1710\text{ cm}^{-1}$  ( $\nu(\text{CO})$ ). The band corresponding to free carbonyl group was observed at  $1740\text{ cm}^{-1}$ . The intensity ratio of the bonded ( $3320\text{ cm}^{-1}$  and  $1710\text{ cm}^{-1}$ ) and the free ( $3600\text{ cm}^{-1}$  and  $1740\text{ cm}^{-1}$ ) forms was increased in favour of the free form by dilution of the solution or by increase of temperature. In alkaline medium the azo compounds *I* are transformed into their mesomeric anions which are readily cyclized to the mesomeric anions of the corresponding benzotriazines giving the compounds *II* on acidification. In strongly acidic medium azo group of the compounds *I* is protonated to give the mesomeric cation which also can readily be cyclized to the corresponding derivatives of 1,2,4-benzotriazine *II*. Thus the cyclization of the compounds *I* differs from all the previous cyclizations of this type<sup>2-6</sup> which are easily accomplished thermally.

We studied the methylation of the most simple derivative *IIIa* which can take place both at the N atom at 4-position and at the O atom at 6-position. It was found that both the methylation with methyl iodide in alkaline medium and that with diazomethane gave 2-phenyl-4-methyl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-dione (*IIIa*). Its structure was confirmed by its  $^1\text{H-NMR}$  spectrum showing a singlet at 3.42 ppm (in  $\text{CDCl}_3$ ) or 3.33 ppm (in hexadeuteriodimethyl sulphoxide) due to

a methyl group bound to N atom. The doublet at 5.86 ppm ( $\text{CDCl}_3$ ) or 5.89 (hexadeuteriodimethyl sulphoxide) corresponds to the proton at 5-position of 1,2,4-benzotriazine cycle, the quartet at 6.56 ppm ( $\text{CDCl}_3$ ) or 6.65 ppm (hexadeuteriodimethyl sulphoxide) corresponds to the proton at 7-position, and the doublet at 7.15 ppm ( $\text{CDCl}_3$ ) or 7.36 ppm (hexadeuteriodimethyl sulphoxide) corresponds to the proton at 8-position. The respective spin-spin coupling constants are:  $J_{\text{H}_5\text{H}_7} = 2.4$  Hz and  $J_{\text{H}_7\text{H}_8} = 10$  Hz. The five protons of the phenyl nucleus bound to N atom are seen in a narrow region with a marked maximum at 7.50 ppm. Also IR spectra with marked maxima at  $1640\text{ cm}^{-1}$  and  $1712\text{ cm}^{-1}$  due to the both carbonyl groups support the structure *IIIa*.



a: R = H  
 b: R =  $\text{CH}_3$   
 c: R = F  
 d: R = Cl

e: R = Br  
 f: R = I  
 g: R =  $\text{CH}_3\text{O}$   
 h: R =  $\text{C}_2\text{H}_5\text{O}$

In the case of the compounds *II* it is possible to presume the existence of 6-hydroxy-2,3-dihydro-3-one form besides 2,3,4,6-tetrahydro-3,6-dione form. However, the course of methylation of the compound *IIa* alone indicated that these compounds exist most probably only in the first of the considered tautomeric structures. This conclusion was confirmed by UV, IR and  $^1\text{H-NMR}$  spectra. Course of the electronic spectra of the compound *IIIa* is almost identical with that of its 4-N-methyl

derivative *IIIa*. Also IR spectra of the both compounds are very similar in the region above  $1600\text{ cm}^{-1}$ . The maxima of the carbonyl groups of the compound *IIa* are, however, somewhat shifted as compared with the N-methyl derivative *IIIa*, the band at  $1730\text{ cm}^{-1}$  being due to the valence vibration of the carbonyl group at 3-position, and the band at  $1650\text{ cm}^{-1}$  can be assigned to the valence vibration of the quinoid carbonyl group at 6-position. A marked maximum at  $3440\text{ cm}^{-1}$  is due to valence vibration of N—H group.

The carbonyl group at 6-position of the compound *II* is in a vinylogous position as the respective carbonyl group of 6-azauracil. The compounds *II* are also weak N—H acids, their  $pK$  (6.60) being close to  $pK$  values of 1-aryl-6-azauracils. Also the abovementioned methylation course of the derivative *IIa* is analogous to that of methylation of 6-azauracils<sup>7,8</sup>.

### EXPERIMENTAL

The melting points were determined with the use of a Boetius apparatus and are not corrected. IR spectra were measured with a UR-20 (Zeiss, Jena) spectrophotometer. The measurements in tetrachloromethane were carried out in 1.4 cm heated cells. Calibration of the IR spectra was carried out with polystyrene. The <sup>1</sup>H-NMR spectra were measured with a 60 MHz apparatus

TABLE I

2-Ethoxycarbonylamino-4-hydroxyazobenzenes *I*

Compound	Formula (m.w.)	Calculated/Found			M.p., °C ethanol
		% C	% H	% N	
<i>Ia</i>	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> (285.3)	63.15	5.30	14.73	212—214
		63.20	5.33	14.90	
<i>Ib</i>	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> (299.3)	64.20	5.72	14.04	223—225
		64.39	5.87	14.08	
<i>Ic</i>	C <sub>15</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>3</sub> (303.3)	59.40	4.65	13.85	237—239
		59.46	4.68	13.58	
<i>Id</i>	C <sub>15</sub> H <sub>41</sub> ClN <sub>3</sub> O <sub>3</sub> (319.7)	56.34	4.41	13.14	256—258
		56.51	4.39	12.92	
<i>Ie</i>	C <sub>15</sub> H <sub>14</sub> BrN <sub>3</sub> O <sub>3</sub> (364.2)	49.46	3.87	11.54	268—270
		49.55	3.84	11.28	
<i>If</i>	C <sub>15</sub> H <sub>14</sub> IN <sub>3</sub> O <sub>3</sub> (411.2)	43.81	3.43	10.22	269—271
		43.66	3.51	9.94	
<i>Ig</i>	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> (315.3)	60.95	5.43	13.32	208—210
		60.90	5.52	13.17	
<i>Ih</i>	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub> (329.4)	61.99	5.82	12.76	224—226
		61.86	5.94	12.61	

Varian A 60 at 35°C in 5% solutions of the compounds in  $\text{CDCl}_3$  or hexadeuteriodimethyl sulphoxide, using tetramethylsilane as internal standard. UV spectra were measured with a spectrophotometer Unicam SP 1800 in 50% ethanol.

### 2-Ethoxycarbonylamino-4-hydroxyazobenzenes *Ia* to *Ih*

The diazonium salt solutions were prepared by addition of 276 mg (4.0 mmol)  $\text{NaNO}_2$  in 10 ml ice water to the solution or suspension of the respective aromatic amine (4.0 mmol) in 3.0 ml 37% HCl, 15 to 50 ml ice water and 10 g crushed ice. The diazonium salt was added to solution of 850 mg (4.69 mmol) ethyl *m*-hydrophenylcarbamate<sup>9</sup> in 500 to 700 ml ice water with 2.0 g NaOH and crushed ice with stirring during 5 min. The mixture was stirred 3–4 min and acidified with acetic acid to pH 5–4. The formed orange precipitate was collected by suction after 2 h, then it was washed with water and dried. The yields of all the raw products were within 86 to 95%. After recrystallization from ethanol the azo compounds *Ia* to *Ih* were obtained in the yields 75 to 87% (with respect to the starting amine). The products form yellow needles and are uniform when chromatographed on silica gel or  $\text{Al}_2\text{O}_3$ . From  $^{15}\text{N}$  aniline the respective azo compound  $^{15}\text{N}$  *Ia* was prepared, too. Table I gives analyses and m.p. of the products.

### 2-Aryl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-diones *Ila* to *Ilh*

a) *By alkaline cyclization*: Mixture of 2 mmol of the respective azo compound *I*, 550 mg  $\text{Na}_2\text{CO}_3$  and 60 to 80 ml water was refluxed 1 h, filtered, and acidified with acetic acid to pH 4.

TABLE II

### 2-Aryl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-diones *II*

Compound	Formula (m.w.)	Calculated/Found			M.p., °C (solvent)
		% C	% H	% N	
<i>Ila</i>	$\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2$ (239.2)	65.26	3.79	17.57	255–257
		65.21	3.81	17.46	(water)
<i>Ilb</i>	$\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2$ (253.3)	66.39	4.38	16.59	278–280
		66.33	4.50	16.32	(ethanol–water)
<i>Ilc</i>	$\text{C}_{13}\text{H}_8\text{FN}_3\text{O}_2$ (257.2)	60.70	3.13	16.34	280–282
		60.63	3.30	16.14	(ethanol–water)
<i>Ild</i>	$\text{C}_{13}\text{H}_8\text{ClN}_3\text{O}_2$ (273.7)	57.05	2.94	15.35	283–285
		56.81	3.10	15.08	(ethanol–water)
<i>Ile</i>	$\text{C}_{13}\text{H}_8\text{BrN}_3\text{O}_2$ (318.1)	49.08	2.53	13.21	287–289
		48.85	2.66	13.05	(ethanol–water)
<i>Ilf</i>	$\text{C}_{13}\text{H}_8\text{IN}_3\text{O}_2$ (365.1)	42.76	2.21	11.51	294–296
		42.61	2.35	11.22	(ethanol)
<i>Ilg</i>	$\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_3$ (269.3)	62.45	4.12	15.61	250–252
		62.26	4.21	15.49	(ethanol–water)
<i>Ilh</i>	$\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$ (283.3)	63.59	4.63	14.83	232–234
		63.41	4.71	14.68	(ethanol–water)

The formed yellow precipitate was collected by suction after several hours; then it was washed with water, dried and weighed. The yields were within 89 to 94%. The samples for analysis were obtained by recrystallization from water or mixture ethanol-water. For the respective data see Table II.

b) *By boiling with hydrochloric acid*: Mixture of 1 mmol of the azo compound *I* and 50 to 70 ml 20% HCl was refluxed 4 h, concentrated to half volume and cooled. After several hours the precipitated solid was collected by suction, washed with water, dried and weighed. The yields were within 75 to 85%. After recrystallization from ethanol-water mixture the products were identical with those of the previous procedure. For further data see Table II.

UV spectrum of the compound *Ila* in ethanol,  $\lambda_{\max}$  (log  $\epsilon$ ): 216 (4.24), 259 (4.15), 377 (4.12). For this compound  $pK_a = 6.60 \pm 0.05$  was determined by the spectrophotometric method in 50% aqueous ethanol, at the concentration  $10^{-4} M$  at the wavelength 400 nm.  $^1H$ -NMR spectrum of *Ila* in hexadeuteriodimethyl sulphoxide ( $\delta$ , ppm): 3.65, 5.73, 6.49, 7.32, 7.35–7.62.

#### 2-Phenyl-4-methyl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-dione (*IIla*)

a) *Methylation with methyl iodide*: Solution of 120 mg (0.5 mmol) compound *Ila* in 20 ml 0.1% aqueous NaOH solution was treated with 0.3 ml methyl iodide, and the mixture was stirred in a closed flask at room temperature for 14 days. The precipitated solid was collected by suction, washed with water and dried. The yield was 95 mg (75.4%). After recrystallization from ethanol it forms yellow crystals, m.p. 182–183°C.

b) *Methylation with diazomethane*: Solution of 120 mg (0.5 mmol) benzotriazine *Ila* in 100 ml ethanol was treated with ethereal solution containing 0.6 mmol diazomethane, the reagent being added in several portions. The mixture was stirred at room temperature for 30 min and concentrated to small volume. The precipitated solid was collected by suction and dried. Yield 115 g (90.8%). After recrystallization from ethanol its m.p. and IR spectrum are identical with those of the product of the above procedure. UV spectrum in ethanol,  $\lambda_{\max}$  (log  $\epsilon$ ): 217 (4.24), 257 (4.13), 386 (4.12).  $^1H$ -NMR spectrum in  $CDCl_3$  ( $\delta$ , ppm): 3.42, 5.86, 6.56, 7.15, 7.17–7.53.  $^1H$ -NMR spectrum in hexadeuteriodimethyl sulphoxide ( $\delta$ , ppm): 3.33, 5.89, 6.65, 7.36, 7.37 to 7.62. For  $C_{14}H_{11}N_3O_2$  (253.3) calculated: 66.39% C, 4.38% H, 16.59% N; found: 66.35% C, 4.25% H, 16.60% N.

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#### REFERENCES

1. Crippa G. B., Gueneri M.: Ann. Chim. (Rome) 42, 336 (1952).
2. Slouka J.: Tetrahedron Lett. 1968, 4007.
3. Slouka J., Peč P.: Monatsh. Chem. 103, 1444 (1972).
4. Slouka J., Bekárek B., Peč P.: Acta Univ. Palacki. Olomuc., Fac. Rerum Natur. 49, 227 (1976).
5. Peč P., Slouka J.: Chem. Zvesti 29, 418 (1975).
6. Slouka J.: This Journal 42, 894 (1977).
7. Cattelain E.: Bull. Soc. Chim. Fr. 12, 59 (1945).
8. Gut J., Prystaš M., Jonáš J., Šorm F.: This Journal 26, 974 (1961).
9. Bauer H.: Ber. Deut. Chem. Ges. 48, 1579 (1915).

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