Condensation of *o*-Aminophenol and α-Dicarbonyl Compounds. Part 1. Benzoxazines

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By condensation with *o*-aminophenol of a series of phenylglyoxal derivatives two species of products were obtained, namely 2-hydroxy-(2*H*)-1,4-benzoxazines (I) and 2′-aryl-2,2′-dibenzoxazolines (II). The structure of compounds I was investigated by ir, uv and pmr spectroscopy and a reaction mechanism was proposed.

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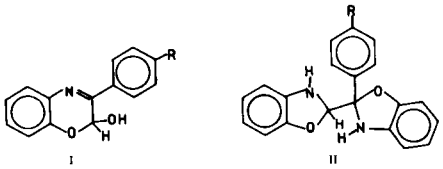
It was reported (2-4) that the condensation of *o*-aminophenol and α-dicarbonyl compounds leads, with molar ratio 2:1, to 2,2′-dibenzoxazolines while, with a molar ratio 1:1, 2-hydroxy-2,3-disubstituted-1,4-benzoxazine derivatives were obtained. In the attempt to further investigate these reactions, we have condensed with *o*-aminophenol, in absolute ethanol solution, a series of phenylglyoxal derivatives employing either an 1:1 or a 2:1 molar ratio. In every case we have obtained two species of products identified as 2-hydroxy-(2*H*)-1,4-benzoxazines (I) and 2′-aryl-2,2′-dibenzoxazolines (II). After separation



I II

I, II a R=H
b =CH$_3$
c =Cl
d =OCH$_3$
e =NO$_2$

by thin layer chromatography it was possible, through ultraviolet investigation, to determine the relative amounts of I and II obtained with the used molar ratios. (See Table I and Experimental.)

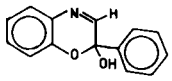
Table I

Relative Percentages of I and II

Compound	Molar ratio 2:1	Molar ratio 1:1	Rf
Ia	12	65	0.14
IIa	88	35	0.40
Ib	10	52	0.20
IIb	90	48	0.48
Ic	16	50	0.11
IIc	84	50	0.21
Id	20	23	0.09
IId	80	77	0.43
Ie	13	28	0.13
IIe	87	72	0.38

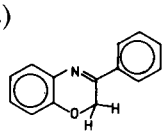
1,4-Benzoxazines (I).

From spectroscopic evidence a sure 2-hydroxy-(2*H*)-3-aryl-1,4-benzoxazine structure (I) was attributed to the obtained compounds instead of the 2-hydroxy-2-aryl-(2*H*)-1,4-benzoxazine one (III) reported (3) for the condensation product between *o*-aminophenol and phenylglyoxal.



III

The infrared absorption spectra of Ia→e show, in the 3000 cm^{-1} region, intermolecular hydrogen bonds; in chloroform solution, in fact, these broad bands disappear while the ν OH free clearly rises at 3560 cm^{-1}. Moreover, the phenyl ring bands and the C-O stretching at about 1050 cm^{-1} can also be noted. A sure assignment of the C=N absorption band is difficult for the other bands are overlapping. All these bands, nevertheless, could agree with the structure III also; a definitive confirmation of the proposed structure I was undertaken through the investigation of the ultraviolet absorption and proton magnetic resonance spectra. In the ultraviolet spectra of Ia→e the broad conjugation band at 300-320 nm must be attributed to a "planar" benzalaniline system; such a configuration can moreover explain the high extinction coefficient found. In fact the low absorptivity of benzalaniline is due to the π conjugation throughout weakened at the nitrogen atom by non coplanarity. It must be noted that the secondary band due to the benzal portion of the molecule undergoes a bathochromic shift, with respect to the corresponding benzalaniline derivatives (5) (for Id, it appears as a shoulder), by the nearness of the conjugation band of the whole system. The spectrum of 2-hydroxy-(2*H*)-3-phenyl-1,4-benzoxazine (Ia), on the other hand, closely resembles the 3-phenyl-(2*H*)-1,4-benzoxazine one (IV). (See Figure 1.)



IV

The pmr spectra of I reveals, together with the other protons signals, two doublets (J = 6.5 Hz), at 6.40 and 7.80 δ due to coupling of H and OH in position 2. Moreover at about 8 δ there are signals that, when R ≠ H,

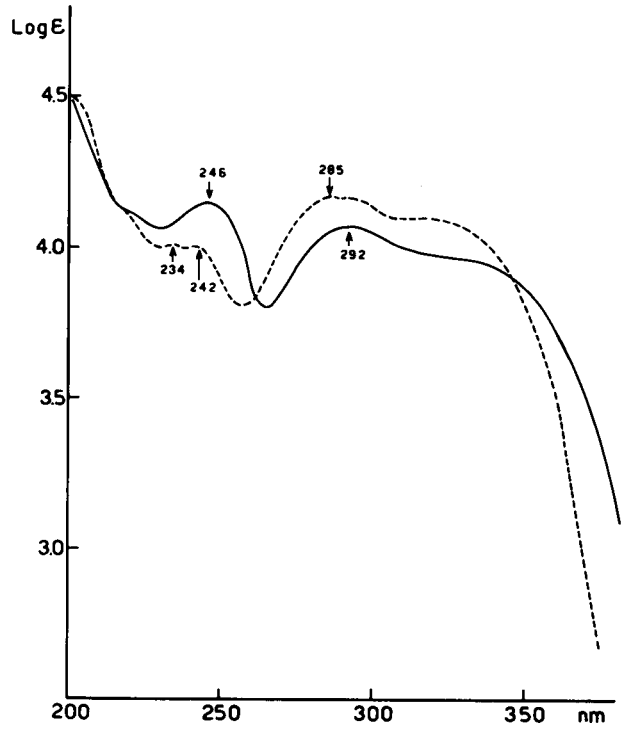
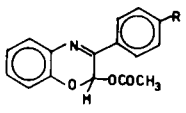


Figure 1. Ultraviolet spectra of: ———— [IV], – – – – [Ia]. Solvent, methanol.

appear as doublets (J = 9 Hz) and by integrating, they correspond to two protons. Such signals were assigned to the *ortho* protons of the phenyl ring bonded in position 3; it is well known, on the other hand, that in this way a compound having a N=C-phenyl system behaves (6). Upon addition of deuterium oxide the OH signal at 7.80 δ disappears while at 6.40 δ we observe the sharp singlet signal of the methine proton. The chemical shifts and the related coupling constants cannot be explained with a structure III for which such a coupling between the OH group in 2 and the proton in position 3 would not occur and, at 8 δ, lacking the N=C-phenyl system, no signals would be found. (See Table II.)

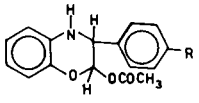
Acetylation of Ia→e with acetic anhydride gives the acetyl derivatives Va→e. The spectroscopic properties, ir,



V

pmr, uv agree with the proposed V structure. (See Table III).

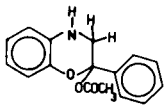
By catalytic hydrogenation of Va we obtained 2-acetoxy-(2*H*)-3-phenyl-3,4-dihydro-1,4-benzaxazine (VI).



VI

The pmr spectrum of VI shows the NH signal at 6.33 δ, two broad signals at 6.42 and 4.62 δ due, respectively, to benzoxazine ring protons in position 2 and 3 and, naturally, no multiplet at 8 δ for the benzaldimine system. Upon addition of deuterium oxide the NH signal disappears and the spectrum reveals two doublets (J = 2 Hz) by the coupling of the protons in positions 2 and 3. From the integration of the several signal intensities it results that every doublet corresponds to one hydrogen atom.

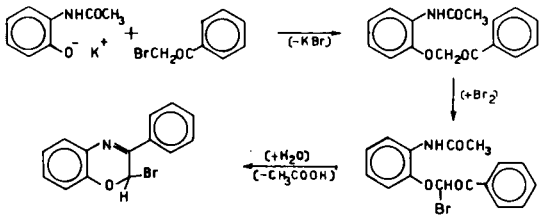
These observations and the absence of whatever signal attributable to a methylene group exclude at all the structure III; in this latter case, in fact, after acetylation and hydrogenation, the resulting product would have the structure VII. For a further confirmation of the proposed



VII

structure we tried to carry out an univocal synthesis of Ia by hydrolysis of the 2-Br-(2*H*)-3-phenyl-1,4-benzoxazine which some Russian authors (7) assert to have obtained with the following scheme.

Scheme 1

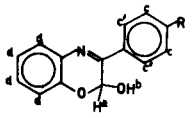


The Br derivative obtained in this way, whose m.p. is the same as the one reported by the above mentioned authors, undergoes no hydrolysis. The examination of its pmr spectrum (DMSO-d_6), reveals a singlet at 5.25 δ (integration corresponding to two hydrogens) attributable to protons in position 2, the chemical shift is the same as found for 3-phenyl-(2*H*)-1,4-benzoxazine (IV), and, moreover, at 7.45 δ appears a multiplet, whose integration corresponds to three hydrogens of the other protons of the benzoxazine ring.

Evidently the bromination of ω-(*o*-acetylaminophenoxy)acetophenone does not occur at the methylene group but at the phenoxy ring. To understand the reaction mechanism, we must note that the compounds I and II were also obtained, in the same proportion, in anhydrous benzene solution or in benzene solution with triethylamine as proton acceptor. No condensation occurs in acidic solution. This behaviour in addition to the fact that the 5-nitro-2-aminophenol and the picrylamine do not react with α-dicarbonyl compounds, as reported (3), confirms that these condensations proceed only with a mechanism

Table II

Analytical and Spectral Data of I

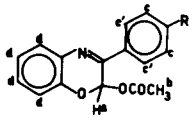


Compound	M.p. °C Solvent	Formula	Analysis (a) C	H	N	Ir ν max, cm^{-1} (b)	Pmr δ, ppm (c)	Uv, nm, (Log ϵ) (d)
Ia	228-229 Ethanol	$C_{14}H_{11}NO_2$	74.55 (74.65)	4.99 (4.92)	6.17 (6.21)	3080 broad, (3560), 1610, 1590, 1565, 1485, 1050, 765.	6.42 (d, H^a, J = 6.5), 7.15 (m, H^c), 7.50 (m, H^d), 7.78 (d, H^b, J = 6.5), 8.06 (m, $H^{c'}$).	234 (4.01), 242 (4.00) 285 (4.17), 315 sh
Ib	218-219 Ethanol	$C_{15}H_{13}NO_2$	75.17 (75.29)	5.23 (5.31)	6.09 (6.15)	3050 broad, (3560), 1610, 1590, 1555, 1480, 1040, 820, 760	2.36 (s, CH_3), 6.36 (d, H^a, J = 6.5), 7.30 (m, $H^c + H^d$), 7.72 (d, H^b, J = 6.5), 7.95 (d, $H^{c'}$, J = 9).	230 (4.07), 236 (4.06), 295 (4.23), 315 sh
Ic	241-243 Ethanol	$C_{14}H_{10}ClNO_2$	64.62 (64.86)	3.95 (3.86)	5.31 (5.40)	3060 broad, (3555), 1610, 1590, 1580, 1480, 1370, 1045, 840, 760.	6.38 (d, H^a, J = 6.5), 7.35 (m, $H^c + H^d$), 7.80 (d, H^b, J = 6.5), 8.05 (d, $H^{c'}$, J = 9).	230 (4.02), 237 (4.04) 293 (4.23), 315 sh
Id	212-213 Ethanol	$C_{15}H_{13}NO_3$	70.45 (70.58)	5.04 (5.13)	5.35 (5.49)	3050 broad, (3560), 1610, 1590, 1580, 1560, 1490, 1050, 840, 760.	3.82 (s, OCH_3), 6.36 (d, H^a, J = 6.5), 7.25 (m, $H^c + H^d$), 7.68 (d, H^b, J = 6.5), 8.02 (d, $H^{c'}$, J = 9).	234 (4.18), 305 sh, 327 (4.28)
Ie	253-255 Dioxane	$C_{14}H_{10}N_2O_4$	62.28 (62.22)	3.72 (3.73)	10.40 (10.37)	3080 broad, (3560), 1600, 1590, 1560, 1510, 1350, 1040, 850, 760.	6.45 (broad s, H^a), 7.30 (m, H^d), 7.95 (broad s, H^b), 8.30 (m, $H^c + H^{c'}$).	258 (4.01), 320 sh, 353 (4.18)

(a) Values in parentheses refer to the calculated percentages. (b) Potassium bromide; values in parentheses refer to chloroform solution. (c) DMSO solution; TMS as internal reference; coupling constants are reported in Hz; chemical shifts quoted in the case of multiplets were measured from the approximate center. (d) Solvent, methanol.

Table III

Analytical and Spectral Data of V



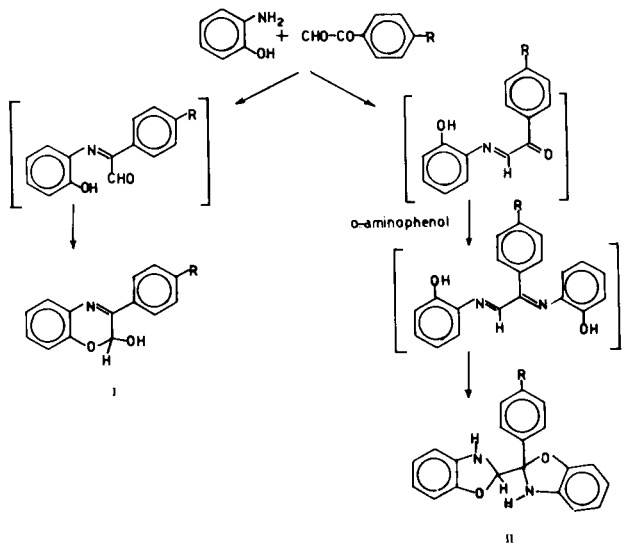
Compound	M.p. °C Solvent	Formula	Analysis (a) C	H	N	Ir ν max, cm^{-1} (b)	Pmr δ, ppm (c)	Uv nm, (Log ϵ) (d)
Va	91-92 Ethanol	$C_{16}H_{13}NO_3$	72.07 (71.90)	4.88 (4.90)	5.26 (5.24)	1750, 1620, 1590, 1570, 1480, 1380, 1210, 990, 940, 760	2.00 (s, H^b), 7.30 (m, $H^c + H^d$), 7.58 (s, H^a), 7.95 (m, $H^{c'}$).	227 (4.03), 234 (4.03) 294 (4.20), 310 sh
Vb	119-120 Ethanol	$C_{17}H_{15}NO_3$	72.59 (72.58)	5.41 (5.37)	5.06 (4.98)	1750, 1615, 1590, 1560, 1480, 1375, 1210, 1000, 930, 840, 760	2.00 (s, H^b), 2.36 (s, CH_3), 7.30 (m, $H^c + H^d$), 7.52 (s, H^a), 7.90 (d, $H^{c'}$, J = 9).	230 (4.15), 235 (4.13) 297 (4.29), 320 (4.29)
Vc	192-194 Ethanol	$C_{16}H_{12}ClNO_3$	63.62 (63.78)	3.99 (4.00)	4.78 (4.65)	1760, 1620, 1600, 1560, 1480, 1380, 1200, 1000, 950, 850, 760	2.00 (s, H^a), 7.30 (m, $H^c + H^d$), 7.64 (s, H^a), 8.00 (d, $H^{c'}$, J = 9)	230 (4.06), 237 (4.05) 300 (4.26), 320 (4.18)
Vd	139-140 Ethanol	$C_{17}H_{15}NO_4$	68.61 (68.68)	5.17 (5.09)	4.78 (4.71)	1760, 1610, 1590, 1570, 1485, 1370, 1200, 990, 930, 840, 765	2.00 (s, H^b), 3.94 (s, OCH_3), 7.25 (m, $H^c + H^d$), 7.52 (s, H^a), 7.95 (d, $H^{c'}$, J = 9)	235 (4.17), 328 (4.39) 335 sh
Ve	180-182 Ethanol	$C_{16}H_{12}N_2O_5$	61.67 (61.54)	3.91 (3.87)	9.04 (8.97)	1760, 1615, 1600, 1565, 1520, 1350, 1200, 990, 940, 860, 765	2.00 (s, H^b), 7.40 (m, H^d), 7.62 (s, H^a), 8.30 (m, $H^c + H^{c'}$)	255 (3.98), 318 sh 345 (4.21)

(a) Values in parentheses refer to the calculated percentages. (b) Potassium bromide. (c) DMSO solution; TMS as internal reference; coupling constants are reported in Hz; chemical shifts quoted in the case of multiplets were measured from the approximate center. (d) Solvent, methanol.

which requires, initially, a nucleophylic attack by the lone pair of nitrogen atom.

We must hypothesize, therefore, that the amino group reacts with the keto carbonyl group to give benzoxazines (I), and with the aldehyde carbonyl group to give dibenzoxazoline (II) as in the following scheme.

Scheme 2



EXPERIMENTAL

Ir spectra were measured with a Perkin-Elmer model 417 spectrophotometer and pmr spectra on a Perkin-Elmer R32 instrument at a probe temperature of about 38°. The uv spectra were recorded on a Cary model 14 spectrophotometer. Melting points are uncorrected.

General Procedure of Condensation Between *o*-Aminophenol and α-Dicarbonyl Compounds.

Molar ratio 1:1 or 2:1 of *o*-aminophenol and phenylglyoxal (or its *p*-substituted derivatives) in absolute ethanol solution were refluxed for three hours, under stirring, in a dry reaction vessel. After cooling the resulting solid benzoxazine (I) was filtered and purified by several recrystallizations from the proper solvents. From the filtered solution, the solvent was evaporated under vacuum. The sticky residue, purified from benzene and then from carbon tetrachloride, gave the solid dibenzoxazoline (II) that were recrystallized several times from proper solvents. For a quantitative determination of the reaction products a better separation was obtained by:

Thin Layer Chromatography.

The crude mixture, obtained from the reaction of *o*-aminophenol with α-dicarbonyl compounds, either with 1:1 or 2:1 molar ratios, were separated on silica gel F_{254} plates (0.25 mm x 20 cm x 20 cm; E. Merck, Darmstadt). Plates were heat-activated at 100° for one hour, stored in a dessiccator and developed using benzene as the mobile phase. The chromatography tank was allowed to equilibrate for 30 minutes at 25° with 5 ml. of the mobile phase in the bottom. The plates were visualized under long-wavelength uv light.

2-Acetoxy-(2*H*)-3-aryl-1,4-benzoxazines (Va→e).

Excess of acetic anhydride (8 ml.) was added to 1 g. of Ia→e. The mixture was boiled for two hours and, after cooling, a solid precipitated upon dilution with an equal volume of water. The crude products were recrystallized from ethanol.

2-Acetoxy-(2*H*)-3-phenyl-3,4-dihydro-1,4-benzoxazine (VI).

A solution of Va in glacial acetic acid (50 ml.) was hydrogenated at atmospheric pressure and room temperature using Adams catalyst. The reaction stopped at the absorption of an equimolecular hydrogen amount. The catalyst was filtered, the solvent was removed under reduced pressure and the product was obtained, white crystals from ethanol, m.p. 147-149°; ir: 3380, 1740, 1615, 1500, 1200, 750 cm^{-1}; pmr (DMSO + deuterium oxide): 1.85 (s, 3H), 4.62 (d, 1H, J = 2 Hz), 6.42 (d, 1H, J = 2 Hz), 6.80 (m, 4H), 7.40 (m, 5H); uv (methanol): 244 (3.94), 293 (3.57).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.25; H, 5.49; N, 5.14.

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(1) The authors are indicated in alphabetical order.

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