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Benzazole derivatives. IX. 2-(4'-aminophenyl)- and 2-(4'-aminophenyl)-1-methyl-benzimidazoles
Reactions with phenolic aldehydes

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Abstract

Some ortho-arylhydroxylated azomethines were synthesized by means of the condensation of 2-(4'-aminophenyl)-benzimidazole and its N-methylated homologue with ortho-phenolic aldehydes, in ethanol, under refluxing, using acetic acid as a catalyst. The N-methylated azomethines and those with free NH differ by colour and solubility in the reaction solvent. Thus, the first are less soluble and separated even during the heating process. The structure of the resulting compounds was confirmed by Ir. spectra, that contain valence vibration absorption for $\nu_{C=N}$ bonds and other characteristic bands. Some of the synthesized compounds were also investigated by means of NMR spectra.

Keywords: 2-(4'-aminophenyl)-benzimidazoles, ortho-phenolic azomethines, condensing reactions, spectral measurements.

Introduction

The 2-phenylbenzimidazoles are already well known for their outstanding biological effects. Recent literature data focused on 2-(aminophenyl)-benzimidazoles that were tested as neoplasm inhibitors [1] and on their derivatives, used as active drugs against malign and non-malign proliferative diseases or as immunosuppressors for transplants [2]. The amines condensation products showed non-tuberculous, anti-inflammatory, antihelmintic activities [3] acting also as regulators for Neural Central System [4]. New investigations made evident the antispasmolitic [5], antiobesity [6] and hypoglycemic [7] effects of some 2-phenylbenzimidazoles. Some benzimidazoles could also be used as receptor modulators for use in the management of pain [8]. p-Phenylbenizimidazoles exhibits non-nucleoside inhibitors of HIV-1 reverse transcriptase, antibacterial and antifungal potential [9, 10]

At the beginning of the researches on 2-phenylbenzimidazoles amines, the first step was to find a simple and efficient synthesis method to obtain the amines. The previous methods described in literature were harder to apply, thus we were perforce to develop a new synthetic path. After many trials we obtained the required results, when we reduced 2-(4'-nitrophenyl)- and 1-methyl-2-(4'-nitrophenyl)-benzimidazoles with Na_2S-$NaHCO_3$ in water-ethanol solutions [11].

Now, having access to the amines, we could use them in various characteristic reactions. Thus, in previous papers we have already described the synthesis of some azomethines derivated from 1-methyl-2-(4'-aminophenyl)-benzimidazole and some aromatic aldehydes [12, 13].

We considered very interesting the continuation of our investigations by studying the azomethines obtained from ortho-phenolic aldehydes. The ortho-hydroxylated azomethines could be used as ligands for metallic complexes. Literature data also present for azomethines the classical dyeing applications (being used for paints, inks, plastics), some of them having special uses, such as DNA markers [14], fluorescent magnetic powders, antifoulling agents, etc [15].

Since the azomethines were obtained from amines having important physiological properties, it would be expected that the new compounds could also have biological applications.

Materials and method

Melting points were measured using a Boetius microscope and are uncorrected. Microanalyses were performed at the "Petru Poni" Macromolecular Chemistry Institute, Iasi. IR spectra were recorded on a Digilab Scimitar Series spectrometer, in KBr pellets, while NMR spectra were registered on a Brücker WM 400 spectrometer, in DMSO-d6 solution.

Synthetic methods were carried out as following:

A. Synthesis of ortho-hydroxyaldehydes

5-Nitrosalycylaldehyde. Salycylaldehyde was nitrated with fumans azotic acid, in acetic acid [16].

5-Bromosalycylaldehyde. Salycylaldehyde was bromided with bromide, in acetic acid [16]

2-Hydroxynaphtaldehyde. Duff method was applied, in which β-naphtol eacted with hexa-methylenetetramine, in acetic acid, when an imine was obtained, that was hydrolized to the formyl derivative [17].

B. Synthesis of the azomethines from 2-(4'-aminophenyl)-1-methyl benzimidazole

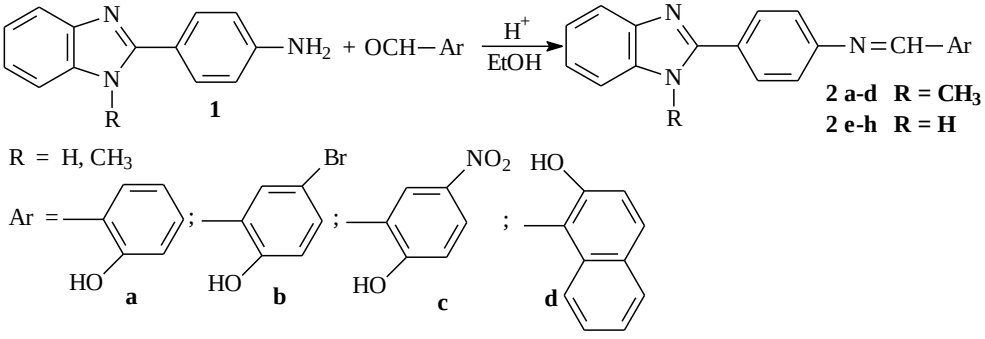
General procedure. Equimolar amounts of amine and phenolic aldehyde, solved in ethanol, were refluxed for 40 minutes, using acetic acid as catalyst. The product separate during heating. For details see table 1.

C. Synthesis of the azomethines from 2-(4'-aminophenyl)-benzimidazole

General procedure. Same as for the methylated isomer. Products separated by cooling and seething for a while.

Results and discussion

We used 2-(4'aminophenyl)-1-methylbenzimidazole and its isomer with free NH group (**1**) in condensing reactions with phenolic aldehydes. The reaction scheme **1** was applied, and the azomethines 2 were obtained.



Scheme 1. Azomethines obtained from ortho-hydroxyarylaldehydes

The condensation reactions were carried out by refluxing in ethanol, for 40-50 minutes, using acetic acid as a catalyst. The N-methylated azomethines frequently separated during the heating period, unlike those with free HN group, which still remained in solution, even after the reaction was over.

Only salycylaldehyde was commercially available, the others having been synthesized. We've tried to condense the N-methylated amine with phenolic ketones, such as o-hydroxyacetophenone. Even when p-toluensulphonic acid was used instead of acetic acid and when the reaction water was azeothropically distillated, the azomethine was only partially obtained.

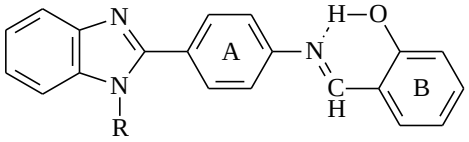
In table 1 are presented the ortho-phenolic azomethines (**2**) and some of their properties.

The yields were between 40-87%. The azomethines purification was made by column chromatography on Al_2O_3 (compound **2a**) and by re-crystallization from various solvents (toluen, benzen, ethylacetate, and methanol). By using ethanol, an insoluble fraction separated from the smaller amount of the soluble one. The product colours are from light to dark yellow and even orange.

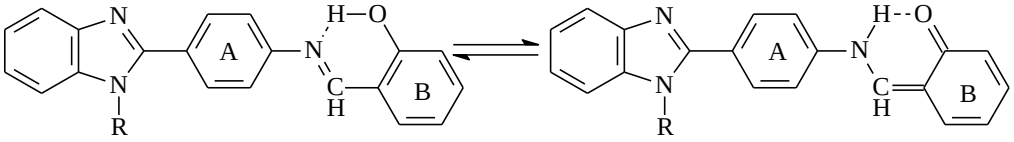
Table 1. Ortho-phenolic azomethines characteristics

No.	Phenolic aldehyde	m.p.	Cryst. Solvent	Colour	Molecular Formula	Analyses N %	
						calc.	exp.
2 a	SA	187-189	fr.insol.ethanol toluen+hexan	yellow	$C_{21}H_{17}N_3O$	12,84	12,96
2 b	HO-NA	182-185	fr.insol.ethanol	orange	$C_{25}H_{19}N_3O$	11,14	11,27
2 c	NO_2SA	265-267	toluen	orange	$C_{21}H_{16}N_4O_3$	15,05	15,17
2 d	BrSA	261-263	fr.insol.ethanol	orange	$C_{21}H_{16}BrN_3O$	10,34	10,45
2 e	NH-SA	200-203	methanol	intense yellow	$C_{20}H_{15}N_3O$	13,41	13,52
2 f	NH-HONA	277-280	methanol	dark yellow	$C_{24}H_{17}N_3O$	11,57	11,68
2 g	NH-NO_2SA	191-193	ethylacetate + ethylic eter	orange	$C_{20}H_{14}N_4O_3$	15,64	15,73
2 h	NH-BrSA	163-165	fr.insol.ethanol	yellow	$C_{20}H_{14}BrN_3O$	10,71	10,81

An important feature of these compounds is the presence of the phenolic hydroxyl group in the ring B, which establishes a H bond with the free electronic pair of the imine N.



The molecule adopts, in his co-planar structure, a trans configuration (at the imino group) that favour the interaction between the free electrons pair of the sp^2 hybridized N and the neighbourhood H atom. The association energy of the H bond stabilizes the molecule on his kelatic structure, by forming a six-membered ring. The substituents on the ring B influence the phenolic group acidity and, thus, the strength of the bond. The nitro group in the compounds **2c, 2g** have a favorable effect on stabilizing the B fragment of the molecule. The ortho-hydroxylated azomethines can adopt a NH-ortho quinolinine structure, by proton transfer.



A study on UV-Vis absorptions would be very useful for establishing these structural aspects. The structure of the compound **2** was investigated by IR and NMR spectral measurements.

The IR spectra show an intense absorption due to νC=N vibration between 1620-1625 cm^{-1}. The benzene rings give a very strong band at 1597 and 1604 cm^{-1}, due to the aromatic νC-C vibrations and at 3026 and 3086 cm^{-1} due to ν=CH vibrations. The methyl groups give weak peaks between 2852 and 2887 cm-1, and 2916 and 2991, respectively, corresponding to sym. and asym. νCH valence vibrations. The δCH_3 deformation vibrations are also to be found between 1460 and 1473 cm^{-1}, and 1361 and 1382 cm^{-1}, respectively.

Table 2. Ir Spectra for ortho-hydroxy azomethines

Comp.	Characteristic bands (cm^{-1}) and their intensity (VS=very strong, S=strong; M=medium; W=weak; VW=very weak)
2 a	439.77 VW, 470.63 VW, 499.56 W, 526.57 W, 553.57 W, 590.22 W, 605.65 W, 651.94 W, 684.73 W, 752.24 VS, 825.53 S, 856.39 M, 908.47 M, 943.19 W, 979.84 W, 1014.55 W, 1033.84 W, 1111.00 W, 1151.50 M, 1172.72 S, 1186.22 M, 1276.87 S, 1325.09 M, 1361.74 M, 1384.89 M, 1415.75 M, 1456.25 S, 1473.61 M, 1490.97 M, 1508.33 M, 1570.05 S, 1598.98 S, 1620.20 VS, 2715.77 VW, 2746.63 VW, 2854.64 VW, 2887.43 VW, 2983.87 VW, 3051.38 VW, 3444.86 W, 3564.44 W.
2 b	433.98 M, 480.27 S, 501.49 S, 653.87 S, 715.59 S, 746.45 VS, 777.31 S, 796.60 S, 839.03 S, 864.11 S, 950.90 S, 968.26 S, 985.62 M, 1035.77 S, 1074.35 S, 1089.78 S, 1141.86 S, 1163.07 VS, 1176.58 VS, 1215.15 S, 1246.01 VS, 1274.94 S, 1315.45 VS, 1346.31 S, 1355.95 M, 1367.53 M, 1402.25 S, 1421.53 S, 1436.96 S, 1465.90 VS, 1512.19 S, 1519.90 S, 1593.20 VS, 1622.13 VS, 1631.77 VS, 2804.49 W, 2889.36 W, 3057.17 W, 3076.45 W, 3400.49 VW.
2 c	445.56 W, 522.71 W, 553.57 W, 642.29 M, 746.45 S, 839.03 M, 902.68 W, 941.26 W, 977.91 W, 1008.77 W, 1091.71 M, 1124.50 W, 1180.43 M, 1226.72 W, 1284.59 S, 1334.74 VS, 1382.96 W, 1435.04 W, 1460.11 M, 1481.33 M, 1529.55 W, 1573.91 M, 1597.06 S, 1620.20 S, 2916.36 VW, 2949.15 VW, 3059.09 VW, 3086.10 VW, 3300.2 VW, 3386.99 W, 3649.31 W, 3674.39 W.
2 d	443.63 W, 526.57 M, 540.07 W, 578.64 W, 592.15 W, 624.93 M, 673.16 W, 702.09 M, 738.73 S, 817.82 VS, 846.75 M, 867.97 M, 916.19 W, 975.98 W, 1008.77 W, 1074.35 M, 1107.14 M, 1170.79 S, 1276.87 VS, 1327.02 M, 1348.24 M, 1382.96 M, 1413.82 M, 1436.96 S, 1473.61 VS, 1504.47 W, 1560.41 S, 1597.06 S, 1616.34 S, 2922.15 VW, 3049.45 W, 3425.57 W.
2 e	439.77 W, 524.64 W, 651.94 VW, 752.24 S, 825.53 S, 854.46 M, 908.47 M, 941.26 W, 979.84 W, 1031.91 W, 1111.00 W, 1151.50 M, 1174.65 S, 1228.65 W, 1251.80 W, 1276.87 S, 1325.09 W, 1348.24 W, 1384.89 M, 1415.75 M, 1452.40 S, 1473.61 M, 1508.33 W, 1570.05 S, 1598.98 S, 1622.13 VS, 2607.75 W, 2713.84 W, 2856.57 W, 2885.50 W, 2924.08 W, 2983.87 W, 3053.31 W, 3444.86 W.
2 f	499.56 W, 565.14 VW, 617.22 W, 684.73 W, 742.59 S, 833.25 M, 962.48 W, 995.27 W, 1039.63 W, 1139.93 M, 1157.29 M, 1211.29 W, 1255.66 W, 1309.66 VS, 1346.31 VS, 1411.89 W, 1442.75 W, 1494.83 M, 1523.76 M, 1544.98 M, 1600.91 VS, 1624.06 VS, 2814.14 W, 2929.86 M, 3032.09 M, 3059.09 M, 3155.54 M, 3419.78 M.
2 g	514.99 W, 588.29 W, 615.29 W, 638.44 W, 744.52 S, 829.39 M, 906.54 W, 945.12 W, 985.62 W, 1006.84 W, 1087.85 M, 1126.43 M, 1184.29 M, 1230.58 S, 1251.80 M, 1284.59 S, 1336.67 VS, 1388.74 W, 1450.47 S, 1479.40 S, 1517.97 S, 1612.49 VS, 2860.43 VW, 2924.08 VW, 2966.51 VW, 3055.24 W, 3381.21 W, 3614.59 VW.
2 h	447.48 VW, 516.92 W, 553.57 VW, 590.22 W, 623.01 M, 671.23 W, 704.02 W, 744.52 M, 777.31 W, 821.67 S, 916.19 W, 979.84 W, 1012.63 W, 1076.28 W, 1128.35 M, 1170.79 VS, 1253.73 M, 1276.87 S, 1350.17 S, 1382.96 M, 1415.75 M, 1454.32 S, 1475.54 VS, 1504.47 M, 1560.41 S, 1597.06 S, 1618.27 S, 2808.35 VW, 2926.01 VW, 3030.16 VW, 3051.38 W, 3425.57 W

The compounds **2c, 2g** show the vibration bands for symmetrical and asymmetrical νNO_2 between 1334 and 1336 cm^{-1}, and 1517 and 1529 cm^{-1}, respectively. Within the high frequency range the valence absorptions vibrations νOH and νNH can be noticed.

The azomethine compounds are frequently used as ligands for metallic complexes, used for cation dosage or in industrial applications as colour substances, fluorescent magnetic powders etc.

Conclusions

Due to te known biological active properties of derivatives of the 2-phenylbenzimidazoles we had to develop a new synthetic method for the p-aminophenyl-benzimidazole from the nitroderivative because the previous methods described in literature were harder to apply [11].

The obtained amines, were then used for condensing reactions with arylaldehydes [12, 13]. We also continuated our investigations by studying the azomethines obtained from ortho-phenolic aldehydes.

Since the azomethines were obtained from amines having important physiological properties, it would be expected that the new compounds could also have biological applications.

Thus, the obtained ortho-hydroxylated azomethines might be used as ligands for metallic complexes. Also, the azomethines could have classical dyeing, DNA markers, antifoulling agents, antioxidants etc. So, the next step will be to try and test the biological activity of the synthetized compounds.

References

1. WEIERSHAUSEN U., SATZINGER G., HERRMANN W., *Pat.Germ. EP 194,529*, 17 Sept 1986., CA. 218879b, **105** (1986).
2. PODUNAVIC-KUZMANOVIC S.O., LEAVIC V.M., ROGAN J., BALIZ J., *J.Serb.Chem.Soc.*, **64**, 381 (1999).
3. MOHAN R., AGARWAL C., AGARWAL R., MISRA V., *Pharmacol.Res.Commun*, **16**(4)**,** 321 (1984).
4. YOKOMORI S., HAYASHI M., HATAYAMA K., SODA K., *JP 63253073* (1987).
5. HAUEL N., MULLER E., AUSTEL V., *Ger.Patt no. DE 3346575* (1983)
6. HOULIHAN W.J., *U.S.Patt. no. US 4212876* (1978)
7. HAYSHIDA H., HATANAKA K., KATO T., *Jap. Patt. WO 2004-JP8064*, (2004)
8. PAGE D., LIU Z., TREMBLAY M., *Eur.Patt no. WO 2005 – SE1404* (2005).
9. SONDI S.M., VERMA R.P. *Indian J.Pharm.Sci.*, **62(1),** 71 (2000).
10. GÖKER H., KÜS C., BOYKIN D.W., YILDIZ S., ALTANLAR N., *Bioorg.Med.Chem.*, **10**, 2589 (2002).
11. CERNATESCU C., COMANITA E., GORDUZA V.M., *Bul. U.T.Iasi,* **Tom XLIX (LIII),** fasc. 5, 2003, p.149-154.
12. CERNATESCU C., COMANITA E., "*Benzazole derivatives. VI. Synthesis of some azomethines from 2-(4'-aminophenyl)-1-methylbenzimidazole*", Chemical Industry & Chemical Engineering Quaterly, in press
13. CERNATESCU C., COMANITA E., "*Benzazole derivatives. VI. Synthesis of some azomethines from 2-(4'-aminophenyl)-benzimidazole. Quaternization reaction of N-methylated azomethines to benzimidazolium salts*", Turkish J.Chem., in press.
14. MOREDA W., FORRESTER A.R., *Tetrahedron*, **53** (37)**,** 12595 (1997).

15. LE BRIS M.T., WAHL H., *Comptes Rendues hebdomadaires des Sciences de l'Academie de Sciences*, **245**, 2058 (1957).
16. GADJEV N.I., DELIGEORGIEV T.G., *Dyes and Pigments*, **14**, 73 (1990).
17. SANIELEVICI H., URSEANU F., *Sinteze de intermediari aromatici*, vol.I, Ed. Tehnica, (1983).
18. MORIARTY R.M., HOU K.CH., PRAKASH I., ARORA S. K., *Org.Synth*, collective vol. **7**, 263.(1989).