A Simple Synthesis of a New Heterocycle from *N,N'*-Bis[2-hydroxybenzylidene]-2-hydroxy-α,α-tolyldiamine and Carbonyl Compounds

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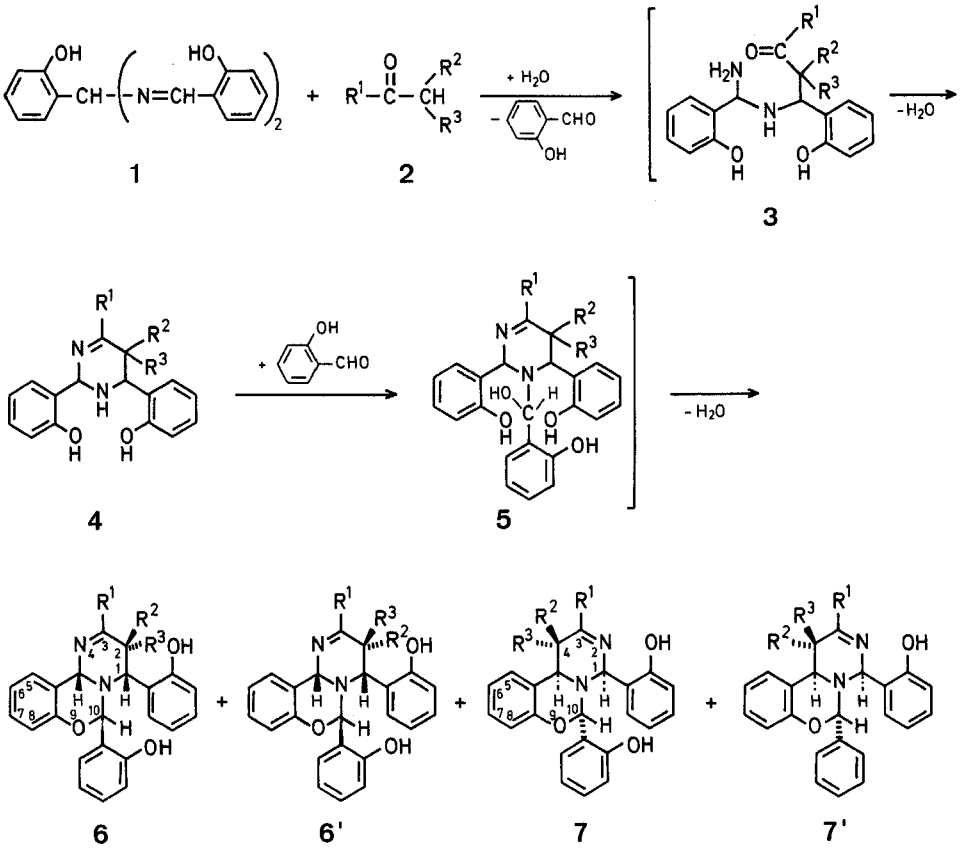
Although a number of investigations has been made concerning the reactions of *N,N'*-dibenzylidene-α,α-tolyldiamine[1,2], little is known of base-catalysed reactions of *N,N'*-bis[2-hydroxybenzylidene]-2-hydroxy-α,α-tolyldiamine (**1**)[3,4]. We now wish to report a one-step synthesis of a new heterocyclic system, 1*H*,2*H*,10*H*-pyrimido[1,2-*c*][1,3]benzoxazine (**6**) from **1** and aldehydes or ketones in the presence of base. An equimolar solution of **1** and an aldehyde or a ketone (**2**) in methanol was stirred at room temperature in the presence of ammonium acetate or potassium carbonate, until no further precipitate was produced. Work-up of the precipitates gave a mixture of **6** and 1*H*, 4*H*, 10*H*-pyrimido[3,4-*c*][1,3] benzoxazine (**7**) in an excellent yield. The reaction is believed to be initiated by the Michael reaction between **1** and the carbonyl compound **2**. The removal of one molecule of salicylaldehyde from the adduct, followed by the cyclization of the intermediate **3** leads to the formation of the intermediate **4**, which in turn condenses again with the salicylaldehyde to produce **5**. The cyclization of **5** could occur in two ways, affording a mixture of two structural isomers, **6** and **7**. Each of the products has sixteen possible geometric isomers about the molecular plane. In fact, however, with each product only two isomers were detected by T.L.C. (The mass spectra revealed that they had the same molecular mass and similar fragmentation patterns). When two substituents, R^2 and R^3, were equal (**6b**) only one isomer was isolated. This fact suggests that the two compounds are

isomeric about the geometric configuration of the substituents R^2 and R^3 at the **2** position. Inspection of molecular models reveals that the conformations (**6** and **7**) are stereochemically most favored. The N.M.R. and mass spectral data also support the assignments: the anisotropic effect of the phenyl groups, the nuclear Overhauser effect between N—CH—N and N—CH—, and the long range coupling constants of R^1 (in case of $R^1=H$) with N—CH—N, were used for the determinations of the conformations.



	R^1	R^2	R^3
a	H	CH_3	CH_3
b	CH_3	CH_3	CH_3
c		H	CH_3

Preparation of *N,N'*-Bis[2-hydroxybenzylidene]-2-hydroxy-α,α-tolyldiamine (1):

To a solution of salicylaldehyde (122 g, 1 mol) in methanol (150 ml), ammonium acetate (78 g, 1 mol) was added and after vigorous stirring at room temperature for 5 h, the mixture was allowed to stand overnight. A resulting greenish-yellow precipitate was filtered, washed with methanol (30 ml) and water, and then recrystallized from tetrahydrofuran/methanol (3:1 volume ratio); yield: 87 g (75%); m.p. 165–166°.

$C_{21}H_{18}O_3N_2$	calc.	C 72.82	H 5.24	N 8.09
(346.4)	found	72.79	5.26	8.02

I.R. (KBr): ν_{max} = 3250, 1620 cm^{-1}.

^{1}H-N.M.R. (DMSO): δ = 8.81 (s, 2H, N=CH—), 7.6–6.7 (m, 12H$_{arom}$), 6.41 ppm (s, 1H, N—CH—N).

1*H*,10*H*-1,10-Bis[2-hydroxyphenyl]-2,2-dimethylpyrimido[1,2-*c*]-[1,3]benzoxazine (6a):

A mixture of **1** (3.5 g, 0.01 mol), methylpropanal (0.87 g, 0.012 mol), and ammonium acetate (0.77 g, 0.01 mol) in methanol (15 ml) was vigorously stirred at 25–35° for 32 h. A pale yellow crystalline matter which precipitated was filtered, washed with methanol (ca. 10 ml), and dried; yield: 3.2 g (82%). N.M.R. spectra of this material showed only the spectra of **6a** form. This was recrystallized from the solution of tetrahydrofuran and methanol: m.p. 177–178°.

$C_{25}H_{24}O_3N_2$	calc.	C 74.98	H 6.04	N 7.00
(400.5)	found	75.03	6.05	7.01

I.R. (KBr): ν_{max} = 3420, 2960, 1625, 1580 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 13.05 (s, 1H, O—H), 12.82 (s, 1H, O—H), 8.63 (d, 1H, N—CH—N, J = 1.8 Hz), 8.48 (s, 1H, O—CH—N), 7.5–6.5 (m, 12H$_{arom}$), 5.38 (d, 1H, N=CH—, J = 1.8 Hz), 4.08 (s, 1H, N—CH—), 1.17 (s, 3H, —CH$_3$), 1.04 ppm (s, 3H, —CH$_3$).

1*H*,10*H*-1,10-Bis[2-hydroxyphenyl]-2,2,3-trimethyl-pyrimido-[1,2-*c*][1,3]benzoxazine (6b) and 1*H*,10*H*-1,10-Bis[2-hydroxyphenyl]3,4,4-trimethyl-pyrimido[3,4-*c*][1,3]benzoxazine (7b):

A mixture of **1** (3.5 g), isopropyl methyl ketone (1.03 g, 0.012 mol), and ammonium acetate (0.77 g) in methanol (15 ml) was vigorously stirred at 25–35° for 4 h and worked up as above to yield a pale yellow crystalline mass which was composed of a mixture of **6b** and **7b** (molar ratio **6b**:**7b** = 7:3); yield: ~3.9 g (94%).

$C_{26}H_{26}O_3N_2$	calc.	C 75.34	H 6.32	N 6.76
(414.5)	found	75.17	6.38	6.72

6b: m.p. 227–228°.

I.R. (KBr): ν_{max} = 3420, 2970, 1624, 1579 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 13.29 (s, 1H, O—H), 13.14 (s, 1H, O—H), 8.51 (s, 1H, N—CH—N), 8.45 (s, 1H, O—CH—N), 7.5–6.7 (m, 12H$_{arom}$), 4.00 (s, 1H, N—CH—), 1.67 (s, 3H, N=C(CH$_3$)—), 1.22 (s, 3H, —CH$_3$), 1.16 ppm (s, 3H, —CH$_3$).

7b: m.p. 196–197°.

I.R. (KBr): ν_{max} = 3420, 2970, 1624, 1579 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 13.14 (br, 2H, O—H), 8.86 (s, 1H, O—CH—N), 8.61 (s, 1H, N—CH—N), 7.6–6.9 (m, 12H$_{arom}$), 4.41 (s, 1H, N—CH—), 1.60 (s, 3H, N=C(CH$_3$)—), 1.20 (s, 3H, —CH$_3$), 0.93 ppm (s, 3H, —CH$_3$).

1*H*,2*H*,10*H*-1,10-Bis[2-hydroxyphenyl]-2-methyl-3-phenylpyrimido[1,2-*c*][1,3]benzoxazine (6c and 6′c) and 1*H*,4*H*,10*H*-1,10-Bis[2-hydroxyphenyl]-4-methyl-3-phenylpyrimido[3,4-*c*][1,3]benzoxazine (7c and 7′c):

A mixture of **1** (17.5 g, 0.05 mol), propiophenone (6.7 g, 0.05 mol), and ammonium acetate (3.8 g, 0.05 mol) in methanol (50 ml) was vigorously stirred at 25–35° for 6 h and worked up as described above to yield a pale yellow crystalline mass which was composed of mixture of **6c, 6′c, 7c**, and **7′c**; yield: 23 g (99%). The mixture was chromatographed over silica gel with chloroform as eluent.

$C_{30}H_{28}O_3N_2$	calc.	C 77.56	H 6.08	N 6.03
(464.5)	found	77.70	6.12	5.94

6c; yield: 6.6 g; m.p. 222–223°.

I.R. (KBr): $\nu_{max} = 3430, 2920, 1623, 1580\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 13.09$ (s, 1H, O—H), 12.84 (s, 1H, O—H), 8.78 (s, 1H, O—CH—N), 8.28 (s, 1H, N—CH—N), 7.65–6.75 (m, 17 H_{arom}), 4.33 (d, 1H, N—CH—, $J = 5.0$ Hz), 2.97 (m, 1H, —CH(CH_3)—), 1.10 ppm (d, 3H, —CH(CH_3)—, $J = 6.8$ Hz).

6′c; yield: 3.9 g; m.p. 202–203°.

I.R. (KBr): $\nu_{max} = 3430, 2920, 1623, 1580\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 12.89$ (s, 2H, O—H), 8.64 (s, 1H, O—CH—N), 8.15 (s, 1H, N—CH—N), 7.65–6.7 (m, 17 H_{arom}), 4.22 (d, 1H, N—CH—, $J = 7.8$ Hz), 2.78 (m, 1H, —CH(CH_3)—), 1.07 ppm (d, 3H, —CH(CH_3)—, $J = 6.8$ Hz).

7c; (containing trace amounts of **7′c** which could not be separated); yield: 0.55 g; m.p. 193–194°.

I.R. (KBr): $\nu_{max} = 3430, 2920, 1623, 1580\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 13.28$ (s, 1H, O—H), 13.12 (s, 1H, O—H), 8.69 (s, 1H, N—CH—N), 8.46 (s, 1H, O—CH—N), 7.9–6.85 (m, 17 H_{arom}), 4.72 (d, 1H, N—CH—, $J = 5.5$ Hz), 2.88 (m, 1H, —CH(CH_3)—), 0.85 ppm (d, 3H, —CH(CH_3)—, $J = 6.8$ Hz).

The reaction of acetaldehyde, cyclopentanone, cyclohexanone, ethyl acetoacetate, pinacoline, methyl isobutyl ketone or many other carbonyl compounds with **1** in the presence of ammonium acetate was similar to that described above. Ammonium acetate was superior to potassium carbonate as the catalyst of the reaction.

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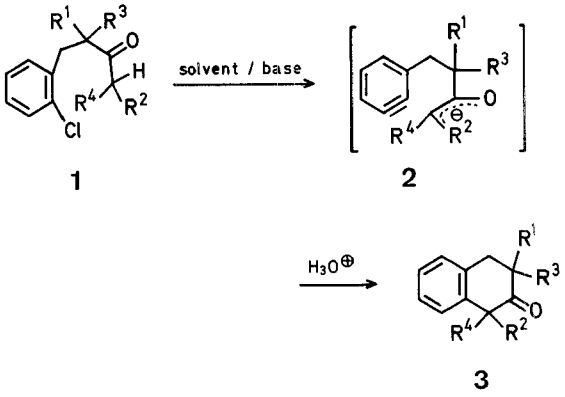
[1] D. H. Hunter, S. K. Sim, *J. Amer. Chem. Soc.* **91**, 6202 (1969).
[2] K. Sugiyama, J. Yoshimura, *Kogyo Kagaku Zasshi* **73**, 2313 (1970).
[3] E. W. Cottman, R. B. Moffett, S. M. Moffett, *Proc. Indiana Acad. Sci.* **47**, 124 (1938).
[4] T. Tsumaki, Y. Muto, M. Tanaka, *J. Chem. Soc. Japan Pure Chem. Sect.* **74**, 161 (1953).

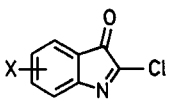
Errata

B. Loubinoux, P. Caubere, *Synthesis* **1974**, 201–203;
The formula scheme (p. 201) should be:



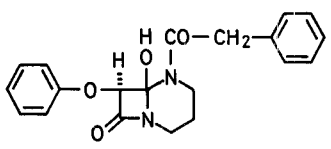
1 2 3

J. Grimshaw, W. J. Begley, *Synthesis* **1974**, 496–498;
The formula **2** in Table 1 (p. 497) should be:



2

A. K. Bose, J. C. Kapur, M. S. Manhas, *Synthesis* **1974**, 891–894;
The formula for compound **18** (p. 891) should be:

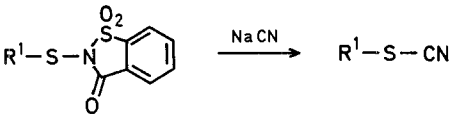


18

H. R. Kricheldorf, E. Leppert, *Synthesis* **1975**, 49–50;
The last entry in the first column of the Table (p. 50) should be:
N-phenyl-*N*-methylimido.

S. Kasina, J. Mematollahi, *Synthesis* **1975**, 162–163;
The name of compound **2** should be:
5,10-dioxo-5*H*,10*H*-diimidazo[3,4-*a*; 3′,4-*d*]pyrazine.

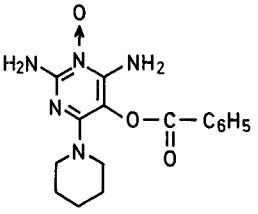
M. Furukawa, T. Suda, A. Tsukamoto, S. Hayashi, *Synthesis* **1975**, 165–167;
The reaction scheme **1**→**4** (p. 166) should be:



1 4

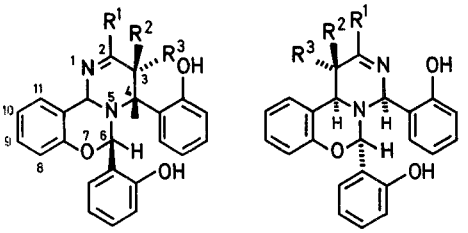
H. Singh, S. Sharma, R. N. Fyer, *Synthesis* **1975**, 325–326;
The name of the title compounds **2** should be:
5-oxobenzimidazo[2,1-*b*][1,3]benzoxazines.

J. M. McCall, R. E. TenBrink, *Synthesis* **1975**, 443–444;
The formula for compound **4** should be:



4

S. Kambe, T. Takajo, K. Saito, T. Hayashi, A. Sakurai, H. Midorikawa, *Synthesis* **1975**, 802–804;



6 7

The names for compounds **6** should be:
6a: 4,6-Bis[2-hydroxyphenyl]-3,3-dimethyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine
6b: 4,6-Bis[2-hydroxyphenyl]-2,3,3-trimethyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1.3]benzoxazine
6c: 4,6-Bis[2-hydroxyphenyl]-2-methyl-3-phenyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine

The names for compounds **7** should be:
7b: 4,6-Bis[2-hydroxyphenyl]-1,1,2-trimethyl-1,4-dihydro-11b*H*-pyrimido[3,4-*c*][1,3]benzoxazine
7c: 4,6-Bis[2-hydroxyphenyl]-1-methyl-2-phenyl-1,4-dihydro-11b*H*-pyrimido[3,4-*c*][1,3]benzoxazine