SYNTHESIS AND PROPERTIES OF sym-TRIAZINES.
10* SYNTHESIS OF 2,4-DIAMINO-sym-TRIAZINES CONTAINING A STERICALLY HINDERED PHENOL SUBSTITUENT

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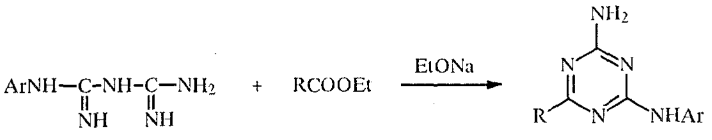
Condensation of N-(4-hydroxy-3,5-di-tert-butylphenyl)biguanide with esters in the presence of catalytic amounts of sodium ethylate gives 2-amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-substituted sym-triazines. When the trichloroacetate ester is used the main product is 2-amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-oxo-1(5)H-sym-triazine.

In continuation of studies on sym-triazines containing a sterically hindered phenol substituent [2-5] we have synthesized N-substituted 2,4-diamino-sym-triazines containing the 2,6-di-tert-butyl-phenol substituent. Compounds of this type show promise as thermostable antioxidants for hydrocarbon fuels, lubricating oils, and polymeric materials [6, 7].

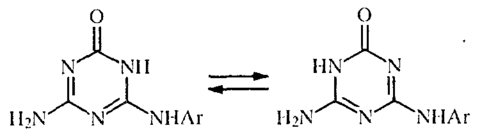
It is known [8] that N-substituted 2,4-diamino-sym-triazines are formed via condensation of biguanides with acid chlorides, esters, or anhydrides. We have studied the potential of this method for synthesis of 2-amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-R-sym-triazines (II).

We used as starting materials N-(4-hydroxy-3,5-di-tert-butyl-phenyl)biguanide (I). N-Substituted 2,4-diamino-sym-triazines IIa-i were generally obtained in high yield (Table 1) by condensation of equimolar amounts of biguanide I with esters in ethanol in the presence of sodium ethylate.



I

IIa-i



III

Ar = 4-HO-3,5-t-$Bu_2C_6H_2$; IIa R = Me, b R = $C_{11}H_{23}$, c R = $ClCH_2$, d R = F_3C, e R = Ph, f R = $ArCH_2CH_2$, g R = 2-furyl, h R = 3-pyridyl, i R = CCl_3

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*For communication 9 see [1].

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TABLE 1. Data for Synthesized Compounds

Compound	Empirical formula	mp, °C*	R_f**	PMR Spectrum, δ, ppm***	Yield, %
II a	$C_{18}H_{27}N_5O$	194...195	0,39 (a)	1,60 (18H,s, *t*-Bu), 2,52 (3H,s, CH_3), 4,87 (1H,s., OH), 5,92 (1H,br.s, NH), 6,82 (2H,br.s , NH_2), 7,15 (2H, s, H_{arom})	74
II b	$C_{28}H_{47}N_5O$	152...153,5	0,50 (b)	1,12 (3H,t, CH_3), 1,72 (18H,s , *t*-Bu), 2,05...2,36 (18H,m , CH_2), 2,92 (2H,t , CH_2), 5,06 (1H,s , OH), 5,84 (1H, br.s, NH), 7,08 (2H,br.s , NH_2), 7,23 (2H, s, H_{arom})	78
II c	$C_{18}H_{26}ClN_5O$	134...136	0,50 (a)	1,58 (18H, s, *t*-Bu), 3,85 (2H,s, CH_2Cl), 4,92 (1H,s , OH), 5,52 (1H,br.s , NH), 6,91 (2H,br.s , NH_2), 7,26 (2H, s, H_{arom})	80
II d	$C_{18}H_{24}F_3N_5O$	122...123,5	0,74 (a)	1,66 (18H, s, *t*-Bu), 4.98 (1H,s, OH), 5,92 (1H br.s, NH), 6,90 (2H,br.s , NH_2), 7,28 (2H s H_{arom})	84
II e	$C_{23}H_{29}N_5O$	218...219	0,58 (b)	1,54 (18H, s, *t*-Bu), 5,08 (1H,s , OH), 5,84 (1H br.s, NH), 6,95 (2H,br.s, NH_2), 7,18 (2H, s, H_{arom}), 7,38...7,56 (5H, m, Ph)	61
II f	$C_{33}H_{49}N_5O_2$	178...179	0,45 (b)	1,54 (18H,s., *t*-Bu), 1,78 (18H, s, *t*-Bu), 4,08...4,20 (4H, m, CH_2CH_2), 4,82 (1H,s, OH), 5,06 (1H, s, OH), 6,08 (1H br.s , NH), 6,86 (2H,br.s, NH_2), 7,16 (2H,s ,H_{arom}), 7,26 (2H, s, H_{arom})	75
II g	$C_{21}H_{27}N_5O_2$	108...109,5	0,70 (b)	1,70 (18H,s, *t*-Bu), 4,82 (1H,s , OH), 5,56 (1H br.s, NH), 6,28 (1H, dd 3-H furan, J_{35}=0,7Hz), 6,54 (1H, dd , 4-H furan, J_{34}=3,5 Hz), 6,88 (2H, br.s , NH_2), 7,15 (2H,s,H_{arom}), 7,32 (1H, dd , 5-H furan, J_{45}=1,8 Hz)	60
II h	$C_{22}H_{28}N_6O$	276...277,5	0,22 (b)	1,60 (18H, s, *t*-Bu), 4,86 (1H,s., OH), 6,02 (1H, br.s, NH), 6,84 (2H, br.s, NH_2), 7,14 (2H,s,H_{arom}), 7,36...7,72 (4H, m , Py)	64
II i	$C_{18}H_{24}Cl_3N_5O$	156...157	0,55 (a)	1,71 (18H,s , *t*-Bu), 5,08 (1H, s, OH), 5,85 (1H,br.s , NH), 6,93 (2H, br.s , NH_2), 7,28 (2H,s , H_{arom})	12 (45)****

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*Compound crystallization: IIa,f,h from aqueous DMF, IIb from ethanol, IIc,e,i from aqueous ethanol, IId from benzene–acetone 3:1.

**Solvent system given in brackets.

***Spectra of IIa,e-i recorded in DMSO-D_6, IIb-d in CD_3OD.

****Yield for trichloroacetic anhydride in brackets.

The reaction times and yields of the sym-triazines IIa-i depend on the nature and reactivity of the starting esters. Hence esters of acetic, lauric, and β-(4-hydroxy-3,5-di-tert-butylphenyl)propionic acids form the 2,4-diamino-sym-triazines IIa,b,f in 74-78% yields after refluxing the reaction mixture for 10-12 h. Compounds IIc,d were obtained in 80-84% yield by heating biguanide I with the chloroacetic and trifluoroacetic esters for only 4-5 h. To obtain sym-triazines IIe,g,h from the benzoic, furan-2-carboxylic, and nicotinic esters it was necessary to heat for 18-20 h. The yields were 60-64%.

When the biguanide I was treated with ethyl trichloroacetate, the desired 2,4-diamino-sym-triazine IIi was only obtained in low yield (12-15%), the main product (73%) being 2-amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-oxo-1(5)H-sym-triazine (III). An oxo-1(5)-sym-triazine has previously been reported [9] as the reaction product of trichloroacetate with N-phenylbiguanide.

In agreement with patent literature [10], N-substituted 2,4-diamino-6-(trichloromethyl)-sym-triazines were obtained by condensation of biguanides with trichloroacetic anhydride. In this work sym-triazine IIi was synthesized in 45% yield by refluxing (5-6 h) biguanide I with excess trichloroacetic anhydride. In this case, substantial amounts of oxo derivative III were isolated from the reaction mixture.

The IR spectra of sym-triazine IIa-i show variable intensity absorptions for the stretching (1565-1550, 1420-1410), "breathing" (1115-1105, 1010-995), out of plane (815-805), and in plane (710-695 cm^{-1}) deformations of the sym-triazine ring [2, 4, 5, 11, 12]. Absorptions for the sterically hindered phenol include: a sharp band (3655-3640) for the shielded hydroxyl [13], two medium intensity bands between 1260 and 1210 (Ar–OH in shielded phenols [14]), and two band groups at 885-870 and 830-820 cm^{-1} for the out of plane deformation of the tetrasubstituted benzene ring.

The NH stretching region of IIa-i shows two broad bands at 3465-3380 and 3190-3130 (ν_{as} and ν_s for NH in primary amino NH$_2$ [1, 11]) and a weak band at 3370-3305 cm^{-1} for νNH in the secondary NH groups [2, 5]. The position and nature of the doublet for the N–H and NH$_2$ stretching point to a strong hydrogen bond in the crystal state [11]. The intense absorption at 1685-1670 is assigned to antisymmetric planar deformation of the primary amino groups and the medium intensity bands at 1520-1505 cm^{-1} to associated amino sym-triazines [11, 12, 15]. The sym-triazines IIc,d,i contain electron acceptor groups and the planar ring vibration absorption and NH deformation are significantly shifted to low frequency compared with the remaining compounds.

Evidence that the sym-triazine III exists as the oxo tautomer in the crystalline state is provided by the strong IR maximum at 1695 cm^{-1} which is typical of carbonyl group absorption in oxo heterocycles [12]. Thus in the crystalline state the oxo tautomer III forms strong intermolecular N–H....O=C hydrogen bonds [12]. The last of the above-listed bands is apparently associated with stretching of the NH bond. This signal assignment at 2985 cm^{-1} is made by comparing the IR spectrum of cyanuric acid [15] in which this band is most typical. In the spectrum of III the planar ring stretching vibrations are shifted to higher frequency at 1585 and 1452 cm^{-1} but the position of the remaining bands is almost unchanged.

The hydroxyl PMR signals of IIa-i appear as a singlet at 4.82-5.08 ppm, typical of phenols [13, 16]. The tert-butyl singlet signals are seen at 1.54-1.74 ppm. The two magnetically equivalent signals for the hydroxyaryl protons appear as singlets at 7.12-7.28 ppm [2, 4, 17] and the primary amino group proton signals as broad singlets at 6.80-7.08 ppm [1, 18]. All of the secondary amino signals are found at higher field [5.52-6.08 ppm] as seen in amino sym-triazines [2, 5, 19].

EXPERIMENTAL

Infrared spectra were recorded on a UR-20 instrument for KBr tablets and NMR spectra on a Bruker WP-80SY using TMS as internal standard. The reaction course and compound purities were monitored by TLC using Al$_2$O$_3$ grade III Brockmann activity using benzene–methanol (20:1) (a) or benzene–methanol (10:1) (b) and iodine vapor visualization. Melting points were determined on a Boetius stage.

The C, H, and N analytical data for the synthesized compounds agreed with that calculated.

N-(4-Hydroxy-3,5-di-tert-butylphenyl)biguanide Hydrochloride (I·HCl, $C_{16}H_{27}N_5O\cdot HCl$). A mixture of 4-hydroxy-3,5-di-tert-butylaniline hydrochloride [20] (25.75 g, 100 mmole) and dicyandiamide (7.04 g, 80 mmole) in dry toluene (200 ml) was refluxed with stirring for 3 h. The product was cooled to 10°C and the precipitate filtered, washed on the filter with dry benzene, and recrystallized from ethanol–ether (5:1) to give I·HCl (30 g, 88%) with mp 160-162.5°C (with decomp.). IR Spectrum: 3645 (OH), 1670 (C=N$^+$), 1655 (C=N), 1265 (C–O), 885 cm^{-1} (C–H).

2-Amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-substituted sym-Triazines (IIa-i) (general method). Hydrochloride I (20.45 g, 60 mmole) was added portionwise with stirring to a solution of sodium ethylate prepared from sodium (1.40 g, 61 mmole) in absolute ethanol (200 ml) kept at 0-5°C. The product was stirred for 30 min at 20°C and sodium chloride filtered off and washed with absolute ethanol (50 ml). The corresponding ester (60 mmole) in absolute ethanol (30 ml) was added to the filtrate and the product was refluxed until disappearance of starting ester (10-12 h according to TLC for IIa,b,f, 4-5 h for IIc,d and 18-20 h for IIe,g,h). Evaporation to dryness in vacuo gave a residue which was chromatographed on an Al_2O_3 column (110 × 5.0 cm) eluting with benzene–methanol (15:1) or chloroform–acetone (10:1) for sym-triazines IIc,d,g. The separated compounds were further purified by recrystallization from a suitable solvent (Table 1) or rechromatography on the Al_2O_3 column (sym-triazine IIg).

2-Amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-oxo-1(5)H-sym-triazine (III, $C_{17}H_{25}N_5O_2$). A solution of ethyl trichloroacetate (1.91 g, 10 mmole) in absolute ethanol (10 ml) was added dropwise with stirring to a solution of biguanide I obtained from hydrochloride I (3.41 g, 10 mmole) and sodium (0.34 g, 15 mmole) in ethanol (30 ml). The reaction mixture was refluxed with stirring for 5 h and evaporated to dryness. The residue was extracted with hot methanol (3 × 25 ml) and crystallized from DMF with the addition of activated carbon. The yield of III was 2.4 g (73%) with mp 302-304°C (with decomp.). PMR Spectrum (DMSO-D_6): 1.58 (18H, s, t-Bu), 4.94 (1H, s, OH), 5.24 (1H, br.s, NH), 5.70 (1H, br.s, NH), 6.64 (2H, br.s, NH_2), 7.18 ppm (2H, s, H_{arom}).

The methanol extract was evaporated and the residue crystallized from aqueous ethanol to give the sym-triazine IIi.

2-Amino-4-(4-hydroxy-3,5-di-tert-butylanilino)-6-trichloromethyl-sym-triazine(IIi). Trichloroaceticanhydride(7.72 g, 25 mmole) was added dropwise with stirring to a solution of biguanide I obtained from hydrochloride I (4.1 g, 12.5 mmole) and sodium (0.29 g, 12.5 mmole) in absolute ethanol (25 ml). The reaction mixture was refluxed with stirring for 6 h and evaporated in vacuo. The residue was washed with ether (2 × 10 ml) and chromatographed on an Al_2O_3 column (75 × 4.5 cm) using chloroform–acetone (10:1) to give sym-triazine IIi (2.91 g, 45%).

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