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SYNTHESIS OF 1-(3,5-DI-tert-BUTYL-4-HYDROXYPHENYL)-2-R-BENZIMIDAZOLES

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Reaction of 2,6-di-tert-butyl-1,4-benzoquinone with o-phenylendiamine gives 2,6-di-tert-butyl-1,4-benzoquinone-4-(N-o-aminophenyl)imine which reacts smoothly with heterocyclic, aromatic and aliphatic aldehydes to form (1-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-substituted benzimidazoles.

It is known that some nitrogen heterocycles, including imidazole and benzimidazole, which contain a 2,6-di-tert-butylphenol residue possess anti-inflammatory and analgesic activity [1] and show anti-oxidant properties [2].

Bisazomethines based on o-phenylendiamine cyclize to form benzimidazole [3]. The reaction conditions decide whether a single compound or a mixture of several substances are formed.

Reaction of 2,6-di-tert-butyl-1,4-benzoquinone with substituted anilines leads to the corresponding iminoquinones [4] but the reaction of this quinone with o-phenylendiamine has not been studied. We have found that reaction of the quinone occurs with one of the amino groups to form the iminoquinone I.

Heterocyclic, aromatic, and aliphatic aldehydes react vigorously with I, apparently via the azomethine iminoquinones II. Further conversion to the benzimidazoles III is possible only through the intramolecular oxidation-reduction of the azomethine bond and the iminoquinone molecular fragment.

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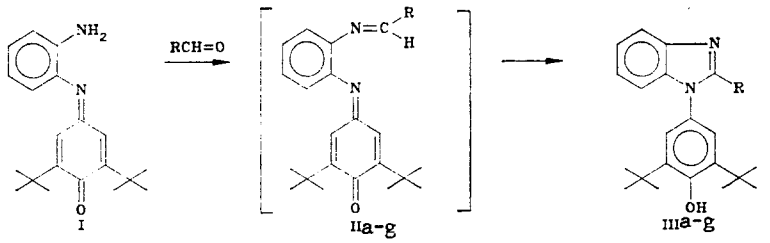

II, III a R=CH_3; b R=$CH(CH_3)_2$; c R=hexyl; d R=C_6H_5; e R=*o*-HO—C_6H_4; f R= 2-furyl ; g R= 2-thienyl

Mixing of iminoquinone I with aldehydes occurs with evolution of heat and formation of blue colored products. Further heating of the reaction mixture at the reflux temperature of the aldehyde for several minutes leads to decolorization and formation of 1-(3,5-di-tert-butyl-4-hydroxphenyl)-2-substituted benzimidazoles IIIa-g, the structure and composition of which were determined by PMR and IR spectroscopy and by elemental analysis.

EXPERIMENTAL

IR spectra were measured on a Specord IR-75 instrument using vaseline mull and on a UR-20 using chloroform. PMR Spectra were obtained in $CDCl_3$ on a Tesla BS-487C (80 MHz) instrument using HMDS internal standard. Elemental analytical data for C, H, and N in IIIa-g agreed with those calculated.

2,6-Di-tert-butyl-1,4-benzoquinone-4-(N-o-aminophenyl)imine (I, $C_{20}H_{26}N_2O$). A solution of 2,6-di-tert-butyl-1,4-benzoquinone (8.80 g, 0.04 mole) and o-phenylendiamine (4.32 g, 0.05 mole) in 1-propanol (10 ml) were refluxed for 4 h, cooled, and water (30 ml) added. The precipitate was triturated, filtered off, and washed with water to give dark claret crystals (11.80 g, 95%) with mp 137°C (from 1-propanol). IR Spectrum (in vaseline mull): 3440, 3300 (NH), 1630 (C=O), 1250 cm^{-1} (t-Bu). PMR Spectrum ($CDCl_3$): 6.97-6.60 (6H, m, arom.); 3.97 (2H, s, NH_2); 1.20 (9H, s, t-Bu); 1.12 ppm (9H, s, t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-methylbenzimidazole (IIIa, $C_{22}H_{28}N_2O$). The iminoquinone I (0.62 g, 2 mmole) and acetaldehyde (2 ml) were mixed. The iminoquinone went into solution, the mixture heated up and the initially dark-red color changed to blue. The product was heated to remove excess aldehyde and held for 2-3 min at 70°C for completion of the reaction. Hexane (5 ml) was added, the solution was refluxed for 1 min and the precipitated solid filtered off and washed with hexane to give colorless crystals of IIIa (0.6 g, 89%) with mp 232-233°C (after successive crystallizations from toluene and methanol). IR Spectrum (in $CHCl_3$): 3630 (OH), 1610 (C=N), 1250 cm^{-1} (t-Bu). PMR Spectrum ($CDCl_3$): 7.63-7.06 (6H, m, arom); 5.83 (1H, s, OH); 2.43 (3H, s, CH_3); 1.36 ppm (18H, s, two t-Bu). The phenolic hydroxyl signal disappeared upon deuteration.

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-isopropylbenzimidazole (IIIb, $C_{24}H_{32}N_2O$). A solution of iminoquinone I (0.31 g, 1 mmole) and isobutyric aldehyde (1 ml) were refluxed for 10 min. The dark red color of the mixture changed to blue. Excess aldehyde was distilled off and the temperature raised to 110°C and held for 5 min to complete the reaction with disappearance of the color. The mixture was cooled, alcohol added (2 ml), and the precipitated solid filtered off to give crystals with mp 223-224°C (from toluene). IR Spectrum (in vaseline mull): 1620 (C=N), 1620 (arom.), 1230 cm^{-1} (t-Bu). PMR Spectrum ($CDCl_3$): 7.70-7.05 (6H, m, arom): 5.63 (1H, s, OH); 2.70 (±H, m, CH); 1.20 (6H, m, two CH_3), 1.36 ppm (18H, s, two t-Bu). The phenolic hydroxyl signal disappeared upon deuteration.

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-n-hexylbenzimidazole (IIIc, $C_{27}H_{38}N_2O$). A mixture of the iminoquinone I (0.31 g, 1 mmole) and n-heptaldehyde (1 ml) were heated to reflux. The solution changed in color from dark red through blue to reddish and was refluxed for 2 min and pentane (3 ml) was added The precipitated solid was filtered off and washed with pentane to give colorless crystals (0.36 g, 90%) with mp 206-208°C (from toluene). PMR Spectrum ($CDCl_3$): 7.70-7.05 (6H, m, arom.); 5.51 (1H, s, OH); 2.77-258 (2H, m, CH_2); 1.18-0.73 (11H, m, CH_3 and four CH_2); 1.37 ppm (18H, s, two t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-phenylbenzimidazole (IIId, $C_{27}H_{30}N_2O$) was obtained similarly to IIIc from iminoquinone I and benzaldehyde (1 ml) as colorless crystals (0.36 g, 90%) with mp 234-235°C (from propanol). IR Spectrum (in vaseline mull): 1610 (C=N), 1600 (arom.), 1250 cm^{-1} (t-Bu). PMR Spectrum ($CDCl_3$): 7.17-7.0 (11H, m, arom.); 5.37 (1H, s, OH); 1.25 ppm (18H, s, two t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-o-hydroxyphenyl-benzimidazole (IIIe, $C_{27}H_{30}N_2O_2$). A mixture of iminoquinone I (0.31 g, 1 mmole) and salicylaldehyde (1 ml) were refluxed for 2-3 min, cooled, alcohol added (3 ml), and the precipitated solid filtered off and washed with alcohol. Colorless crystals (0.4 g, 95%) were obtained which changed to a bluish color with mp 196-197°C (from 1-propanol). IR Spectrum (in $CHCl_3$): 3500 (OH), 1630 (C=N), 1600 (arom.), 1250 cm^{-1} (t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-furyl) benzimidazole (IIIf, $C_{25}H_{28}N_2O_2$). Iminoquinone I (0.62 g, 2 mmole) and furfural (2 ml) were mixed. In the process, heating caused the mixture to crystallize rapidly to a dark blue mass which then became colorless. The mixture was held for 2 min at 160°C, cooled and 1-propanol (2 ml) added. The precipitate was filtered off to give colorless needles with mp 261-263°C (0.7 g, 90%) (from propanol). IR Spectrum (in vaseline mull): 1610 (C=N), 1600 (arom), 1250 cm^{-1} (t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-thienyl)benzimidazole (IIIg, $C_{25}H_{28}N_2O$). A mixture of iminoquinone I (0.62 g, 2 mmole) and thiophen-2-aldehyde (1 ml) were heated to 190°C, held at this temperature for 2 min, cooled, and 1-propanol (2 ml) added. The precipitate was filtered off and washed with propanol and hexane to give yellowish crystals (0.5 g, 61%) with mp 254-255°C (from toluene). PMR Spectrum ($CDCl_3$): 7.12-6.94 (9H, m, arom); 5.45 (1H, s, OH); 1.35 ppm (18H, s, two t-Bu).

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BROMINATION OF 3-ACYL-2-AMINOINDOLES

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Unlike 3-acylindoles, 3-acyl-2-aminoindoles display high selectivity on being electrophilically attacked in the benzene ring, and are substituted at the 6-position. At the same time, an unco-subsitution of the acyl group takes place (to the greatest extent – the formyl group). Direct bromination of 3-acyl- and 3-cyano-2-aminoindoles provides the 6-bromo- and 6,4-dibromo-2-aminoindoles and their derivatives.

In our preceeding publications dealing with the reactions of 2-aminoindoles with electrophilic agents, it was shown that in 2-aminoindole, present in the aminoindolenine and iminoindoline tautomeric forms, and also in its salts, having the structure of an amidinium cation, substitution proceeds preferentially at the 5-position of the indole ring, while in the 2-aminoindole tautomeric form proper – it generally takes place at the 3-position, even if there is a substituent present at this position, as for example in the case of 3-formyl-2-aminoindole I [1, 2].

In the present work we made a detailed study of the bromination of 3-acyl-2-aminoindole in order to establish the orientation of entry of the substituent into the benzene ring of these compounds. It might be assumed that by creating steric hindrances for the unco-attack at the 3-position (in the reagent or in substrate), it would be possible to effect the substitution into the benzene ring. Nevertheless, treatment of compound I with dioxane dibromide led to the same previously obtained 3-bromo derivative II, although the reaction is considerably slowed down (it does not proceed to completion at 0°C in the course of two days). At the same time, we were able by the action of pyridine dibromide, after the usual processing (alkanization, extraction with chloroform, column chromatography)

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