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Urotropin Synthesis of 3,5-Di-*tert*-butylsalicylic Acid Derivatives

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Abstract—The stability of 3,5-di-*tert*-butylsalicylic aldehyde against oxidation is due to autoinhibiting of the chain process. However its oxidation into 3,5-di-*tert*-butylsalicylic acid was performed at the use of acetyl protection of the hydroxy group. In reaction of 6-bromo-2,4-di-*tert*-butylphenol with urotropin the formation was discovered of 3,5-di-*tert*-butylsalicylic acid, its nitrile and amide.

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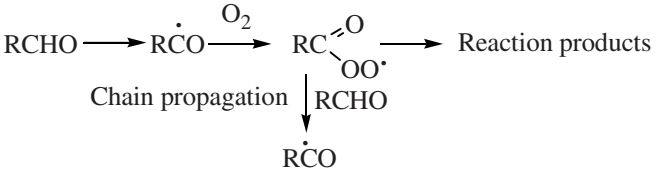
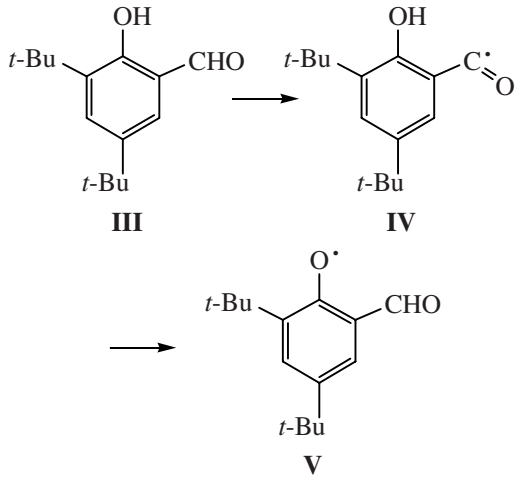
Salicylic acid is prepared by the Kolbe–Schmitt reaction or by oxidation of salicylic aldehyde. Neither of these procedures permits the preparation of 3,5-di-tert-butylsalicylic acid (**I**) from 2,4-di-*tert*-butylphenol (**II**) or 3,5-di-*tert*-butylsalicylic aldehyde (**III**). The stability against oxidation of aldehyde **III** uncommon for a5romatic aldehydes is especially surprising. Revealing the reasons of this stability and the ways to overcome it is interesting from scientific and practical viewpoint. For instance, acid **I** is used as a coordinating ligand for metal complex catalysts. Aldehyde **III** became more accessible thanks to a new modification of its synthesis from phenol **II** and urotropin in the solution of lower carboxylic acids that considerably increased its yield [1].

Aldehydes are known [2] to suffer in the liquid phase autooxidation whose radical chain mechanism involves in the chain initiation stage a formation of an acyl radical by hydrogen abstraction from the formyl group. Further O_2 addition to the acyl radical provides an acylperoxy radical that continues the chain and leads to the formation of the reaction products.

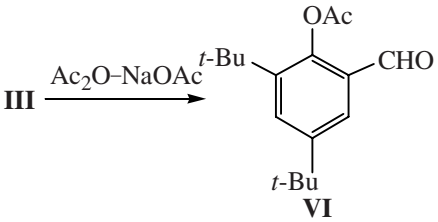


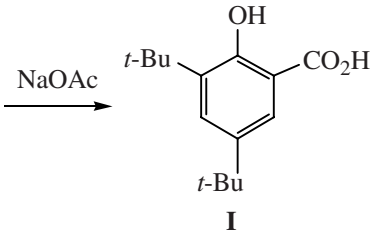
It is natural to presume that the stability of aldehyde **III** against the oxidation is due to autoinhibiting the radical process by the intramolecular hydrogen transfer converting the active acyl radical **IV** into aroxyl radical **V** uncapable of chain propagation.



In this event to achieve the formyl group oxidation it is necessary to block the OH group of aldehyde **III**. To this purpose the acetyl protection is optimum for it is stable to oxidation and readily removed by hydrolysis.

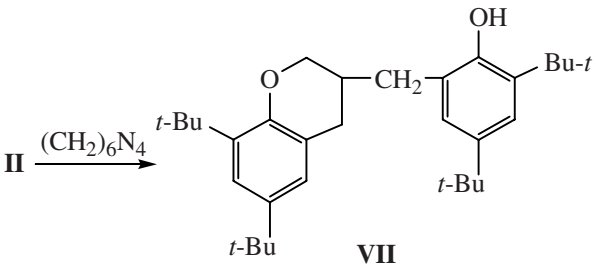
Acetylsalicylic aldehyde (**VI**) was obtained by treating aldehyde **III** with Ac_2O in the presence of NaOAc. The thermolysis of aldehyde **VI** in a melt in the presence of NaOAc resulted in a complete conversion of the aldehyde into acid **I**.

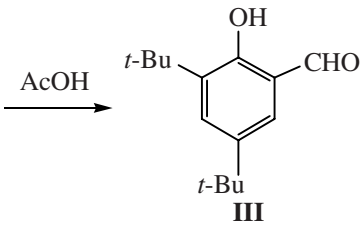




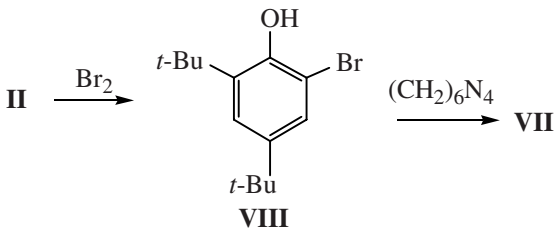
The deprotection from the acetyl group occurred spontaneously in the process of the autooxidation of aldehyde **VI**. At the microwave heating the reaction time is reduced to 10–15 min.

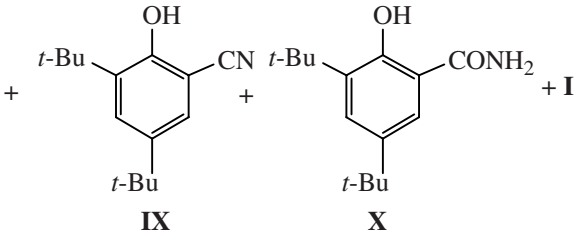
We formerly established that the synthesis of aldehyde **III** from phenol **II** and urotropin under the standard conditions of Duff reaction involved a formation of 6,8-di-*tert*-butyl-3-(3,5-di-*tert*-butyl-2-hydroxybenzyl)-2*H*-3,4-dihydrobenz-1,3-oxazine (**VII**) transforming into the aldehyde through a series of solvolytic and redox reactions [1].



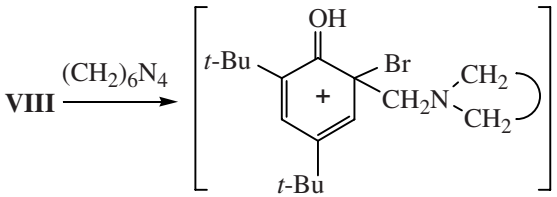


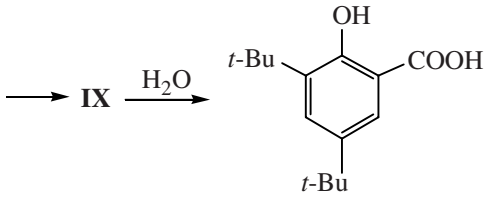
In this study we showed that in the reaction with urotropin a direct introduction is possible of the carboxy (nitrile and amide) functions into the ortho-position of phenol **II** when preliminary into this position was introduced a substituent capable of taking part in the redox reactions of the intermediate as an oxidant. It was revealed by an example of 6-bromo-2,4-di-*tert*-butylphenol (**VIII**) which in reaction with urotropin alongside benzoxazine **VII** gave acid **I**, its nitrile **IX**, and amide **X**.



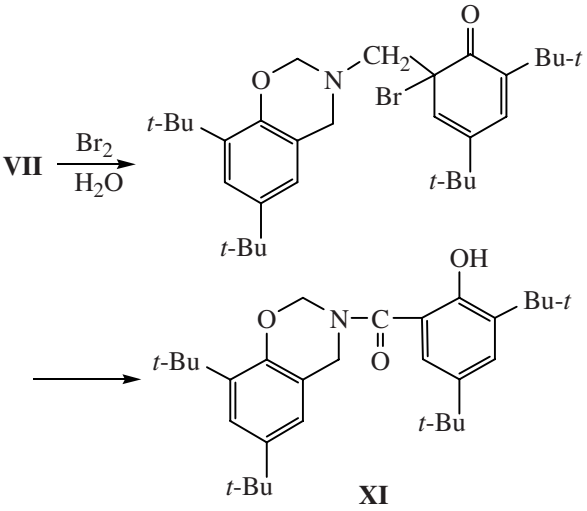


The oxidation of the introduced function most likely occurred as a result of hydride shifts in the stage of a quinolide intermediate

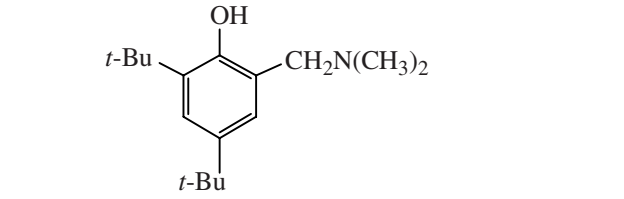




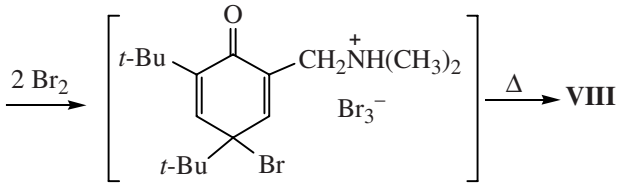
Taking into account these results we performed a conversion of benzoxazine **VII** into N-substituted amide **XI** by treating with bromine.



The presence of a redox-labile dimethylamine moiety is evidently an indispensable condition of such functionalization. This statement is confirmed in particular by comparison with the bromination results of 2,4-di-*tert*-butyl-6-dimethylaminomethylphenol (**XII**) proceeding as *ipso*-substitution and giving bromophenol **VIII**. No derivatives of acid **I** were obtained in this process. In studying probable intermediates we succeeded in detecting an adduct of initial phenol **XII** with two bromine molecules identified as salt **XIII** that possesses limited stability and gradually converted into bromide **VIII**.



XII



XIII

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer WH-250 (250 MHz), internal reference TMS. Mass spectra were measured on a Hitachi M-80 A instrument (electron impact, 70 eV). TLC analysis of the reaction mixtures was carried out on Silufol UV-254 plates.

3,5-Di-*tert*-butylacetylsalicylic aldehyde (VI). To 0.47 g (2 mmol) of aldehyde **III** and 0.31 g (3 mmol) of acetic anhydride was added 0.2 g (2 mmol) of freshly calcined sodium acetate and 2 ml of anhydrous pyridine. The reaction mixture was heated on an oil bath at 160–170°C for 5 h, then it was treated with water acidified with HCl. The formed oily substance was extracted into ether, the extract was dried with Na_2SO_4, the solvent was evaporated, and the residue of the reaction product was recrystallized from hexane. Yield 0.52 g (93%), mp 88–89°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 s (9H), 1.39 s (9H), 2.42 s (3H), 7.68 d (1H), 7.70 d (1H, J_μ 2.4 Hz), 9.91 C (1H). Found, %: C 73.65; H 8.54. $C_{17}H_{24}O_3$. Calculated, %: C 73.80; H 8.75.

3,5-Di-*tert*-butylsalicylic acid (I). A mixture of equimolar quantities of aldehyde **VI** and sodium acetate was heated for 2.5 h at 170–180°C in a flask equipped with an air condenser. To the cooled melt was added water acidified with HCl, the product was extracted into ether, the extract was dried, the solvent was evaporated, and the residue was dried in a vacuum and recrystallized from hexane. Yield 97%, mp 163–164°C (164–165°C [3]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.22 s (9H), 1.34 s (9H), 7.13 d (1H), 7.61 d (1H, J_μ 2.2 Hz, OH in exchane with COOH). Mass spectrum, *m/z*: 250 $[M]^+$. Found, %: C 71.65; H 8.43. $C_{15}H_{22}O_3$. Calculated, %: C 72.00; H 8.75. At melting aldehyde **III** with sodium acetate under similar conditions the initial aldehyde was recovered.

Conversion of 2,4-di-*tert*-butyl-6-bromophenol (VIII) under conditions of Duff reaction. In 24 ml of ethylene glycol 0.7 g (2.4 mmol) of bromophenol **VIII** [4] and 1.4 g (10 mmol) of urotropin was heated for 1 h at 140°C. The reaction mixture was poured into water, extracted with ether, and the solvent was evaporated. Yield of benzoxazine **VII** 0.44 g (78%), mp 169–170°C (from hexane–methanol, 10:1). From the mother liquor was isolated 0.09 g (15%) of nitrile **IX**, mp 52–53°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.33 s (9H), 1.44 s (9H), 7.27 d (1H), 7.58 d (1H, J_μ 2.4 Hz), 8.62 (OH). Mass spectrum: *m/z* 231 $[M]^+$. In the sample of nitrile **IX** was detected the presence of amide **X**, *m/z* 249 $[M]^+$. By TLC acid **I** was also detected in the mother liquor.

2,4-Di-*tert*-butyl-6-{[6,8-di-*tert*-butyl-2*H*-1,3-benzoxazin-3(4*H*)-yl]carbonyl}phenol (XI). To 0.46 g (1 mmol) of benzoxazine **VII** in hexane was added dropwise at stirring 0.3 ml of Br_2. The reaction mixture was diluted with ether and washed with water. On evaporating the solvent the residue was crystallized from a mixture hexane–methanol, 10:1. We obtained 0.3 g (67%) of amide **X**, mp 190–191°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 s (9H), 1.29 s (9H), 1.35 s (9H), 1.37 s (9H), 4.64 s (2H), 5.43 s (2H), 7.18 d (1H), 7.20 d (1H), 7.49 d (1H), 7.69 d (1H, $J_\mu \approx {}^1J_\mu$ 2.2 Hz), 9.13 (OH). ^{13}C (DMSO-d_6), δ, ppm: 25.66, 29.85, 31.19, 31.51 (CH_3, *t*-Bu), 33.92, 34.29, 34.57, 34.80 (C_{quat}, *t*-Bu), 44.88 (NCH_2), 77.69 (OCH_2), 122.07, 123.36, 124.80, 128.59 (CHAr), 118.326, 123.55, 137.01, 137.34, 141.45, 144.51, 151.68, 154.55 (CAr), 163.76 (C=O). Mass spectrum: *m/z* 479 $[M]^+$. Found, %: C 77.39; H 9.51. $C_{31}H_{45}NO_3$. Calculated, %: C 77.61; H 9.69.

Treatment with bromine of 2,4-di-*tert*-butyl-6-dimethylaminophenol (XII). To 0.52 g (2 mmol) of phenol **XII** prepared by procedure [5] in hexane solution was added dropwise 0.5 ml Br_2. The separated yellow precipitate of 4-brom-2,4-di-*tert*-butyl-6-(dimethylaminomethyl)cyclohexa-2,5-dien-1-one tribromohydrate (**XIII**) was recrystallized from a mixture hexane–dichloromethane. Yield 0.5 g (43%), mp 154–155°C. UV spectrum: λ_{max} 255 nm. Found, %: C 35.11; H 5.24. $C_{17}H_{29}Br_4NO$. Calculated, %: C 35.00; H 4.99. In the course of crystallization a partial thermolysis of salt **XIII** occurred providing bromide **VIII** identified by TLC on comparing with an authentic sample.

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