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To the 80th Anniversary of B.I. Ionin

Reaction of Alkyl Splitting of 4-Acetylamino-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-benzenesulfonamide

Yu. N. Oludina, E. D. Ibatullina, S. V. Bukharov, G. N. Nugumanova, R. G. Tagasheva, and R. Ya. Deberdeev

Kazan National Research Technological University, ul. K. Marksa 68, Kazan, Tatarstan, 420015 Russia
e-mail: gulia_nn@yahoo.com

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Abstract—Alkyl splitting of 4-acetylamino-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzenesulfonamide with alkali solution has been discovered, the reaction being uncommon for amides. The driving force of the process is the tendency of 3,5-di-*tert*-butyl-4-hydroxybenzyl derivatives to eliminate 2,6-di-*tert*-butyl-4-methylenecyclohexa-2,5-dienone in the presence of bases.

Keywords: alkyl splitting, sulfonamide, 3,5-di-*tert*-butyl-4-hydroxybenzyl derivative

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Acid-catalyzed hydrolysis of esters is known to proceed via alkyl splitting if stable carbocations are formed in the course of the process [1]. For example, many acid-catalyzed reactions involving 3,5-di-*tert*-butyl-4-hydroxybenzylacetate (**I**) proceed via alkyl splitting with formation of 3,5-di-*tert*-butyl-4-hydroxybenzyl carbocation. Under conditions of basic catalysis, the alkyl splitting of compound **I** occurs with formation of highly reactive 2,6-di-*tert*-butyl-4-methylene-cyclohexa-2,5-dienone (**II**) [2]. At the same time, the alkyl splitting is uncommon in the case of amides [1].

In case of acetyl deprotection of 4-acetylamino-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzenesulfonamide (**III**) in an alkaline solution (standard procedure for preparation of amide N-substituted sulfonamides [3]), alkyl splitting of the substrate occurred. When using a 10 wt % solution of alkali, inseparable mixture of products was formed, whereas in the case of 4 wt % solution of KOH compound **IV** was isolated.

In another experiment, it was shown that aniline N,N-disubstituted sulfanilamides reacted with compound **I** under conditions of methylenequinone **II** generation from the latter. For example, reaction of sulfanilamide **VII** with compound **I** (alkaline catalysis with 4% solution of KOH) gave a mixture of tri- and tetrabenzylated derivatives **VIII** and **IX**, according to gas chromatography – mass spectrometry (MALDI) data. Mass spectrum of the reaction mixture contained signals with *m/z* 850 (**VIII**, $[M + Na]^+$), 866 (**VIII**, $[M + K]^+$), 1068 (**IX**, $[M + Na]^+$), 1084 (**IX**, $[M + K]^+$) (Schemes 1, 2).

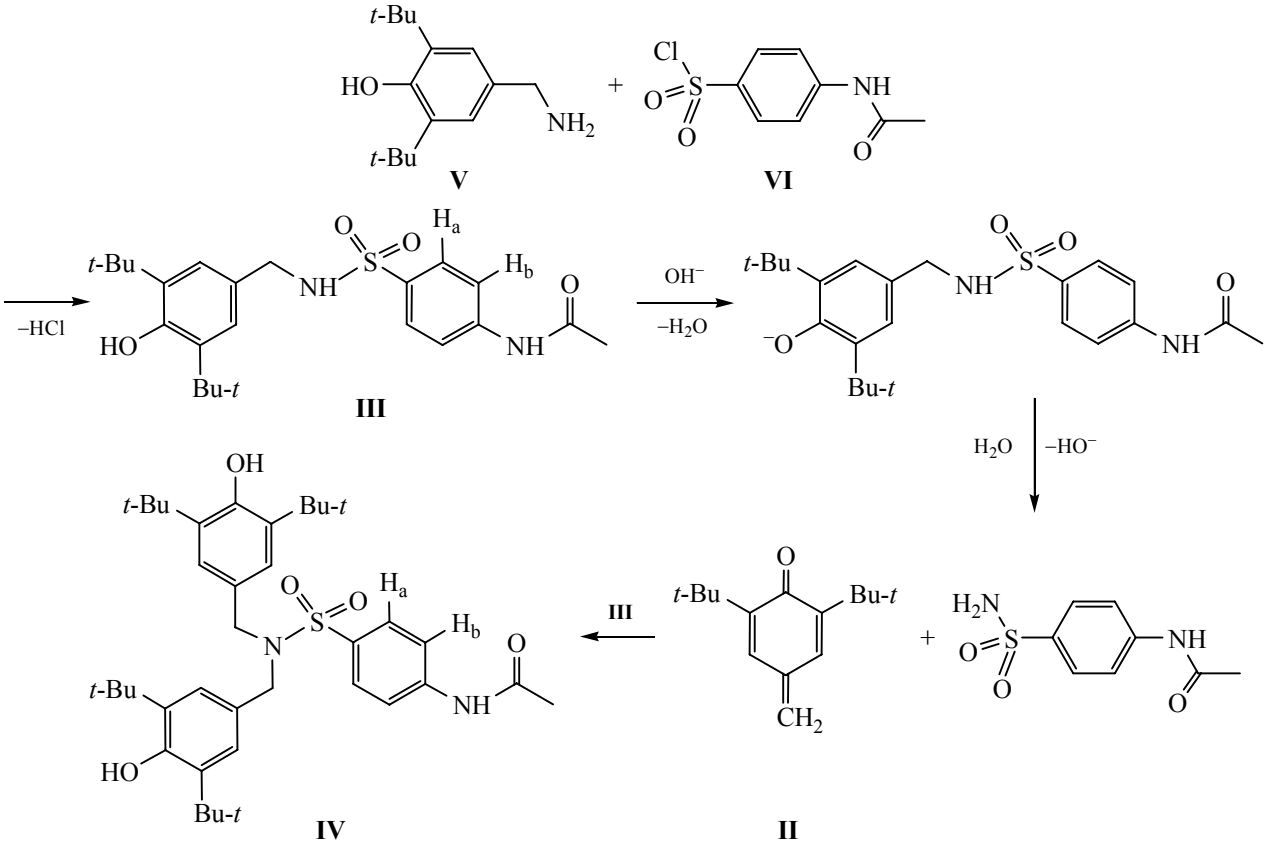
To conclude, the above-described transformation of sulfanilamide **III** can be regarded as the reaction of alkyl splitting of sulfonamides via the B_{AL} mechanism.

The driving force of the discussed reaction of sulfanilamide **III** is ability of 3,5-di-*tert*-butyl-4-hydroxybenzyl derivatives to eliminate methylene-quinone **II** in the presence of bases. This is confirmed by smooth acetyl deprotection of sulfanilamide **X**, containing no 3,5-di-*tert*-butyl-4-hydroxybenzyl fragment and not capable of the elimination of methylene-quinone **II** (Scheme 3).

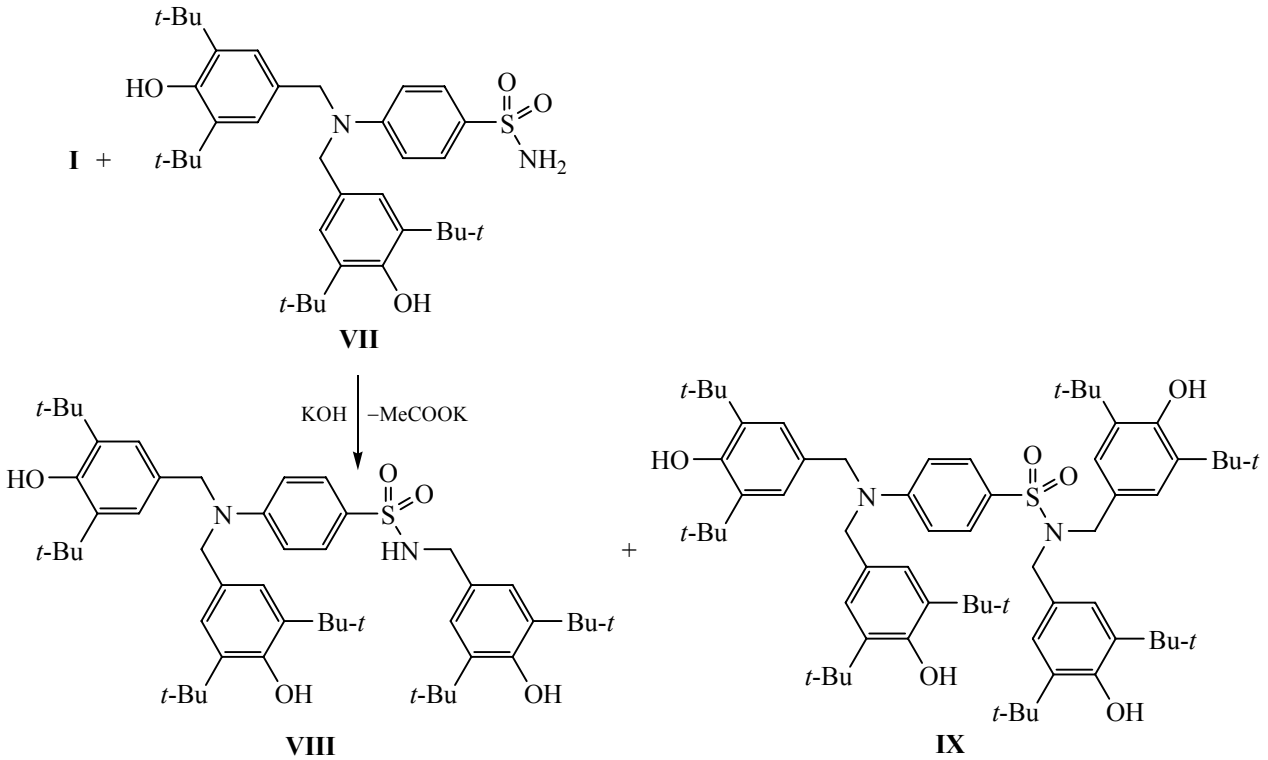
EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker MSL-400 spectrometer at 400 MHz relative to the

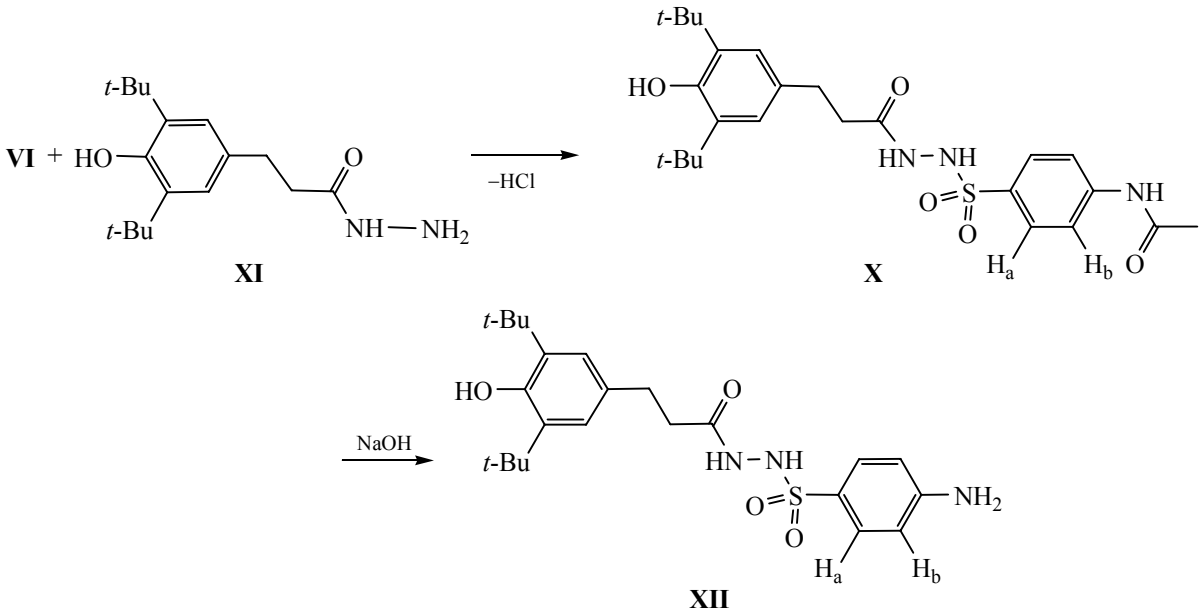
Scheme 1.



Scheme 2.



Scheme 3.



signals of residual protons of the deuterated solvents. Mass-spectra (MALDI) were obtained using a Bruker Ultraflex III TOF/TOF mass-spectrometer (2,5-dihydroxybenzoic acid as matrix). Elemental analysis was performed using an Euro EA 3000 CHNS-analyzer.

3,5-Di-*tert*-butyl-4-hydroxybenzylamine (**V**) was synthesized as described elsewhere [4].

4-(Acetylamino)-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzenesulfonamide (III). 4.4 g (0.019 mol) of *N*-acetylsulfanilchloride **VI** was added to a solution of 4 g (0.017 mol) of benzylamine **V** in 50 mL of pyridine cooled to 15°C, portionwise over 15 min. The resulting mixture was stirred at room temperature during 2 h and then heated at 55°C during 2 h. After cooling, the reaction mass was neutralized with 10% HCl solution. The reaction product was extracted with diethyl ether and dried over $MgSO_4$. After removal of the solvent, the precipitate was washed with hexane. Yield 5.6 g (76%), mp 180–181°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 s (18H, CMe_3), 2.08 s (3H, CH_3), 3.86 d (2H, CH_2NH, ^3J 6.2 Hz, 6.79 s (1H, OH), 6.91 s (2H, ArH), 7.64–7.75 m (4H, H_a, H_b), 7.84 t (1H, NH, ^3J 6.2 Hz), 10.26 s (1H, NH). Mass spectrum (MALDI): *m/z* 455 $[M + Na]^+$. Found, %: C 63.55; N, 7.55; N, 6.87. $C_{23}H_{32}N_2O_4S$. Calculated, %: C 63.86; N, 7.46; N, 6.48.

4-(Acetylamino)-*N*,*N*-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzenesulfonamide (IV). A mixture of 5.6 g (0.013 mol) of compound **III** and 40 mL of 4% aqueous solution of KOH was stirred at 70°C during 6 h, cooled to room temperature, and acidified with 10% HCl to pH 4. The precipitate was filtered off, washed with water, and dried in air to constant mass. Yield 1.52 g (36%), mp 170–172°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 s (36H, CMe_3), 2.23 s (3H, CH_3), 4.27 s (4H, CH_2), 5.14 s (2H, OH), 6.95 s (4H, ArH), 7.45 s (1H, NH), 7.61 d (2H, H_b, ^3J 8.6 Hz), 7.75 d (2H, H_a, ^3J 8.6 Hz). Mass spectrum (MALDI), *m/z*: 673 $[M + Na]^+$, 689 $[M + K]^+$. Found, %: C 69.88; H 8.49; N 4.53. $C_{38}H_{54}N_2O_5S$. Calculated, %: C 70.12; H 8.36; N, 4.30.

***N*'-[4-(Acetylamino)benzenesulfonyl]-3-(3-di-*tert*-butyl-4-hydroxyphenyl)propanehydrazide (X)** was obtained similarly to compound **III** from 4 g (0.0137 mol) of hydrazide of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propionic acid **XI**, 50 mL of pyridine and 3.5 g (0.015 mol) of *N*-acetylsulfanilylchloride **VI**. Yield 5.3 g (79%), mp 255–256°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 s (18H, CMe_3), 2.09 s (3H, CH_3), 2.22 t (2H, CH_2Ar, ^3J 7.9 Hz), 2.53 t [2H, $CH_2C(O)$, ^3J 7.9 Hz], 6.68 s (1H, OH), 6.86 s (2H, ArH), 7.72 s (4H, H_a, H_b), 9.60 br.s (1H, $NHSO_2$), 9.97 s [1H, C(O)<u>NH</u>NH], 10.29 s [1H, <u>NH</u>C(O)CH_3]. Mass spectrum (MALDI), *m/z*: 512 $[M + Na]^+$, 528 $[M + K]^+$ Found, %: C 61.11; H 7.42; N 8.81. $C_{25}H_{35}N_3O_5S$. Calculated, %: C 61.35; H 7.16; N 8.59.

***N*'-[(4-aminophenyl)]sulfonyl]-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanehydrazide (XII)**

was obtained similarly to compound **IV** from 3 g (0.006 mol) of the compound **XI** and 25 mL of 10% aqueous solution of NaOH. Yield 1.62 g (59%), mp 133–135°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 s (18H, CMe_3), 2.21 t (2H, CH_2Ar, ^3J 8.0 Hz), 2.53 t [2H, $CH_2C(O)$, ^3J 8.0 Hz], 5.95 s (2H, NH_2), 6.55 d (2H, H_b, ^3J 8.6 Hz), 6.68 br.s (1H, OH), 6.88 s (2H, ArH), 7.40 d (2H, H_a, ^3J 8.6 Hz), 9.01 br.s (1H, $NHSO_2$), 9.87 s [1H, C(O)NHNH]. Mass spectrum (MALDI), *m/z*: 470 $[M + Na]^+$, 486 $[M + K]^+$ Found, %: C 61.74; H 7.38; N 9.40. $C_{23}H_{33}N_3O_4S$. Calculated, %: C 61.72; H 7.43; N 9.39.

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