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Synthesis of Ethophenprox*

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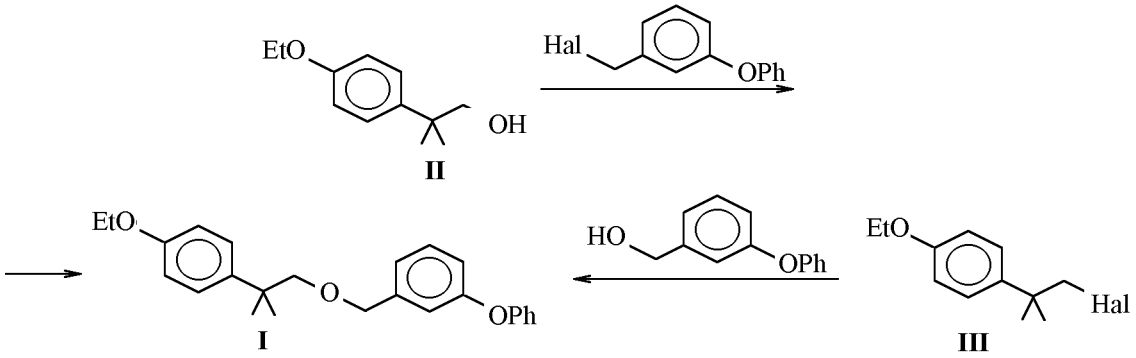
Abstract—An ethophenprox synthesis from easily available *p*-nitroneophyl chloride was developed. The reduction of the latter to aniline derivative followed by Sandmayer's and Claisen's reactions furnished *p*-ethoxyneophyl chloride that by condensation with 3-phenoxybenzyl alcohol in the presence KOH in DMSO yielded ethophenprox.

Insecticide ethophenprox [2-(*p*-ethoxyphenyl)-methylpropyl *m*-phenoxybenzyl ether] (**I**) according to mechanism of its action belongs to pyrethroids although it does not contain cyclopropane and ester groups [1]. It is prepared by condensation of *p*-ethoxyneophyl and *m*-phenoxybenzyl components.

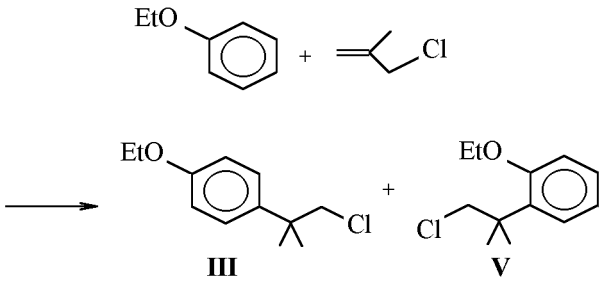


m-Phenoxybenzyl halide and *m*-phenoxybenzyl alcohol are semiproducts in production of drugs phenotrin and permetrin [2], therefore the development of a feasible procedure for preparation of *p*-ethoxyneophyl alcohol (**II**) and *p*-ethoxyneophyl halide (**III**) is an interesting problem.

Alcohol **II** is known to be obtained [3] from the nitrile of the *p*-ethoxyphenylacetic acid (**IV**) that in its turn is prepared from the *p*-chloromethylphenetole. The phenetole chloromethylation is accomplished by Blanc procedure [4, 5] and results in a hard-to-separate mixture of *para*- and *ortho*-isomers [6].

The other reaction sequence starts with *p*-cresol: its ethyl ether is transformed into nitrile **IV** by successive treatment with *N*-bromosuccinimide (NBS) [7, 8] and KCN [9].

The phenetole alkylation with methallyl chloride in the presence of H_2SO_4 affords compound **III** in an yield no more than 70% [ratio (**III**):(**V**) = 4:1, GLC] [10, 11].



All attempts to increase the regioselectivity and the yield in this reaction by variation of the process conditions and by the use of other catalysts failed.

We tried to synthesize p-ethoxyneophyl alcohol (**II**) by alkylation of phenetole with methallyl alcohol

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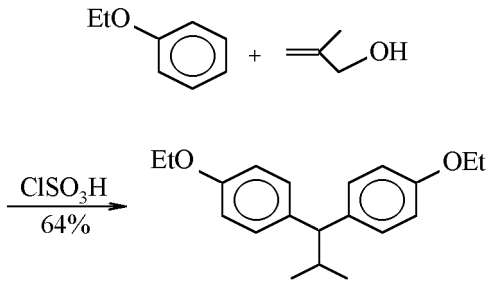
under acid catalysis conditions. It was established that irrespective the reagents ratio in the presence of H_2SO_4 formed a complex mixture of products; the main among them was dimer of the methallyl alcohol 4-[(2-methyl)allyl-3-oxy]-2-methyl-*n*-propanol (53%) [12]. The catalysis with $ClSO_3H$ provided product **VI**, a known DDT analog [13].

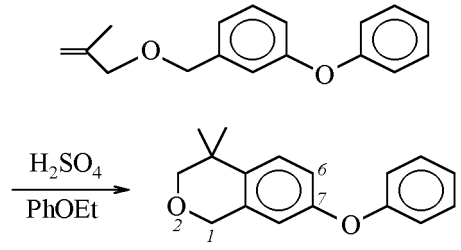


VI

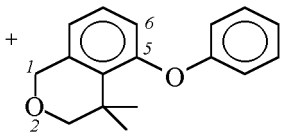
The same result was obtained with $TiCl_4$ as catalyst: alkylation occurred virtually immediately, but was accompanied with a strong tarring of the reacting mixture. The catalysis with H_3PO_4 required heating to 80°C and yielded the same product. Compound **VI** was also obtained in high yield by alkylation phenetole in the presence of $ClSO_3H$ or $TiCl_4$ with methallyl pentafluorobenzyl ether (**VII**), methallyl acetate, methallyl chloride, and methacrolein.

Ether **VII** was synthesized from methallyl alcohol and pentafluorobenzyl bromide. At the use of methallyl chloride and pentafluorobenzyl alcohol arose high-melting yellow-brown powder of unknown structure. Compound **VII** is a strong lacrimator.

An attempt to alkylate phenetole with methallyl *m*-phenoxybenzyl ether (prepared from methallyl alcohol and *m*-phenoxybenzyl bromide) in the presence of H_2SO_4 as catalyst resulted in a complex mixture of products where prevailed isochromans **VIII** and **IX** isolated by column chromatography on silica gels as a 1 : 1 mixture (GLC) in an overall yield 46%.



VIII

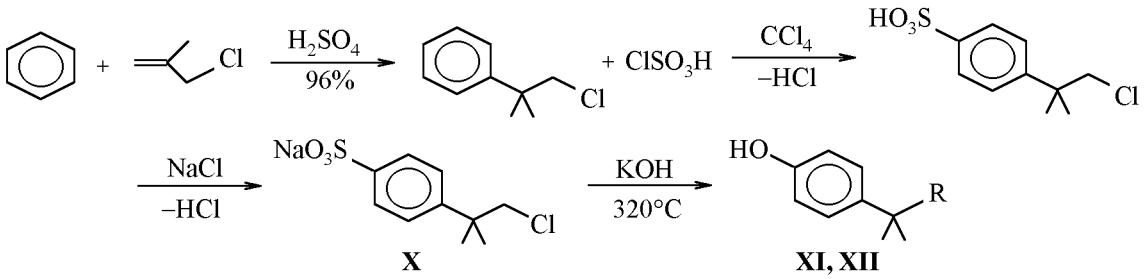


IX

In the ^{13}C NMR spectrum of compounds **VIII** and **IX** the chemical shifts of the gem-dimethyl groups are different: in compound **VIII** axial group gives a signal at 19.38 ppm [14], and equatorial group at 21.54 ppm. In the spectrum of 5-phenoxy isomer **IX** the respective signals appear at 32.30 and 33.55 ppm. In the ^1H NMR spectrum of the mixture of compounds **VIII** and **IX** the protons from the axial methyl of the 5-phenoxy isomer **IX** give rise to a signal at 0.89 ppm whereas those from the axial methyl of the 7-phenoxy isomer **VIII** resonate at 0.92 ppm. The methylene protons signals appear as complex multiplets in the region 3.35–3.60 and 4.46–4.56 ppm.

We investigated the possibility to obtain *p*-ethoxyneophyl chloride (**III**) from the easily available neophyl chloride.

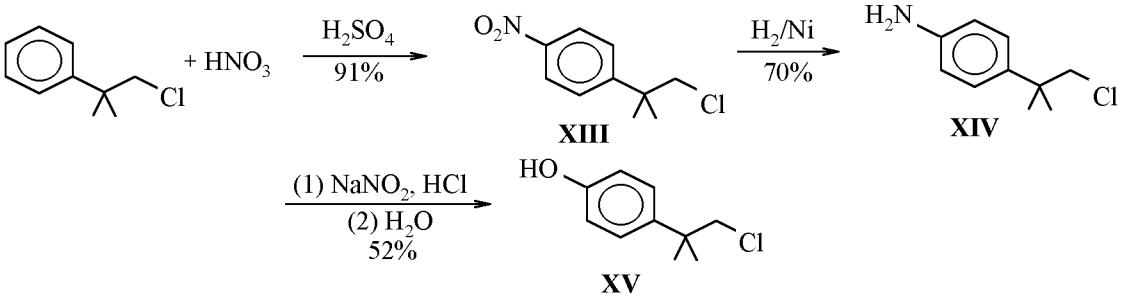
It was established that sulfonation of neophyl chloride with chlorosulfonic acid by procedure [15] occurred in the *para*-position, but although alkaline melting of the sodium salt **X** as in [16] resulted in complete substitution of the sulfo group by hydroxyl, it was accompanied by dehalogenation and partial degradation of the carbon skeleton thus giving rise to a mixture of *p*-alkylphenols.



X **XI, XII**

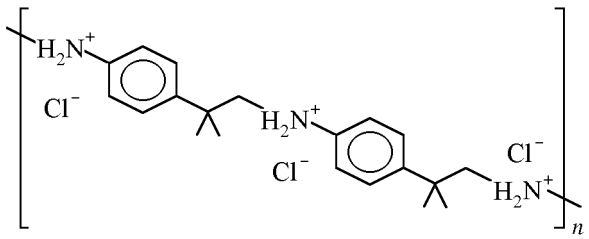
R = H, Me.

The reaction products did not contain chlorine and sulfur as shown by elemental analysis. The analysis of the complicated set of signals in the upfield part of their ^{1}H NMR spectra together with the mass-spectral data permitted a conclusion that the main reaction products were *p*-*tert*-butylphenol (**XI**) (*m/z* 150) and *p*-iso-propylphenol (**XII**) (*m/z* 136). The nitration of neophyl chloride under the common conditions [17] also occurred exclusively in the *para*-position in a high yield [18]. By hydrogenation



in the pressure reactor on Renay nickel in ethanol [19] we obtained from *p*-nitroneophyl chloride (**XIII**) *p*-aminoneophyl chloride (**XIV**) in 70% yield.

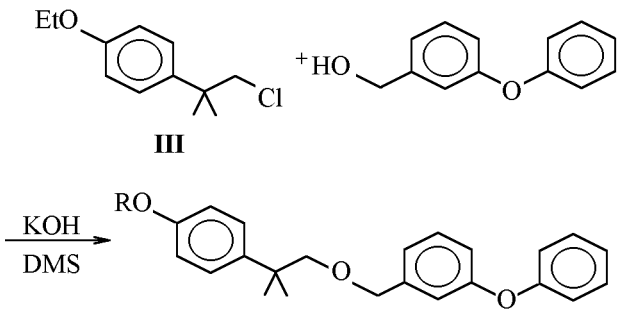
In the IR spectrum of amine **XIV** were observed the stretching vibrations (as a broad "hump" with a maximum at 2600 cm^{-1}) and bending vibrations (narrow peak at 1584 cm^{-1}) of the NH group that are characteristic of quaternary ammonium salts $R_2NH_2^+$, and also weak broad absorption bands with a fine structure corresponding to the nonbonded amine at 3328 and 3240 cm^{-1}. In the ^{1}H NMR spectrum the protons attached to nitrogen appear as a signal at 7.26 ppm as is common for compounds of $R_2NH_2^+$ type. The elemental analysis indicated that about 95% of chlorine in the product was present as chloride ion. On addition of hydrochloric acid to the alcoholic solution of the aniline no blue shift of absorption maxima in the UV spectrum was observed. These data indicate that aniline **XIV** obtained nearly completely exists as an ammonium salt that apparently arises from intermolecular interactions.



It is possible that the quaternization is due to the severe reaction conditions (high temperature and pressure). However the attempts to reduce nitro compound **XIII** under mild conditions (with iron metal in benzene [20] and tin chloride in hydrochloric acid [21]) were not satisfactory. The reduction of compound **XIII** with a mixture of nickel chloride and aluminum powder in THF [22] gave rise to a complex mixture of products. Diazotization of aniline **XIV** with sodium nitrite in dilute hydrochloric acid by the usual procedure [23] afforded p-(1-chloro-2-methyl-iso-propyl)phenol (**XV**) [24] in 52% yield. The side product of this reaction was neophyl chloride (yield 15%).

The alkylation of phenol **XV** with ethyl bromide in the presence of NaOH [25] or under conditions of the phase-transfer catalysis is accompanied by a side process, alkylation with the alkyl chloride moiety of the other molecule **XV**. The reaction carried out in acetone at 40°C in the presence of potassium carbonate resulted in 67% yield of ether **III**, but at boiling the yield fell to 56%.

The condensation of chloride **III** with *m*-phenoxybenzyl alcohol was accomplished with good yield in solution of 1,3-dimethyl-2-imidazolidinone in the presence of solid KOH [27]. Also the other polar aprotic solvents (DMSO, DMF, HMPA etc.) and



R = Et (**I**), R = H (**XVI**).

bases (NaOH, *tert*-BuOK, NaH etc.) are also used [28]. It should be taken into consideration that the condensation of 2-(4-ethoxyphenyl)-2-methylpropyl chloride (**III**) with 3-phenoxybenzyl alcohol proceeds under severe conditions and is usually accompanied with hydrolysis of the ethoxy group and formation of 2-(4-hydroxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether (**XVI**). The latter compound requires repeated ethylation [29].

We chose reaction conditions suppressing the side process. Thus, at 1:1 molar ratio of chloride **III** to 3-phenoxybenzyl alcohol (KOH/DMSO) at 130–140°C in 5 h compounds **I** and **XVI** arise in the ratio 2:3 in an overall yield of 56%, i.e. the yield of ethophenprox attains ~22%.

At 110–120°C in 15 h was obtained mainly ethophenprox (**I**), and its yield reached 42.5% [(**I**):(**XVI**) ratio was 5:1, overall yield 51%].

Thus we developed a procedure for ethophenprox synthesis from the available neophyl chloride.

EXPERIMENTAL

IR spectra were measured on spectrometer UR-20 from films. ^{1}H and ^{13}C NMR spectra were registered on Bruker AM-300 instrument at operating frequencies 300.13 and 75.75 MHz respectively, solvent CDC_3. Chemical shifts are given in δ scale from TMS. Mass spectra were obtained on MKh-1303 and MKh-1320 devices at the temperature in the ionization chamber 100–180°C, ionizing voltage 70 eV. UV spectra were recorded on spectrophotometer Specord M-40 from solutions in ethanol. GLC analysis were performed on chromatograph Chrom-5, stationary phase 5% SE-30 on carrier N-AW-DMCS, column 1200 mm, oven programming from 50 to 300°C at a rate 14 deg/min, carrier gas helium.

General procedure for phenetole alkylation. To a mixture of 1.69 g (13.85 mmol) of phenetole and 2.77 mmol of olefin stirred by magnetic stirrer was added at room temperature 2 mmol of a catalyst. After 5 h the reaction mixture was treated with Na_2CO_3 solution till pH 8 and extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered, the excess phenetole was distilled off at 80°C and 2 mm Hg, and the product obtained was when necessary subjected to distillation.

1-Chloro-2-[2(4)-ethoxyphenyl]-2-methylpropanes (III) and (V) were obtained in overall yield 94% by phenetole alkylation with methallyl chloride in the presence of H_2SO_4. The obtained mixture of *meta* and *para*-isomers in 4:1 ratio was separated by column chromatography on silica gel L 40–100, eluent hexane–ethyl acetate, 9:1.

1-Chloro-2-(2-ethoxyphenyl)-2-methylpropane (V). ^{1}H NMR spectrum, δ, ppm: 1.42 t (3H, CH_2CH_3, *J* 1.7), 1.59 s [6H, $C(CH_3)_2$], 3.02 s (2H, CH_2Cl), 4.04 q (2H, CH_2CH_3, *J* 1.7), 6.50–7.35 s (4H, C arom H). Found, %: C 67.12; H 8.27; Cl 16.55. $C_{12}H_{17}ClO$. Calculated, %: C 67.75; H 8.07; Cl 16.66.

1,1-Di(h-ethoxy)phenyl-2-methylpropane (VI). (a) The alkylation of phenetole with 0.26 g of methallyl chloride in the presence of 0.23 g (2 mmol) of chlorosulfonic acid afforded 0.4 g (64%) of compound **VI**. (b). Reaction catalyzed with 0.38 g (2 mmol) of $TiCl_4$ occurred virtually immediately and with strong tarring of the reaction mixture. Yield 0.38 g (60%). (c). With 0.25 g (2 mmol) of 80% H_3PO_4 as catalyst the reaction mixture was heated to 80°C. Yield 0.9 g (63%).

2-Methylallyl pentaflyorobenzyl ether (VII). In a flask equipped with a reflux condenser and a mechanical stirrer was mixed 11.3 g (43.3 mmol) of pentafluorobenzyl bromide, 3.12 g (43,3 mmol) of methallyl alcohol, 15 ml of anhydrous THF, 2.85 g (43.3 mmol) of 80% KOH, and 0.05 g of Bu_4NI. The stirring at reflux was continued for 6 h, then the reaction mixture was filtered through a thin bed of silica gel and subjected to distillation to give 10.14 g (93%) of ether **VII**, bp 60°C (5 mm Hg), $n_D^{19.1}$ 1.5495. IR spectrum, ν, cm^{-1}: 1666 C=C. ^{1}H NMR spectrum, δ, ppm: 1.72 s (3H, CH_3), 3.97 s (2H, CH_2C=), 4.61 s (2H, CH_2C arom), 4.90 s (1H, *cis* HC=C), 4.98 s (1H, *trans* HC=C). Found, %: C 52.51; H 3.24; F 37.00. $C_{11}H_9F_5O$. Calculated, %: C 52.39; H 3.60; F 37.67.

4,4-Dimethyl-7-phenoxyisochroman (VIII) and 4,4-dimethyl-5-phenoxyisochroman (IX). ^{1}H NMR spectrum, δ, ppm: 0.89 s (3H, CH_3, ax, IX), 0.90 s (3H, CH_3, ax, **VIII**), 0.91 s (3H, CH_3, eq, IX), 0.92 s (3H, CH_3, eq, **VIII**), 3.35–3.60 m (4H, $2C^3H_2$), 4.46–4.56 m (4H, $2C^1H_2$), 6.91–7.42 m (16H, Carom, H). ^{13}C NMR spectrum, δ, ppm: 19.38 (CH_3, **VIII**, ax), 21.54 (CH_3, **VIII**, eq), 32.30 (CH_3, **IX**, ax), 33.66 (CH_3, **IX**, eq), 64.78 ($\underline{C}H_2C$ arom, **VIII**), 65.79 ($\underline{C}H_2C$ arom, **IX**), 71.72 ($\underline{C}H_2CMe_2$, **VIII**), 72.91 ($\underline{C}H_2cme_2$, **IX**), 114.19 (C^8arom, **VIII**), 116.66 (C^6arom, **IX**), 117.04 ($C^{2'}$arom, **IX**), 118.51 (C^6arom, **VIII**), 118.80 (C^8arom, **IX**), 118.97 ($C^{2'}$arom, **VIII**), 121.44 ($C^{4'}$arom, **IX**), 123.62 ($C^{4'}$arom, **VIII**), 128.72 (C^5arom, **VIII**), 129.08 ($C^{3'}$arom, **IX**), 129.69 ($C^{3'}$arom, **VIII**), 129.86 (C^5arom, **IX**),

134.20 (C arom CH_2, **VIII** and **IX**), 140.48 (C arom CMe_2, **IX**), 141.00 (C arom CMe_2, **VIII**), 152.10 (C^5aromO, **IX**), 156.31 ($C^{1'}$arom O, **VIII** and **IX**), 157.41 (C^7arom O, **VIII**). Found, %: C 80.19; H 7.09. $C_{17}H_{18}O_2$. Calculated, %: C 80.29; H 7.15. *m/z*: 254 $M^{+\cdot}$, 224 $(M–CH_2O]^{+\cdot}$).

***p*-(1-Chloro-2-methyl-2-propyl)benzenesulfonic acid sodium salt (X)** was prepared by procedure from [15] in 1.05 g (66%) yield, light gray crystals. IR spectrum, ν, cm^{-1}: 824 (Carom-Cl); 1040, 1240 (RSO_3^-); 1128, 1176, 1376, 1400 (CMe_2). UV spectrum, λ_{max}^{MeCN}, nm (log ε): 223 (3.0234), 252 (0.8304), 268.5 (1.1071). ^{1}H NMR spectrum, δ, ppm [$(CD_3)_2SO$]: 1.32 s (6H, CH_3), 3.60 s (2H, CH_2), 7.35 d (2H, HCCC, *J* 7.89), 7.45 d (2H, HCCS, *J* 7.89). Found, %: C 44.28; H 4.50; Cl 13.40; Na (ash) 8.54; S 11.54. $C_{10}H_{12}ClNaO_3S$. Calculated, %: C 44.36; H 4.48; Cl 13.10; Na 8.49; S 11.84.

***p*-(1-Chloro-2-methyl-2-propyl)aniline (XIV).** mp 175°C. IR spectrum, ν, cm^{-1}: 3328, 3240 (NH_2); 1390, 1376, 1165, 1136 (CMe_2); 848 (CCl). ^{1}H NMR spectrum, δ, ppm: 1.48 s (6H, CH_3), 3.68 s (2H, CH_2), 7.26 s (2H, $R_2NH_2^+$), 7.53 d (2H, HCCC, *J* 9.0), 8.20 d (2H, HCCN, *J* 9.0). Found, %: C 64.42; H 7.59; Cl 18.95; N 6.80. $C_{10}H_{14}ClN$. Calculated, %: C 65.39; H 7.65; Cl 19.34; N 7.63. *m/z*: 183 $M^{+\cdot}$, 134 $(M–CH_2Cl)^+$, 118 $(M–CH_2Cl\_NH_2)^+$.

1-Chloro-2-(*p*-ethoxyphenyl)-2-methylpropane (III). To a mixture of 1 g (5 mmol) of phenol (XIII), 1.2 g of K_2CO_3 in 5 ml of dry acetone at 40°C while stirring was added under argon 0.9 g (8 mmol) of ethyl bromide. The stirring at 40°C was continued for 15 h. Then the reaction mixture was cooled, diluted with 20 ml of water, and the products were extracted into ether. The extract was washed with NaOH solution, with solution of NaCl, and dried with calcium chloride. The solvent was evaporated, the product was subjected to column chromatography on silica gel, eluent hexane–ether, 10 : 1. We obtained 0.77 g (67%) of compound **III**.

2-(4-Ethoxyphenyl)-2-methylpropyl phenoxybenzyl ether (I). A mixture of 0.5 g (2.4 mmol) of 2-(4-ethoxyphenyl)-2-methylpropyl chloride (**III**), 0.68 g (3.4 mmol) of 3-phenoxybenzyl alcohol, and 0.5 g of KOH powder in 2 ml of DMSO was heated to 110–120°C under argon atmosphere for 15 h. The reaction mixture was cooled, diluted with water, extracted with ether, the extract was washed in succession with solutions of NaOH and NaCl, and dried on $CaCl_2$. The solvent was evaporated, and 1.1 g of the mixture obtained was subjected to column chromatography on silica gel, eluent hexane–ether, 10 : 1. We obtained 0.28 g (42,5%) of compound **I** with physical constants consistent with the published data[1], and 0.07 g (8.5%) of 2-(4-hydroxyphenyl)-2-methylpropyl phenoxybenzyl ether (**XVI**). ^{1}H NMR spectrum (XVI), δ, ppm: 1.30 s [6H, $C(CH_3)_2$], 3.44 s (2H, CH_2CMe_2), 4.47 s (2H, CH_2Ar), 4.80 s (1H, HOAr), 6.71–7.37 m (13H, C arom H).

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