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# Synthesis and Antibacterial Activity of Benzenesulfonylhydrazone Derivatives of Methyl Dehydroabietate

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**Abstract**—Six benzenesulfonylhydrazone derivatives of methyl dehydroabietate are synthesized via esterification, benzylic oxidation, condensation with hydrazine hydrate, and following nucleophilic substitution reaction with a variety of substituted benzenesulfonyl chloride. The structures of the synthesized compounds are characterized by $^1$H NMR and MS spectra. Antibacterial activity of the target compounds is evaluated by disk diffusion method against *E. coli*, *S. aureus*, and *B. subtilis*. The results demonstrate that benzenesulfonylhydrazone derivatives of methyl dehydroabietate exhibit inhibitory activity. Among the six compounds, *p*-fluorobenzenesulfonylhydrazone of methyl dehydroabietate exhibits the highest antibacterial activity with the zone of inhibition of 17.3 mm against *B. subtilis* and 16.5 mm against *S. aureus*.

**Keywords:** methyl dehydroabietate, benzenesulfonylhydrazone, sythesis, antibacterial

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## INTRODUCTION

Dehydroabietic acid **1**, a natural occurring diterpene resin acid, can be extracted from *Pinus* rosin or commercial disproportionated rosin. Dehydroabietic acid and its derivatives have been reported to possess a broad spectrum of biological activities including antimicrobial [1–3], antiviral [4], antitumor [5–7], antiulcer [8], antiinflammatory [9], and BK channel-opening [10]. Effective biological activity of dehydroabietic acid and its derivatives prompted us to search for new rosin acid derivatives. Li et al [11] synthesized a series of dehydroabietic acid derivatives bearing an acylhydrazone moiety by condensation of dehydroabietic acylhydrazide with a variety of substituted arylaldehydes, many products showed moderate to high levels of anticancer activity. Gu et al [12] synthesized *N*-acylhydrazone derivatives by the reactions of dehydroabietic acid hydrazide with a variety of substituted arylaldehydes. Several accumulated products exhibited the pronounced antibacterial activities.

These studies highlighted the value of dehydroabietic acid as a starting points for the development of new antimicrobial agents. In this paper, we report the synthesis of benzenesulfonylhydrazone derivatives of methyl dehydroabietate **5a**–**5f** (Scheme 1) from dehydroabietic acid via esterification, benzylic oxidation, and condensation with hydrazine hydrate, followed by nucleophilic substitution reactions with a variety of benzenesulfonyl chloride derivatives.

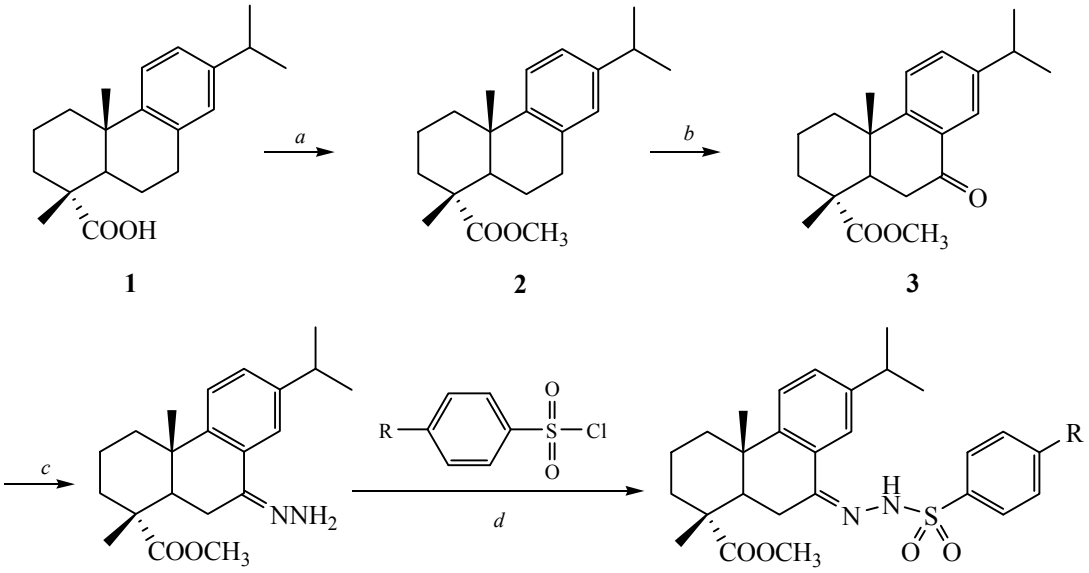
The synthesized products were tested for their antibacterial activity.

## RESULTS AND DISCUSSION

As presented in Scheme 1, dehydroabietic acid **1** was esterified by MeOH in the presence of $SOCl_2$ with formation of compound **2**. Oxidation of the intermediate **2** by an excess of *t*-BuOOH (8 equiv.) and $CrO_3$/pyridine mixture in $CH_2Cl_2$ [13] gave $C^7$ benzylic oxidation product **3**. The following reaction of the intermediate **3** with hydrazine hydrate yielded the corresponding methyl 7-oxodehydroabietate hydrazone **4**. Treatment of the mixture of compound **4** with $Et_3N$ by a solution of one of substituted benzenesulfonyl chlorides in dry THF led to the corresponding target products **5a**–**5f**.

**Antibacterial activity.** The accumulated data of antimicrobial activity of the synthesized compounds by the diffusion method (see the table) indicated their inhibitory activity against *E. coli*, *S. aureus*, and *B.*

**Scheme 1.**




R = $CH_3$ (**5a**), $OCH_3$ (**5b**), $NO_2$ (**5c**), F (**5d**), $CF_3$ (**5e**), Br (**5f**). Reagents and conditions: *a*, $SOCl_2$, benzene, MeOH, reflux; *b*, *t*-BuOOH, $CrO_3$, pyridine, $CH_2Cl_2$, room temperature; *c*, $NH_2NH_2 \cdot H_2O$, EtOH, reflux; *d*, THF, $Et_3N$, room temperature.

*subtilis* bacterial strain. *p*-Nitrobenzenesulfonylhydrazone of methyl dehydroabietate **5c** and *p*-fluorobenzenesulfonylhydrazone of methyl dehydroabietate **5d** exhibited relatively highly inhibitory activity against two bacterial strains, including *B. subtilis* and *S. aureus*. Among the six compounds, the product **5d** demonstrated the highest antibacterial activity against *B. subtilis* and *S. aureus*.

Antibacterial activity of compounds **5a**–**5f** determined by the diffusion method

| Compound | Zone of inhibition, mm | | |
|---|---|---|---|
| | *E. coli* | *S. aureus* | *B. subtilis* |
| **5a** | 7.0 | 8.1 | 8.9 |
| **5b** | 8.1 | 9.8 | 7.7 |
| **5c** | 12.3 | 13.9 | 15.1 |
| **5d** | 13.0 | 16.5 | 17.3 |
| **5e** | 12.1 | 13.2 | 14.7 |
| **5f** | 11.6 | 12.4 | 10.1 |
| Chloramphenicol | 23.6 | 24.2 | 22.7 |

## EXPERIMENTAL

All chemicals and solvents were obtained from commercial sources and used as received or dried according to the standard procedures. Column chromatography was performed on silica gel (ZCXII, ~100–200 mesh). Chemical reactions were monitored by TLC using precoated silica gel GF254 plates. Melting points were determined on a RY-1G melting point apparatus and were uncorrected. NMR spectra were measured on a Bruker AVANCE AV-500 spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. ESI mass spectra were measured on an Agilent 1100 Capillary LC/Micromass Q-TOF micromass spectrometer. Microanalytical data were obtained on an Elementar Vario EL III elemental analyzer.

**(1*R*,4a*S*)-Methyl 1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (2).** To a solution of dehydroabietic acid (10 g, 33.28 mmol) in benzene (80 mL) was added slowly $SOCl_2$ (5.96 g). The mixture was stirred and refluxed for 3 h. After cooling down, the solvent and excess of $SOCl_2$ were evaporated in vacuum to yield the yellow oily compound. MeOH (40 mL) Was added to it, and the mixture was refluxed for 2 h then cooled down to room temperature and concentrated in vacuum. The product was recrystallized from ethanol as a white solid. Yield 84.4%, mp 63–65°C. $^1$H NMR spectrum, δ, ppm: 7.15 d ($J$ = 8.2 Hz, 1H), 6.98 d.d ($J$ = 8.2, 1.5 Hz, 1H), 6.87 d ($J$ = 1.5 Hz, 1H), 3.65 s (3H), 2.92–

2.81 m (3H), 2.31 d ($J$ = 12.3 Hz, 1H), 2.25 d.d ($J$ = 12.4, 2.1 Hz, 1H), 1.71–1.60 m (5H), 1.58 s (3H), 1.51 m (1H), 1.43 m (1H), 1.27 s (3H), 1.23 d ($J$ = 7.1 Hz, 6H). MS, *m/z*: 314.2 $[M]^+$. Found, %: C 80.28; H 9.57. $C_{21}H_{30}O_2$. Calculated, %: C 80.21; H 9.62.

**(1*R*,4a*S*)-Methyl 1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-9-oxophenanthrene-1-carboxylate (3).** To a suspension of $CrO_3$ (135 mg, 0.135 mmol) in $CH_2Cl_2$ (200 mL) were added 65% *t*-BuOOH (34.8 mL, 216.9 mmol) and pyridine (0.22 mL, 2.72 mmol). The mixture was stirred for 3 min at room temperature, then compound **2** (8.52 g, 27.11 mmol) was added to it. After 25 h of stirring the mixture at room temperature it was treated with 5% NaOH (2×60 mL) and brine (2×60 mL), dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromatography (petroleum ether/eacetone, 100:1) to give compound **3** as yellow oil. Yield 70.6%. $^1$H NMR spectrum, δ, ppm: 7.86 d ($J$ = 2.0 Hz, 1H), 7.39 d.d ($J$ = 8.1, 2.1 Hz, 1H), 7.28 d ($J$ = 8.1 Hz, 1H), 3.64 s (3H), 2.90 septet ($J$ = 7.0 Hz, 1H), 2.75 m (2H), 2.41–2.26 m (2H), 1.83–1.59 m (5H), 1.35 s (3H), 1.26 s (3H), 1.25 d ($J$ = 7.0 Hz, 6H). MS, *m/z*: 328.2 $[M]^+$. Found, %: C 76.72; H 8.64. $C_{21}H_{28}O_3$. Calculated, %: C 76.79; H 8.59.

**(1*R*,4a*S*)-Methyl 9-hydrazono-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (4).** Compound **3** (5.22 g, 15.90 mmol) was dissolved in EtOH (80 mL), and the mixture was stirred upon refluxing. Then 98% hydrazine hydrate (1.04 g, 20.67 mmol) was added to it dropwise. The mixture was refluxed upon stirring for 1 h. After evaporation of the solvent under reduced pressure, the residue was recrystalized from ethanol to afford compound **4** as a light yellow solid. Yield 87.8%, mp 152–154°C. $^1$H NMR spectrum, δ, ppm: 7.58 d ($J$ = 2.0 Hz, 1H), 7.24 d.d ($J$ = 8.0 Hz, 2.0 Hz, 1H), 7.16 d ($J$ = 8.0 Hz, 1H), 5.32 br s (2H), 3.64 s (3H), 2.89 septet ($J$ = 7.0 Hz, 1H), 2.76 m (2H), 2.45–2.36 m (2H), 1.81–1.54 m (5H), 1.34 s (3H), 1.25 s (3H), 1.24 d ($J$ = 7.0 Hz, 6H). MS, *m/z*: 343.2 $[M+H]^+$. Found, %: C 73.62; H 8.80; N 8.16. $C_{21}H_{30}N_2O_2$. Calculated, %: C 73.65; H 8.83; N 8.18.

**Synthesis of benzenesulfonylhydrazone derivatives of methyl dehydroabietate (5a–5f).** The mixture of compound **4** (1.50 g, 4.38 mmol) with $Et_3N$ (0.66 g, 6.52 mmol) was dissolved in dry THF (20 mL), then solution of an appropriate phenylsulfonyl chloride (4.51 mmol) in dry THF (15 mL) was added dropwise upon stirring. The reaction mixture was stirred for 1 h at room temperature, concentrated to approximately 15 mL under reduced pressure and cooled in an ice bath. The resulting precipitate was filtered off and washed with distilled water to give the crude product, which was recrystalized from ethanol to afford the corresponding compound **5a–5f.**

**(1*R*,4a*S*)-Methyl 9-(*p*-tosylhydrazono)-1,2,3,4,4a,-9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5a).** Light yellow solid, yield 69.4%, mp 172–174°C. $^1$H NMR spectrum, δ, ppm: 7.94 s (1H), 7.84 d ($J$ = 2.0 Hz, 1H), 7.75 d ($J$ = 8.4 Hz, 2H), 7.38 d ($J$ = 8.2 Hz, 2H), 7.28 d ($J$ = 8.0 Hz, 1H), 7.21 d.d ($J$ = 8.0 Hz, 2.0 Hz, 1H), 3.64 s (3H), 2.87 septet ($J$ = 6.8 Hz, 1H), 2.72 d.d ($J$ = 17.4, 4.0 Hz, 1H), 2.43 s (3H), 2.34–2.18 m (3H), 1.88–1.56 m (5H), 1.36 s (3H), 1.25 s (3H), 1.24 d ($J$ = 6.9 Hz, 6H). MS, *m/z*: 497.2 $[M+H]^+$. Found, %: C 67.65; H 7.28; N 5.61. $C_{28}H_{36}N_2O_4S$. Calculated, %: C 67.71; H 7.31; N 5.64.

**(1*R*,4a*S*)-Methyl 9-(*p*-methoxybenzenesulfonylhydrazono)-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5b).** White solid, yield 65.8%, mp 178–180°C. $^1$H NMR spectrum, δ, ppm: 7.90 s (1H), 7.83 d ($J$ = 2.0 Hz, 1H), 7.70 d ($J$ = 8.4 Hz, 2H), 7.29 d ($J$ = 8.0 Hz, 1H), 7.21 d.d ($J$ = 8.0 Hz, 2.0 Hz, 1H), 7.05 d ($J$ = 8.2 Hz, 2H), 3.79 s (3H), 3.64 s (3H), 2.87 septet ($J$ = 6.8 Hz, 1H), 2.79 d.d ($J$ = 17.4, 4.0 Hz, 1H), 2.17–2.02 m (2H), 1.91–1.43 m (6H), 1.35 s (3H), 1.26 s (3H), 1.23 d ($J$ = 6.9 Hz, 6H). MS, *m/z*: 513.2 $[M+H]^+$. Found, %: C 65.56; H 7.11; N 5.43. $C_{28}H_{36}N_2O_5S$. Calculated, %: C 65.60; H 7.08; N 5.46.

**(1*R*,4a*S*)-Methyl 9-(*p*-nitrobenzenesulfonylhydrazono)-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5c).** Light yellow solid, yield 68.7%, mp 195–197°C. $^1$H NMR spectrum, δ, ppm: 8.38 d ($J$ = 8.4 Hz, 2H), 8.12 s (1H), 8.05 d ($J$ = 8.2 Hz, 2H), 7.82 d ($J$ = 2.0 Hz, 1H), 7.30 d ($J$ = 8.2 Hz, 1H), 7.22 d.d ($J$ = 8.2 Hz, 2.0 Hz, 1H), 3.63 s (3H), 2.88 septet ($J$ = 6.8 Hz, 1H), 2.75 d.d ($J$ = 17.5, 4.1 Hz, 1H), 2.15–1.94 m (3H), 1.89–1.37 m (5H), 1.35 s (3H), 1.24 s (3H), 1.20 d ($J$ = 6.9 Hz, 6H). MS, *m/z*: 528.2 $[M+H]^+$. Found, %: C 61.43; H 6.25; N 7.94. $C_{27}H_{33}N_3O_6S$. Calculated, %: C 61.46; H 6.30; N 7.96.

**(1*R*,4a*S*)-Methyl 9-(*p*-fluorobenzenesulfonylhydrazono)-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5d).** White solid, yield 67.3%, mp 187–189°C. $^1$H NMR spectrum,

δ, ppm: 8.01 s (1H), 7.98 d ($J$ = 8.4 Hz, 2H), 7.80 d ($J$ = 2.0 Hz, 1H), 7.40 d ($J$ = 8.2 Hz, 2H), 7.29 d ($J$ = 8.2 Hz, 1H), 7.21 d.d ($J$ = 8.2 Hz, 2.0 Hz, 1H), 3.64 s (3H), 2.86 septet ($J$ = 6.8 Hz, 1H), 2.79 d.d ($J$ = 17.3, 4.0 Hz, 1H), 2.39–2.24 m (2H), 2.10–1.54 m (6H), 1.35 s (3H), 1.25 s (3H), 1.22 d ($J$ = 6.9 Hz, 6H). MS, *m/z*: 501.2 $[M+H]^+$. Found, %: C 64.71; H 6.67; N 5.57. $C_{27}H_{33}FN_2O_4S$. Calculated, %: C 64.78; H 6.64; N 5.60.

**(1*R*,4a*S*)-Methyl 9-(*p*-trifluoromethylbenzenesulfonylhydrazono)-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5e).** White solid, yield 63.2%, mp 191–193°C. $^1$H NMR spectrum, δ, ppm: 8.12 s (1H), 7.81 d ($J$ = 2.0 Hz, 1H), 7.76 d ($J$ = 8.4 Hz, 2H), 7.65 d ($J$ = 8.2 Hz, 2H), 7.28 d ($J$ = 8.2 Hz, 1H), 7.20 d.d ($J$ = 8.2 Hz, 2.0 Hz, 1H), 3.63 s (3H), 2.86 septet ($J$ = 6.8 Hz, 1H), 2.71 d.d ($J$ = 17.4, 4.1 Hz, 1H), 2.19–2.05 m (2H), 1.83–1.56 m (6H), 1.35 s (3H), 1.26 s (3H), 1.23 d ($J$ = 7.0 Hz, 6H). MS, *m/z*: 551.2 $[M+H]^+$. Found, %: C 61.03; H 6.02; N 5.07. $C_{28}H_{33}F_3N_2O_4S$. Calculated, %: C 61.08; H 6.04; N 5.09.

**(1*R*,4a*S*)-Methyl 9-(*p*-bromobenzenesulfonylhydrazono)-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5f).** White solid, yield 60.3%, mp 178–180°C. $^1$H NMR spectrum, δ, ppm: 8.10 s (1H), 7.88 d ($J$ = 2.0 Hz, 1H), 7.81 d ($J$ = 8.4 Hz, 2H), 7.69 d ($J$ = 8.2 Hz, 2H), 7.29 d ($J$ = 8.2 Hz, 1H), 7.21 d.d ($J$ = 8.2 Hz, 2.0 Hz, 1H), 3.64 s (3H), 2.87 septet ($J$ = 6.8 Hz, 1H), 2.73 d.d ($J$ = 17.4, 4.0 Hz, 1H), 2.39–2.20 m (3H), 1.89–1.78 m (2H), 1.64–1.56 m (3H), 1.35 s (3H), 1.25 s (3H), 1.21 d ($J$ = 7.0 Hz, 6H). MS, *m/z*: 561.1 $[M+H]^+$. Found, %: C 57.70; H 5.95; N 4.97. $C_{27}H_{33}BrN_2O_4S$. Calculated, %: C 57.75; H 5.92; N 4.99.

**Antibacterial activity.** Antibacterial activity of the synthesized compounds was evaluated against three bacteria strains: *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*. Screening of the prepared compounds was performed according to the disk diffusion method [14]. Filter paper disks of 7 mm diameter were sterilized in an autoclave for 15 min at 121°C. Compounds **5a**–**5f** were dissolved in DMF to give the 30 mg/mL solutions, and the sterile disks were impregnated with the prepared solutions for 10 min. Agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5°C for 1h to permit good diffusion and then incubated at 35°C for 48 h. The inhibition zones were measured.

## CONCLUSIONS

A series of benzenesulfonylhydrazone derivatives of methyl dehydroabietate is synthesized and tested for antibacterial activity against *E. coli*, *S. aureus*, and *B. subtilis* by disk diffusion method. The experimental results indicate that the synthesized compounds possess *pronounced* antibacterial activity, among these *p*-fluorobenzenesulfonylhydrazone of methyl dehydroabietate demonstrates the best activity against *B. subtilis* and *S. aureus*.

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## CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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