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Synthesis of Methyl 3,6-Dioxo-*endo*-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-2-carboxylate as Synthetic Intermediate for Conduritol Derivatives*

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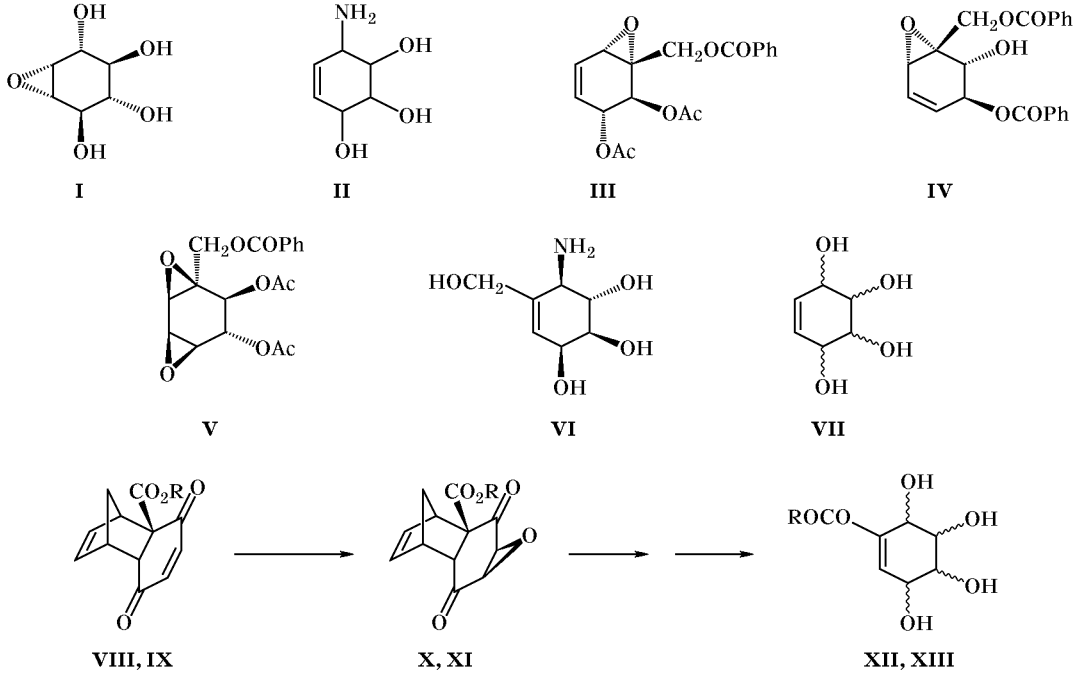
Abstract—Gentisic acid reacted with methyl iodide in HMPA to give 94% of the corresponding methyl ester. Its oxidation with Ag_2O in toluene afforded 57% of methoxycarbonylbenzoquinone as yellow crystals. Reaction of the latter with cyclopentadiene resulted in formation of methyl 3,6-dioxotricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-2-carboxylate (21%).

Synthesis of polyhydroxycyclohexene derivatives is the subject of extensive studies [1]. Such compounds are widely spread in the nature, and they usually exhibit biological activity [2, 3]. Typical examples are epoxytetrahydroxycyclohexane **I**, aminoconduritol **II** (which acts as glycosidase inhibitor), epoxy derivatives **III**–**V** (plant metabolites possessing tumorostatic, antileukemic, and antibiotic activity [1]), streptol (**VI**), and conduritols **VII**, the latter existing as six stereoisomers [1] (Scheme 1). Methods for

Scheme 1.



VIII, **X**, **XII**, R = Me; **IX**, **XI**, **XIII**, R = Et.

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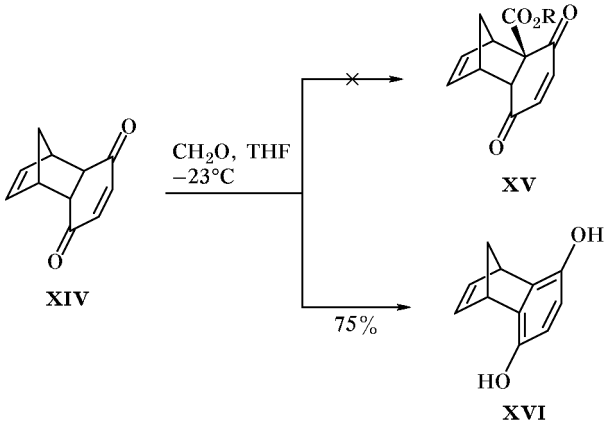
preparation of these compounds were reported in [2–6]. The present study was aimed at developing methods for preparation of alkyl 3,6-dioxo-*endo*-tricyclo[6.2.0^{2,7}]undeca-4,9-diene-2-carboxylates **VIII** and **IX** as potential intermediate products in the synthesis of conduritols and their derivatives.

Our attempt to synthesize precursor of ester **VIII** by reaction of *endo*-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (**XIV**) (which was prepared by the Diels–Alder reaction from cyclopentadiene and benzoquinone) [7] with formaldehyde in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) using THF as solvent was unsuccessful. Instead of the expected 2-hydroxymethyl-*endo*-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (**XV**) we isolated 75% of 5,8-dihydro-5,8-methano-1,4-dihydroxynaphthalene (**XVI**). In this reaction the hydroxymethylation process was preceded by aromatization (Scheme 2).

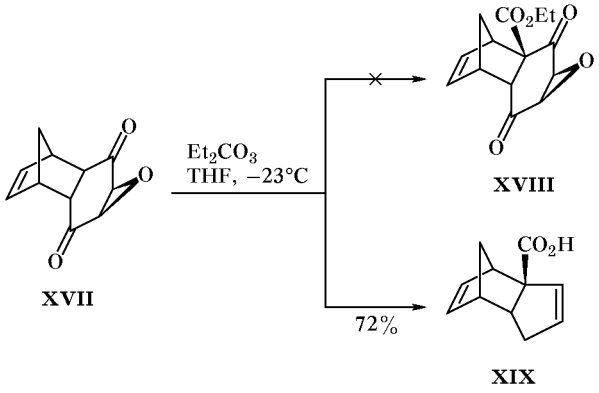
Scheme 2.



In order to avoid aromatization of adduct **XIV** in the presence of a base (DBU), it was subjected first to epoxidation and treatment with diethyl carbonate in the presence of DBU as base catalyst. However, this reaction gave no desired product **XVIII** but 5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-diene-2-carboxylic acid (**XIX**, yield 72%; Scheme 3). The structure of product **XIX** was confirmed by the IR, ^{1}H NMR, and mass spectra which were consistent with the data reported in [8]. Acid **XIX** was formed as a result of the Favorsky rearrangement on treatment with 5% hydrochloric acid. The synthetic potential of tricyclic carboxylic acid **XIX** was illustrated by the synthesis of naturally occurring clavulones via halodecarboxylation [9] and by the preparation of biologically active cyclopentanoids [10].

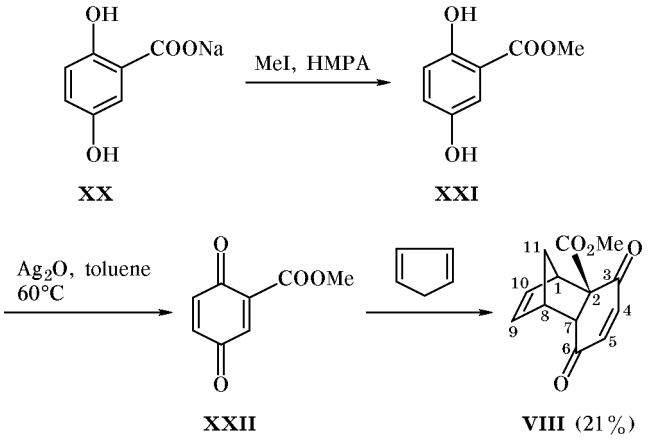
We succeeded in obtaining ester **VIII** (R = Me) using sodium 2,5-dihydroxybenzoate (**XX**) as starting

Scheme 3.



compound (Scheme 4). This procedure is fairly convenient, but the yield of the target product is poor. Among other factors, the low yield of **VIII** is explained by formation of quinhydrone at the stage of oxidation of methyl ester **XXI**.

Scheme 4.



EXPERIMENTAL

The melting points were measured on an Electro Thermal instrument and are uncorrected. The IR spectra were recorded on a Shimadzu IR-470 spectrometer. The ^{1}H NMR spectra were obtained on a Bruker AC instrument (Fourier transform, 80 MHz) in $CDCl_3$ using TMS as internal reference. The mass spectra (electron impact) were run on a Varian 5970 spectrometer. Merck Kieselgel 60H ASTM 35-70 plates were used for thin-layer chromatography.

Methyl 2,5-dihydroxybenzoate (XXI). Methyl iodide, 20 g (140 mmol), was added dropwise to a solution of 13 g (70 mmol) of sodium 2,5-dihydroxybenzoate in 10 ml of HMPA. The mixture was stirred for 3 h at room temperature, diluted with

350 ml of 5% hydrochloric acid, and extracted with ether (3 × 250 ml). The combined extracts were washed with water, dried over magnesium sulfate, and evaporated on a rotary evaporator. The residue was recrystallized from water. Yield 11 g (65 mmol, 94%), mp 86–87°C; published data [11]: mp 88°C. IR spectrum (KBr), ν, cm^{-1}: 3320 v.s, 3010 m, 2930 m, 1685 v.s, 1615 s, 1500 m, 1220 s, 1185 s, 810 w, 870 s, 680 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 10.17 s (1H), 7.20 s (1H), 6.85 m (2H), 5.0 s (1H), 3.9 s (3H).

Methyl 3,6-dioxo-1,4-cyclohexadienecarboxylate (XXII). Anhydrous Na_2CO_3, 5 g (36.2 mmol), and freshly prepared Ag_2O, 7.5 g (32.4 mmol), were added to a solution of ester **XXI**, 2.5 g (14.9 mmol), in 25 ml of toluene. The mixture was heated in the dark to 60°C, stirred for 1 h at that temperature, and filtered while hot (in the dark), and the precipitate was washed with 50 ml of hot toluene. The filtrate was dried over K_2CO_3 and evaporated under reduced pressure, and the residue was recrystallized from dry carbon disulfide. Yield 57%, yellow crystals, mp 50–52°C; published data [12]: mp 53.5–54°C. IR spectrum (CS_2), ν, cm^{-1}: 2950 m, 2800 m, 1645 s, 1660 v.s, 1360 s, 1045 m, 850 s.

Methyl 3,6-dioxo-*endo*-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-2-carboxylate (VIII). A solution of 0.44 g (6.66 mmol) of freshly distilled cyclopentadiene in 5 ml of toluene was added to a cold (0°C) solution of 1.02 g (6.66 mmol) of quinone **XXII** in 25 ml of toluene. The mixture was allowed to warm up to room temperature and was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography using hexane–ethyl acetate (3:2) as eluent. A fraction containing the target product and traces of ester **XXI** was collected. The latter was removed by dissolving the product in Et_2O and shaking the solution with 5% aqueous sodium hydroxide. The ether solution was washed with water, dried over $MgSO_4$, and evaporated to obtain 0.3 g (1.3 mmol, 21%) of compound **VIII** as an oily substance. IR spectrum (CCl_4), ν, cm^{-1}: 3050 w, 2950 s, 1745 s, 1685 v.s, 1230 s, 1200 m, 920 w, 840 w, 700 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.23 br.s (2H, 4-H, 5-H), 5.58–6.16 m (2H, 9-H, 10-H), 3.66 s (3H, OCH_3), 3.33 m (2H, 1-H, 8-H), 2.80 m (1H, 7-H), 0.9–1.6 m (2H, 11-H). Mass spectrum, *m*/*z* (I_{rel}, %): 232 M^+ (0.39), 168 (17.5), 150 (4.85), 137 (13.19), 136 (50.54), 108 (30.87), 91 (2.7), 66 (9.3), 59 (7.90).

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