ALKYLATION OF ENOLATES BY 3-METHYL-4-CHLORO-4,5,6,7-TETRAHYDROBENZ[1,2-d]ISOXAZOLE

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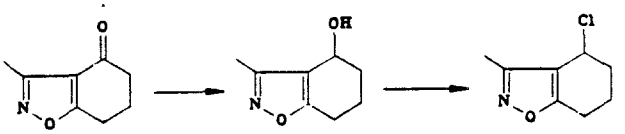
3-Methyl-4-chloro-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole was synthesized from 3-methyl-4-oxo-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole. The compound is used in the alkylation of malonic ester and methoxytetralone enolates. Bi- and tetracyclic derivatives of the pyridine and hydropyridine series were obtained by catalytic hydrogenation of the alkylation products.

Isoxazole derivates are widely used in the synthesis of biologically active compounds because of the latent bifunctionality of the isoxazole ring, which is readily realized at a certain stage of the synthesis by reductive or base-catalyzed splitting off of the heterocyclic ring [1-3]. Their stability under the conditions of many reactions and the possibility of obtaining them by various methods (including the nitroxide method), makes it possible to consider isoxazoles as an agent for protection and/or generation of bifunctionality, the synthetic aspects of which can be expanded because of the possibility of introducing isoxazole-containing blocks into the starting molecule, for example by means of alkylation [4].

It was of interest to study the alkylating properties of the previously unknown 3-methyl-4-chloro-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole (III) that we synthesized from isoxazole (I), the latter being readily obtainable by a classical method [5] or by a method described in [6]. Compounds of type III comprise an 8-carbon synthone, which can be used, for example, for the formation of a CD fragment of a steroid skeleton.

Reduction of the carbonyl group of isoxazole I by sodium borohydride in ethanol, in analogy to [7], gave hydroxyisoxazole II, the substitution of the hydroxy group in which by a chlorine atom by the action of thionyl chloride led to chloroisoxazole III. The spectral data of compounds II and III correspond to the proposed structures. Thus, in the IR spectrum of II there is an absorption band of the hydroxyl group at 3610 cm^{-1}, which is absent in III. In the PMR spectra of compounds II and III there are signals in the 1.87-2.75 and 2.00-2.67 ppm regions, corresponding to methylene protons of the six-membered ring, singlets of the methyl (2.33 and 2.29 ppm) and multiplets of methine protons at 4.75 and 5.05 ppm, respectively. The mass spectrum of compound III has a characteristic signal of the molecular ion with m/z 171, 173 and a peak intensity ratio of 1:3, which corresponds to the presence of chlorine atom in the molecule [8].



I II III

Alkylation in ethanol of a sodium-malonic ester (IV) with chloroisoxazole III gives isoxazole V in a good yield.

In the IR spectrum of compound V characteristic absorption bands of ester groups were observed in the 1735-1755 cm^{-1} region and a band at 1635 cm^{-1} due to the presence of an isoxazole ring. In the PMR spectrum, besides the proton signals of the unchanged fragments of the molecule, there is a triplet of the methyl (1.23 ppm), a quartet of the methylene (4.17 ppm) protons of the ester groups of the substituent at $C_{(4)}$, and two resonance signals of the adjacent methine protons: a multiplet at 3.49 ppm and a doublet at 3.70 ppm.

The use of chloroisoxazole III for the annelation of the CD fragment of the steroid molecule implies the alkylation by it of bicyclic ketones with the formation of a tetracyclic skeleton of the D-homogonane series. For this purpose we studied the

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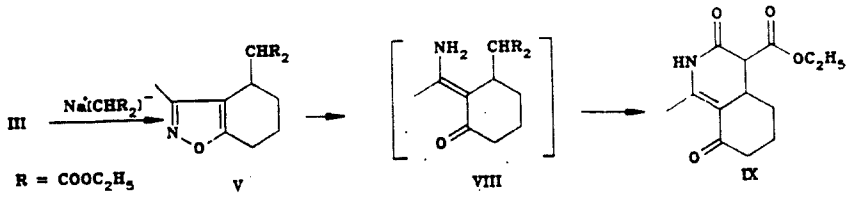
reaction of methoxytetralone VI with isoxazole III in the presence of sodium amide. The carbanion was generated by boiling the solution of compound VI in absolute THF in the presence of sodium amide, after which isoxazole III was added to the mixture.

The tetracyclic isoxazole VII resulting from the reaction was obtained in a 52% yield. Its structure was verified by physicochemical methods and elemental analysis. Thus, the IR spectrum has an absorption band of the carbonyl group at 1680 cm^{-1}. In addition to the signals of all the main structural fragments of the molecule in the expected regions, the PMR spectrum also contains signals of two methyl groups (2.37 and 3.87 ppm) and multiplets of the methine protons (2.97 and 3.75 ppm). The mass spectrum gives a peak of the molecular ion with m/z 311.



3-Substituted isoxazoles undergo opening of the isoxazole ring at the N–O bond under the catalytic hydrogenation conditions with the formation of enamino-ketones [3]. Hydrogenation of compound V over Raney nickel in ethanol leads to the formation of two products. One of them, mp 117-119°C, could be isolated by crystallization from ether. The IR spectrum of this compound contains three bands in the region of 1670-1750 cm^{-1}, corresponding to the vibrations of carbonyl groups and a stretching vibration band of the CO–NH group at 3400 cm^{-1}. There are signals in the PMR spectrum belonging to the ester group [1.35 (CH_3) and 4.32 ppm (CH_2)], a singlet of the methyl group (2.38 ppm) and a signal of the amide proton (8.34 ppm). Based on the spectral characteristics and the elemental analysis, the structure of the bicyclic ethyl ester of 1-methyl-3,8-dioxo-2,3,4,4a,5,6,7,8-octahydroisoquinoline-4-carboxylic acid (IX) was ascribed to this compound. Attempts to isolate its precursor, the enamino-ketone VIII in a pure state, which we probably recorded by TLC as the second hydrogenation reaction product, were unsuccessful, because of its lability and tendency to cyclization. It should be noted that treatment of the reaction mixture, obtained as a result of hydrogenation, with sodium acetate or triethylamine leads to a single reaction product – compound IX.

As in the case of V, compound VII may undergo reductive splitting. Thus, during hydrogenation in the presence of Raney nickel in ethanol or glacial acetic acid, and also over the palladium catalyst in a 3-4% ethanolic solution of potassium hydroxide, or a triethylamine–ethyl acetate (1:1) mixture, compound XIII, mp 148-150°C, is formed in a good yield. Its structure conforms well with its spectral and elemental analysis data. In the IR spectrum of compound XIII there is an intense absorption of the carbonyl group (1680 cm^{-1}) and the absorption band in the 3000-3500 cm^{-1} region of the NH group is absent. The PMR spectrum contains signals of aromatic protons, two methyl groups at 2.89 and 3.87 ppm, and multiplets of the methylene groups at 2.15 ppm and on the 2.68-2.89 ppm region.

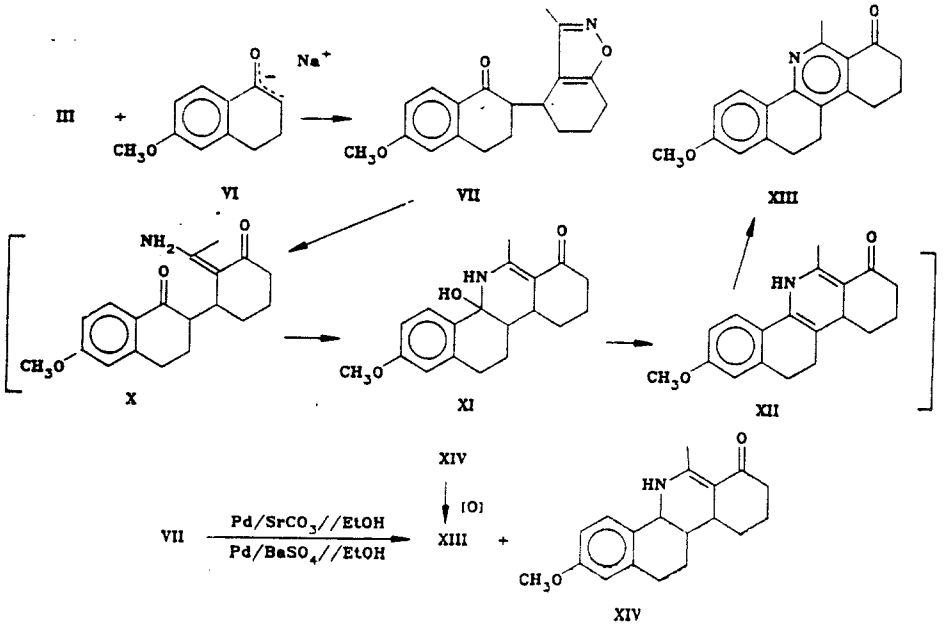


TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	T_{mp} °C	M*	IR spectrum, cm^{-1}	PMR spectrum (in $CDCl_3$), ppm	Yield, %
II	$C_8H_{11}NO_2$	79...80**	153	1640 (C=N), 3610 (OH)	1,87 (2H, m, CH_2); 2,00 (2H, m, CH_2); 2,33 (3H s CH_3); 2,75 (2Hm , CH_2); 4,75 (1H, m 4-CH)	86
III	$C_8H_{10}ClNO$	—	171, 173	1640 (C=N)	2,00 (2H, m, CH_2); 2,13 (2H, m, CH_2); 2,29 (3H, s, CH_3); 2,67 (2H, m, CH_2); 5,05 (1H, м, 4-CH)	83
V	$C_{15}H_{21}NO_5$	—	295	1635 (C=N), 1735...1755 (C=O)	1,23 (6H, t, OCH_2CH_3); 1,91 (4H, m, $2CH_2$); 2,24 (3H, s, CH_3); 2,67 (2H, m, CH_2); 3,49 (1H, m, 4-CH); 3,70 (1H, d $CH(COOC_2H_5)_2$); 4,17 (4H,q , OCH_2CH_3)	71
VII	$C_{19}H_{21}NO_3$	145...147	311	1575, 1595, 1680 (C=O)	1,90 (6H, m, $3CH_2$); 2,37 (3H, s CH_3); 2,65 (2H, m, CH_2); 2,93 (2Hm CH_2); 2,97 (1H, m, 2'-CH); 3,75 (1H, m , 4-CH); 3,87 (3H, s OCH_3); 6,68...8,05 (3H, m, arom.)	52***
IX	$C_{13}H_{17}NO_4$	117...119	251	1670, 1710, 1745 (C=O), 3400 (CO—NH)	1,35 (3H, t, OCH_2CH_3); 2,38 (3H, s , CH_3); 4,32 (2H, q , OCH_2CH_3); 8,34 (1H, s, NH)	67
XIII	$C_{19}H_{19}NO_2$	148...150	293	1555, 1610, 1680 (C=O)	2,15 (2H, m, CH_2); 2,68 (2H,m , CH_2); 2,89 (9H,m , CH_3, $3CH_2$); 3,87 (3H, s , OCH_3); 6,75...8,35 (3H, m , arom.)	93
XIV	$C_{19}H_{23}NO_2$	249...251	297	1500, 1610, 1675 (C=O), 3250 (NH)	2,37 (3H, s, CH_3); 3,80 (3H, s, OCH_3); 4,32 (1H, t , CH); 4,88 (1H, br.s , NH); 6,66...7,15 (3H, m, arom.)	13

*IR spectra of compounds II, IX, and XIV – in $CHCl_3$, of compounds III, V, VII – in KBr.

**From hexane.

***The yield based on methoxytetralone VI that entered the reaction.

Compound XIII is probably formed as the result of a series of consecutive reactions, including an intramolecular cyclization of the enamino ketone X into the enaminocarbinol XI. These compounds are readily dehydrated into 1,4-dihydropyridines, which in turn may undergo spontaneous oxidation [9] and/or disproportionation [10] with the formation of pyridine and hydropyridine derivatives. During the hydrogenation of compound VII in the presence of a 10% $Pd/BaSO_4$ and 30% $Pd/SrCO_3$, a compound was separated out, to which structure XIV was ascribed on the basis of spectral and elemental analysis data. The IR spectrum of compound XIV reveals absorption in the 1500-1675 cm^{-1} region characteristic for β-aminovinyl ketones [11]. The band at 3250 cm^{-1} corresponds to the stretching vibrations of the NH group. In the PMR spectrum there are signals of aromatic protons, two singlets of the methyl groups at 2.37 and 3.80 ppm, and a broadened signal of the amino group (4.88 ppm). On standing in air, compound XIV spontaneously oxidizes with the formation of the pyridine derivative XIII.

The results obtained indicate the possibility of using the halogen derivatives of tetrahydrobenzisoxazole III, synthesized by us, in the heteroannelation processes. The end products of the transformations, the condensed pyridine, and/or hydropyridine derivatives IX, XIII, are of interest as physiologically active compounds, while isoxazoles of the V, VII type may also be used for constructing hetero- and carbocyclic structures.

EXPERIMENTAL

The melting points were determined on a Boetius stage. The IR spectra were obtained on a UR-20 spectrophotometer and the PMR spectra on JNM-PS-100 (100MHz) and Bruker WM-360 (360 MHz) spectrometers, using TMS as internal standard. The mass spectra were obtained on a Varian MAT-311 mass spectrometer at an energy of the ionizing radiation of 70 eV. The course of the reaction and the individual state of the products were monitored by TLC on Silufol UV-254 plates, and silica gel L 40/100 μ was used for the column chromatography.

The characteristics of the synthesized compounds are given in Table 1.

The data of the elemental analysis for C, H, and N for compounds II, III, V, VII, IX, XIII, and XIV correspond to the calculated values.

3-Methyl-4-hydroxy-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole (II). A 2-ml portion of water was added to a solution of 1.4 g (9 mmoles) of isoxazole I in 120 ml of ethanol, and then 0.38 g (10 mmoles) of $NaBH_4$ was added in portions in the course of 10 min. The reaction mixture was stirred for 2 h at 20°C. The solvent was evaporated in vacuo to 3/4 of its volume, 20 ml of water was added, and the mixture was extracted with ether (4 × 20 ml). The ether extract was dried over $MgSO_4$, and ether was evaporated under vacuum. Yield 1.2 g of compound II.

3-Methyl-4-chloro-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole (III). A 1.85-ml portion (26 mmoles) of thionyl chloride was added to a solution of 2 g (13 mmoles) of compound II in 100 ml of dry chloroform. The mixture was allowed to stand for 24 h at 20°C, and was then washed with water (2 × 20 ml), a 10% solution of $NaHCO_3$ to pH 7, and dried over $MgSO_4$. Chloroform was evaporated under vacuum. Yield 1.85 g of an oily compound III.

2-Methyl-4-(biscarbethoxy)methyl-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole (V). A solution of 1.6 g (10 mmoles) of chloroisoxazole III in 50 ml of absolute ethanol was added to sodium ethyl malonate obtained from 0.33 g (14 mmoles) of sodium and 2.22 g (14 mmoles) of malonic ester in 30 ml of absolute ethanol. The reaction mixture was stirred for 2 h at 60°C. The solvent was evaporated under vacuum, 20 ml of water was added, the mixture was extracted with ether (4 × 50 ml), and the extract was dried over $MgSO_4$. After the evaporation of the solvent under vacuum, the residue was chromatographed on a column (3 × 25 cm), using a hexane–ether (9:1) mixture as eluent. Yield 2.1 g of isoxazole V in the form of an oil.

3-Methyl-4-(6'-methoxy-1'-oxo-1',2',3',4'-tetrahydronaphthyl-2')-4,5,6,7-tetrahydrobenz[1,2-d]-isoxazole (VII). A solution of 3 g (17 mmoles) of compound VI in 50 ml of absolute THF was added to a mixture of 2.4 g (60 mmoles) of $NaNH_2$, and 3.54 ml of hexamethylphosphoramide in 20 ml of absolute THF. The reaction mixture was heated in an argon current for 5 h at 60°C, then cooled to 0°C, and a solution of 3.7 g (21 mmoles) of chloroisoxazole III in 30 ml of absolute THF was added in the course of 20 min. The mixture was heated for 8 h at 60°C, and after adding 20 ml of water and a 5% solution of HCl to pH 7, was extracted with chloroform (4 × 100 ml), and the extract was dried over $MgSO_4$. The solvent was evaporated under vacuum, and the residue was chromatographed on a column (40 × 350 mm), using a hexane–ether (7:3) mixture as eluent. Yield 0.54 g (18%) of unreacted VI and 2.24 g of compound VII.

Ethyl Ester of 1-Methyl-3,8-dioxo-2,3,4,4a,5,6,7,8-octahydroisoquinoline-4-carboxylic Acid (IX). A 1.8-g portion (6 mmoles) of compound V in 30 ml of ethanol was hydrogenated in the presence of 0.6 g of Raney nickel

for 12 h. The catalyst was filtered off and the solvent was evaporated under vacuum. Crystallization from ether gave 1.2 g of compound IX.

Hydrogenation of Compound VII. A. A 0.22-g portion (0.7 mmole) of compound VII in 40 ml of ethanol was hydrogenated at 20°C, under normal pressure, in the presence of 0.25 g of Raney nickel. The catalyst was filtered off, the solvent was evaporated under vacuum, and the residue was recyrstallized from ethanol. Yield 0.2 g (93%) of **3-methoxy-12-methyl-11-aza-D-homogona-1,3,5(10),8(14),9(11),12(13)-hexaen-17a-one (XIII).**

B. A 0.17-g portion (0.6 mmole) of compound VII was hydrogenated in a solution containing 1.5 g of KOH in 40 ml of ethanol over 0.08 g of Pd/C (10%). The catalyst was filtered off, the solvent was evaporated under vacuum, and 20 ml of water was added to the residue. The mixture was extracted with chloroform (3 × 40 ml) and the extract was dried over $MgSO_4$. Chloroform was evaporated under vacuum, and the residue was crystallized from ethanol. Yield 0.13 g (82%) of crystals, mp 147-150°C, which were identical with compound XIII.

C. A 0.05-g portion (0.16 mmole) of compound VII was hydrogenated in the presence of 0.04 g of Pd/C (10%) in 20 ml of an Et_3N–EtOAc (1:1) mixture. The reaction product was separated and purified as under **A**. Yield 0.02 g (40%) of compound identical with XIII.

D. A 0.17-g portion (0.6 mmole) of isoxazole VII in 20 ml of glacial acetic acid was hydrogenated with 0.7 g of Raney nickel. The treatment was carried out by the method described under **A**. Yield 0.14 g (82%) of crystals, mp 147-149°C, which were identical with XIII.

E. A 0.2-g portion (0.64 mmole) of VII in 40 ml of ethanol was hydrogenated in the presence of 0.05 g of $Pd/SrCO_3$ (30%). The treatment was carried out by the method described under **A**, whereby 0.19 g of a reaction product comprising a mixture of compounds was isolated, one of which corresponds chromatographically to XIII. Crystallization from ethyl acetate gave 25 mg of **3-methoxy-12-methyl-11-aza-D-homogona-1,3,5(10),12(13)-tetraen-17a-one (XIV).**

Separation of the mixture remaining on the column (20 × 150 mm), using a hexane–ether (9:1) mixture as eluent results in the disappearance of compound XIV and isolation of a product mp 147-149°C, which was identical with XIII.

F. A 0.35-g portion of isoxazole VII was hydrogenated over $Pd/BaSO_4$ in ethanol. At the end of the hydrogenation, the treatment was carried out as in experiment **A**. Thus, 0.3 g of a reaction mixture was obtained, from which compound XIII [0.12 g (41%)] and XIV [0.01 g (3%)] were isolated by fractional crystallization from ethanol.

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