ON EQUILIBRATION OF QUASSIN AND 4-EPIQUASSIN

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

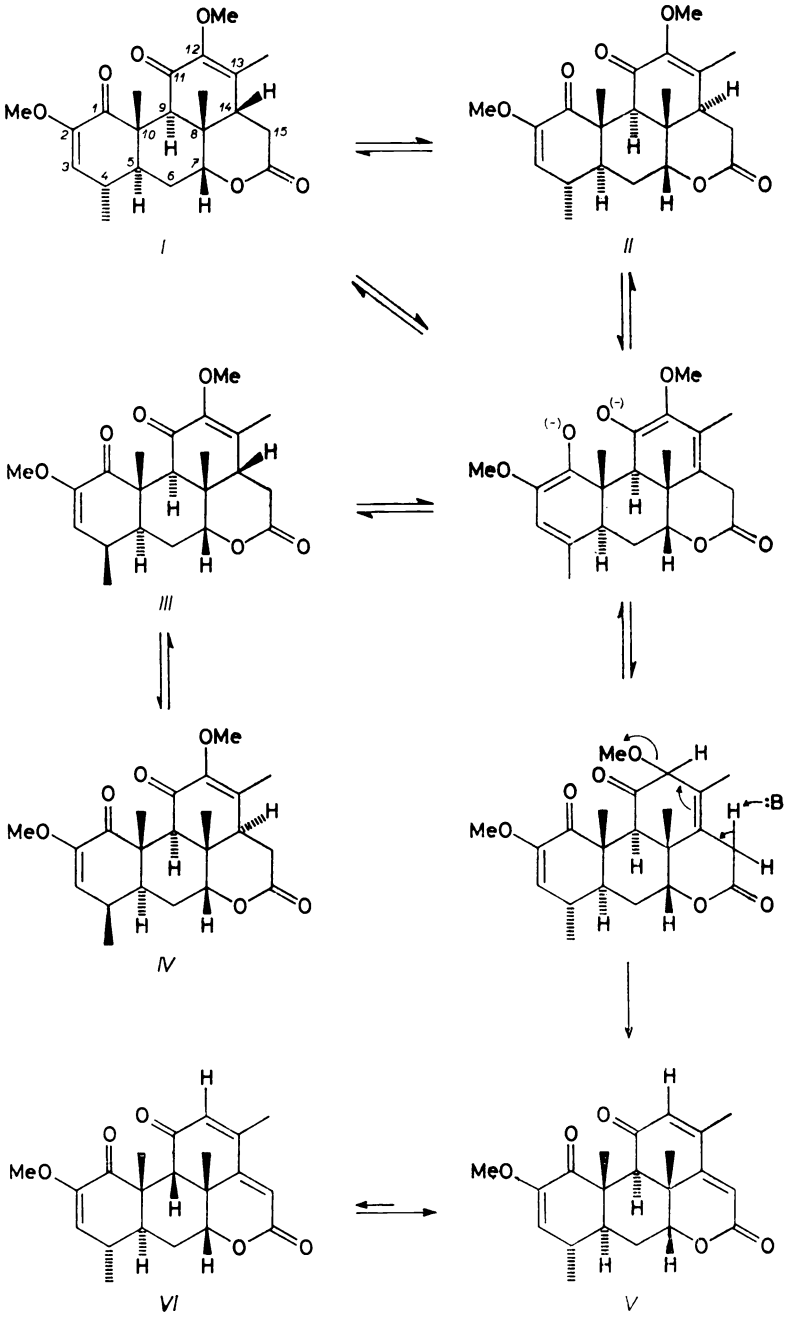
Equilibration of quassin and 4-epiquassin is described. Various quassin derivatives are characterized and their relationship to quassin (*I*) is discussed. A regioselective deprotonation is achieved in quassin and 4-epiquassin (*III*) by the introduction of a diosphenolate grouping which makes a potentially acidic H-atom unavailable for attack by base.

During the early 1950s, Robertson and co-workers[1] were able to separate and characterize two major constituents of *Quassia amara*, quassin $C_{22}H_{28}O_6$ and its hemiacetal, neoquassin $C_{22}H_{30}O_6$.

An extensive chemical study was conducted towards obtaining various transformation products of quassin and establishing their structures. The complete structure and stereochemistry of quassin (*I*) was deduced[2] in the 1960s. It had been known from the work of Robertson and co-workers[3] that prolonged treatment of quassin with boiling acetic acid or with 5% methanolic hydrochloric acid at room temperature gave an equilibrium mixture of quassin and a less soluble isomer, isoquassin (m.p. 292°C), which could be separated by extensive fractional crystallization from chloroform–light petroleum ether. The same equilibrium mixture was produced starting from isoquassin, under the same reaction conditions[3]. It was deduced later[2] that the pair quassin (*I*) – isoquassin (*II*) (Scheme 1) differs only in stereochemistry at C-14.

In our approach to the total synthesis of quassin, we prepared[4] a series of racemic 4-epi compounds, including 4-epiquassin (*III*). A comparison of the coupling constants of the ^{1}H NMR signal corresponding to the olefinic proton at C-3 in quassin (*I*) and in 4-epiquassin (*III*) (Table I) clearly showed that the C-4 methyl group is axial in 4-epiquassin and equatorial in quassin. An X-ray analysis of an earlier synthetic intermediate[5] had indicated previously that all our synthetic compounds had the unnatural C-4 configuration.

In order to complete the total synthesis of quassin, it thus became necessary to find acidic or basic conditions under which 4-epiquassin (*III*), prepared by synthesis,



SCHEME 1

would equilibrate efficiently to the mixture of quassin and isoquassin (*II*) or, preferably, to quassin alone. Under Robertson's conditions[3] (methanolic HCl), only traces of isomer *IV* were detected, along with unchanged 4-epiquassin (*III*). It thus became clear that the deprotonation at C-4 would be very difficult to achieve under acidic conditions and a non-nucleophilic base, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), was chosen for a thorough equilibration study of quassin and 4-epiquassin. The ^{1}H NMR data for all the compounds obtained in this study are listed in Table I.

Treatment of quassin with an excess of DBN in anhydrous benzene in a dilute solution at reflux for 5–10 h gave an equilibrium mixture of quassin (*I*) and isoquassin (*II*). However, when quassin was heated at reflux with an excess of DBN in anhydrous acetonitrile for 5–10 h, the reaction mixture contained three major compounds, quassin (*I*), isoquassin (*II*) and compound *V*. In addition, compound *VI* could be isolated in very small quantity (<2%) on careful chromatography. The same mixture of four products was obtained with an excess of DBN in refluxing benzene when the concentration of quassin was about 0·05 mol l^{-1}. As expected, starting from isoquassin (*II*), reflux with DBN in acetonitrile produced the same mixture of four compounds.

After treatment of 4-epiquassin (*III*) with an excess of DBN in refluxing anhydrous benzene in a dilute solution, only 4-epiquassin and its C-14 epimer *IV* could be

TABLE I

^{1}H NMR data (in deuteriochloroform) of compounds *I*–*VI*, coupling constants in parentheses. For other conditions see Experimental

Compound	H-3	H-7	CH_3O-2	CH_3O-12	H-9	CH_3-13
I	5·28 d (2·54)	4·26 t	3·55 s	3·63 s	2·96 s	1·85 s
II	5·42 d (2·65)	4·09 t	3·53 s	3·64 s	3·41 s	1·79 s
III	5·46 d (4·84)	4·30 t	3·59 s	3·64 s	2·91 s	1·85 s
IV	5·70 d (5·78)	4·13 t				
V	5·29 d (2·54)	4·31 t	3·56 s	—	3·11 s	2·08 d (1·48)
VI	5·41 d (2·40)	4·50 dd (5·04) (9·16)	3·53 s	—	2·36 s	1·98 d (1·27)

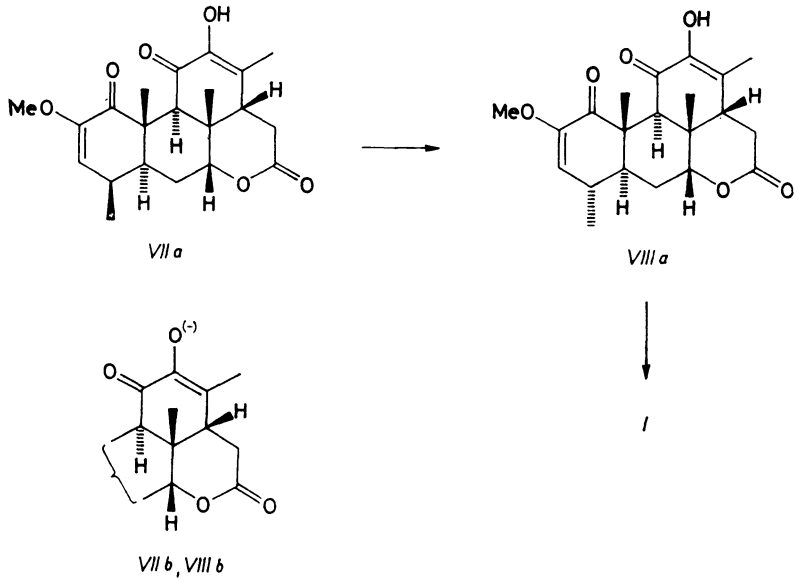
detected. Heating 4-epiquassin (*III*) with an excess of DBN in anhydrous acetonitrile at reflux for 6 – 10 hours produced a mixture of six compounds. Listed in the order of decreasing R_F values, these were: desmethanol compound *V*, quassin (*I*), 4-epiquassin (*III*), desmethanol 9-epimer *VI* (traces), isoquassin (*II*) and 4-epi-isoquassin (*IV*). The same mixture of six compounds was obtained by refluxing 4-epiquassin (*III*) with an excess of DBN in anhydrous benzene in a more concentrated solution (0·05 mol l^{-1}).

Spectroscopic data clearly showed that compounds *V* and *VI* are stereoisomers. The most notable feature of the ^{1}H NMR spectrum of desmethanol compound *VI* is the signal for the C-7 proton (see Table I). It is a well resolved double doublet, while the corresponding signal in the spectra of all the other compounds reported here is a triplet. Inspection of molecular models clearly showed that a change of configuration at C-9 in the *V* → *VI* isomerization strongly affects the geometry of the C-7 proton.

The surprising formation of compounds *V* and *VI* can be understood as a base-catalyzed enolization of the ketones in rings A and C, a subsequent protonation of the resulting dianion at C-4 and at C-12 by $DBNH^+$ and, finally, an elimination of methanol made possible by the activation of the protons at C-15 by the lactone carbonyl groups (Scheme 1). It should be noted that this sequence includes the seldom encountered formal conversion of a (methylated) enol to a (methylated) allyl alcohol. This, of course, is made possible by the assistance of the C-11 carbonyl group and is characteristic of the diosphenol grouping. The fact that the C-4 epimers of compounds *V* and *VI* are not formed during the equilibration of 4-epiquassin (*III*) deserves comment. Clearly, a deprotonation at C-14 and thus an anion formation in ring C must take place during the *III* ⇌ *IV* equilibration (Scheme 1). It must then be assumed that, in the case of this monoanion, the protonation at C-12 and/or the subsequent elimination of methanol do not take place. The simplest explanation of the data is provided by the postulate of a powerul long-range conformational effect by which the nature of ring A (C-4 methyl group axial or equatorial or ring A enolate) determines whether the methanol elimination will take place. The dianion shown in Scheme 1 may, in fact, not be an intermediate. It is possible, or even likely, that the deprotonation–protonation sequences are consecutive and that the methanol elimination only takes place when the C-4 methyl group has the quassin configuration.

Clearly, while some quassin was produced, the equilibration of 4-epiquassin described above was not acceptable as the final step in the total synthesis of quassin. Since all the undesirable by-products resulted from the deprotonation at C-14, a question could be formulated: How could C-14 be protected against deprotonation while the configuration at C-4 was being changed? It could reasonably be expected that the presence of a ring C diosphenolate grouping in a selectively demethylated 4-epiquassin (*III*) (see *VIIb* in Scheme 2) would drastically reduce the rate of de-

protonation at C-14 in base. The required racemic 4-epinorquassin *VIIa* was therefore prepared[4] and subjected to equilibration with DBN in boiling benzene. This produced norquassin *VIIIa* (Scheme 2) without any by-products and its methylation



SCHEME 2

provided *d,l*-quassin (*I*), m.p. 187–188°C, in good yield. The presence of a ring C diosphenol anion in *VIIb* and *VIIIb* (Scheme 2) thus served as an effective protection against the formation of a second anion in the same ring.

EXPERIMENTAL

All reactions were performed in flame-dried glassware, under an inert atmosphere of dry argon or nitrogen. Benzene (SP Mallinckrodt AR) was dried by distillation from sodium. Acetonitrile (Fisher, Cert. ACS) was dried over 3Å Molecular Sieves. DBN was supplied by Aldrich and used without further purification. Dimethyl sulfate was distilled. Separation or purification of mixtures was performed on silica gel 60G (Merck) on column or plates (0·5 and 0·25 mm). ^{1}H NMR spectra were recorded in deuteriochloroform solution (without tetramethylsilane) using a Varian XL-200 instrument. Chemical shifts are given in ppm (δ-scale), coupling constants (J) are in Hz. IR spectra were taken in chloroform solution (wavenumbers in cm^{-1}) on Perkin–Elmer Model 727B. Mass spectra were obtained on Kratos MS50 TC instrument. Melting points were taken on Reichert hot stage apparatus and are uncorrected. Quassin, Koch-Light Laboratories Ltd., was purified by oxidation with Ag_2O in aqueous ethanol and recrystallized (ethyl acetate–hexane).

Equilibration of Quassin (*I*) with DBN

a) In anhydrous benzene (dilute solution): A solution of 21·0 mg (0·054 mmol) of quassin (*I*) in 5 ml of anhydrous benzene and 85·2 μl (0·690 mmol) of DBN was heated under reflux for 6 h. The cold reaction mixture was diluted with chloroform and washed successively with cold aqueous HCl solution, water and brine. The organic solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a crude mixture (19·0 mg) of two compounds, quassin (*I*) and isoquassin (*II*) in a 3·6 : 1 ratio. The ratio of quassin and isoquassin may vary with reaction time and dilution of the solution. Separation on silica gel plate furnished pure quassin (*I*) (7·0 mg) whose ^{1}H NMR and IR spectra were identical to an authentic sample, and pure isoquassin (*II*), lower spot (2·0 mg). IR spectrum: 2 940, 2 840, 1 745, 1 690, 1 680, 1 635, 1 445, 1 380, 1 330, 1 100, 1 065. ^{1}H NMR spectrum: 5·42 (d, 1 H, J = 2·65); 4·09 (t, 1 H); 3·64 (s, 3 H); 3·53 (s, 3 H); 3·41 (s, 1 H); 1·79 (s, 3 H); 1·45 (s, 3 H); 1·19 (s, 3 H); 1·14 (d, 3 H, J = 6·52). HRMS calculated for $C_{22}H_{28}O_6$ m/z 388·1878, found m/z 388·1818.

b) In anhydrous acetonitrile: A solution of 260·0 mg (0·670 mmol) of quassin (*I*) in 25 ml of dry acetonitrile and 1·159 ml (9·38 mmol) of DBN was refluxed for 10 h. After the work-up (as above) 254·6 mg of a crude mixture, containing four compounds, was isolated (*I* + *II* + *V* + *VI*, Table I). The ratio of these compounds in the crude mixture (from ^{1}H NMR) was *I* : *II* : : *V* : *VI* = 45 : 24 : 23 : 8. The mixture was chromatographed on silica gel plates (0·5 mm, pure ethyl acetate as eluent) and provided, in order of decreasing R_F values, compounds *V*, *I*, *VI*, and *II*.

Compound *V* (16·4 mg, 6·87%) m.p. 232–234°C. IR spectrum: 2 970, 2 945, 2 860, 1 730, 1 700, 1 685, 1 635, 1 450, 1 435, 1 380, 1 270, 1 095. ^{1}H NMR spectrum: 6·04 (s, 1 H); 5·99 (br s, 1 H); 5·29 (d, 1 H, J = 2·54); 4·31 (t, 1 H); 3·56 (s, 3 H); 3·11 (s, 1 H); 2·08 (d, 3 H, J = 1·48); 1·47 (s, 3 H); 1·26 (s, 3 H); 1·14 (d, 3 H, J = 6·84). HRMS calculated for $C_{21}H_{24}O_5$ m/z 356·1623, found m/z 356·1610. The spectra of *I*, quassin (99·6 mg, 38·31%) are identical in all respects with those of an authentic sample.

The fraction containing compound *VI* (17·6 mg) was contaminated with quassin, and therefore rechromatographed twice and crystallized from ethyl acetate–ether–pentane, to provide pure crystalline compound (2·4 mg, 1%), m.p. 215–217°C. IR spectrum: 2 960, 2 930, 2 870, 1 730, 1 700, 1 690, 1 630, 1 450, 1 385, 1 100, 1 065, 900. ^{1}H NMR spectrum: 6·26 (br s, 1 H); 5·60 (s, 1 H); 5·41 (d, 1 H, J = 2·40); 4·50 (dd, 1 H, J = 5·04, 9·16); 3·53 (s, 3 H); 2·36 (s, 1 H); 1·98 (d, 3 H, J = 1·27); 1·30 (s, 3 H); 1·25 (s, 3 H); 1·09 (d, 3 H, J = 6·84). HRMS calculated for $C_{21}H_{24}O_5$ m/z 356·1623, found m/z 356·1616. The spectra of isoquassin (*II*) (15·0 mg, 5·77%) were identical in all respects with those of an authentic sample.

c) In anhydrous benzene (concentrated solution): The very same mixture of four compounds (as under *b*)) was obtained.

Equilibration of Isoquassin (*II*) with DBN

In anhydrous acetonitrile: A solution of 10·0 mg (0·0257 mmol) of isoquassin (*II*) in 2 ml of anhydrous acetonitrile and 44·5 μl (0·3608 mmol) of DBN was refluxed for 6 h. After the work-up (as in the previous reactions), the isolated crude material, 8·9 mg, contained all four compounds: *V*, *I*, *VI*, *II*.

Equilibration of 4-Epiquassin (*III*) with DBN

a) In anhydrous benzene (dilute solution): A solution of 4·0 mg (0·0103 mmol) of 4-epiquassin[4] (*III*) (m.p. 217–219°C. ^{1}H NMR spectrum: 5·46 (d, 1 H, J = 4·84); 4·30 (t, 1 H); 3·64 (s, 3 H);

3·59 (s, 3 H); 2·91 (s, 1 H); 1·85 (s, 3 H); 1·57 (s, 3 H); 1·21 (d, 3 H, $J = 6·39$); 1·20 (s, 3 H). HRMS calculated for $C_{22}H_{28}O_6$ m/z 388·1878, found m/z 388·1904) in 3 ml of anhydrous benzene and DBN (0·1442 mmol) (from a fresh DBN stock solution in benzene) was refluxed for 6 h. The solvent and some DBN was removed in vacuo, and the NMR spectrum of the crude mixture was taken. On a silica plate the mixture showed two spots with R_F values corresponding to starting material, 4-epiquassin (*III*), and lower spot corresponding to 4-epi-isoquassin (*IV*) (Table I). The mixture was not separated, but it was subjected to equilibration in acetonitrile.

b) *In anhydrous acetonitrile*: The above crude mixture, containing 4-epiquassin (*III*) and 4-epi-isoquassin (*IV*), was dissolved in 2·5 ml of anhydrous acetonitrile and 0·144 mmol of DBN was added. The reaction mixture was heated under reflux for 6 h, cooled and diluted with methylene chloride. The organic phase was successively washed with cold aqueous HCl solution, water and brine, and dried ($MgSO_4$). The concentration of the filtrate provided 3·8 mg of a crude mixture of five compounds (in order of decreasing R_F values) *V*, *I*, *III*, *VI*, *IV* (*II* could not be detected from this mixture). By prolonged heating of this mixture (for 13 h) more of quassin was produced along with compounds *V* and *VI*.

c) *In anhydrous benzene* (*concentrated solution*): A solution of 4·3 mg (0·011 mmol) of 4-epiquassin (*III*) in 200 µl of anhydrous benzene and 0·155 mmol of DBN was heated under reflux for 9 h. The work-up (as under *b*)) provided 4·2 mg of a crude mixture containing all five compounds. The mixture was chromatographed on silica and the NMR spectra of isolated compounds were compared with those of the authentic samples isolated from the equilibration of quassin. The isolated compounds were characterized as follows, in order of decreasing R_F values (pure ethyl acetate). Compound *V*, 0·5 mg, HRMS calculated for $C_{21}H_{24}O_5$ m/z 356·1621, found m/z 356·1587, ^{1}H NMR as in Table I. Compound *I*, quassin, 0·4 mg with ^{1}H NMR spectrum: 5·29 (d, 1 H, $J = 2·47$); 4·26 (t, 1 H); 3·65 (s, 3 H); 3·57 (s, 3 H); 2·97 (s, 1 H); 1·86 (s, 3 H); 1·55 (s, 3 H); 1·18 (s, 3 H); 1·10 (d, 3 H, $J = 6·95$). HRMS calculated for $C_{22}H_{26}O_6$ m/z 388·1878, found m/z 388·1911.

Mixture *I* + *III*, 1·4 mg of the mixture of quassin and 4-epiquassin (quassin and 4-epiquassin were very close on TLC plate (silica), the latter having R_F value slightly lower than that of quassin) ^{1}H NMR spectrum: 5·46 (d, $J = 5·12$) and 5·29 (d, $J = 2·54$); 4·30 (t) and 4·26 (t); 2·97 (s) and 2·91 (s) being the most distinguishable chemical shifts in the mixture of two. Compound *VI* was not isolated, but evident from the crude mixture. Compound *IV* (with traces of *II*), 0·3 mg.

Norquassin (*VIIIa*)

4-Epinorquassin[4] (*VIIa*) (^{1}H NMR spectrum: 6·13 (s, 1 H); 5·46 (d, 1 H, $J = 5·01$); 4·29 (t, 1 H); 3·59 (s, 3 H); 3·02 (s, 1 H); 1·86 (s, 3 H); 1·50 (s, 3 H); 1·21 (s, 3 H); 1·17 (d, 3 H, $J = 6·53$)), 7·2 mg (0·019 mmol) in 500 µl of anhydrous benzene and 29 µl of DBN was heated under reflux for 10 h. The cold reaction mixture was diluted with methylene chloride and washed successively with cold aqueous hydrochloric acid solution, water and brine. The organic solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to yield 5·4 mg (75%) of a crude *VIIIa* which was chromatographed on silica gel. Elution with ethyl acetate–hexane (1 : 1) afforded pure norquassin, 2·8 mg, ^{1}H NMR spectrum: 6·11 (s, 1 H); 5·30 (d, 1 H, $J = 2·22$); 4·26 (br s, 1 H); 3·57 (s, 3 H); 3·08 (s, 1 H); 1·87 (s, 3 H); 1·49 (s, 3 H); 1·20 (s, 3 H); 1·10 (d, 3 H, $J = 6·66$).

d, *l*-Quassin (*I*)

To a solution of 2·3 mg (0·006 mmol) of pure *VIIIa* in 300 µl of 2M aqueous sodium hydroxide solution, a large excess of dimethyl sulfate was added dropwise via a syringe until the mixture

became acidic (500 μl). The reaction mixture was stirred overnight. The second portion of base (200 μl) was added followed by dimethyl sulfate. After 5 h the acidic mixture was neutralized with saturated aqueous sodium bicarbonate solution and thoroughly extracted with chloroform. The organic phase was evaporated in vacuo at 45°C and the residue was chromatographed on silica gel. Elution with ethyl acetate–hexane (5 : 1) provided 1·7 mg (71%) of synthetic *d, l*-quassin, m.p. 187—188°C (ether–pentane). ^{1}H NMR spectrum: 5·29 (d, 1 H, $J = 2·57$); 4·26 (t, 1 H, $W_{1/2} = 6$); 3·65 (s, 3 H); 3·57 (s, 3 H); 2·97 (s, 1 H); 1·86 (s, 3 H); 1·54 (s, 3 H); 1·18 (s, 3 H); 1·10 (d, 3 H, $J = 6·91$). HRMS calculated for $C_{22}H_{28}O_6$ m/z 388·1878, found m/z 388·1900.

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REFERENCES

1. London E., Robertson A., (in part) Worthington H.: J. Chem. Soc. *1950*, 3431.
2. Valenta Z., Gray A. H., Orr D. E., Papadopoulos S., Podesva C.: Tetrahedron *18*, 1433 (1962).
3. Hanson K. R., Jaquiss D. B., Lamberton J. A., Robertson A., Savige W. E.: J. Chem. Soc. *1954*, 4238.
4. Stojanac N., Valenta Z.: Can. J. Chem. *59*, 853 (1991).
5. Stojanac N., Stojanac Z., White P. S., Valenta Z.: Can. J. Chem. *57*, 3346 (1979).