STRUCTURE AND STEREOCHEMISTRY OF THE ANTIBIOTIC ABIKOVIROMYCIN

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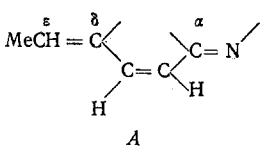
The antibiotic abikoviromycin was first found in the culture liquid from Streptomyces abikoensis by H. Umezawa et al. [1], and later, under the name of latumcidin, it was isolated and described by another group of workers [2, 3]. It possesses a pronounced activity against a number of supercapsidic viruses such as the causative agents of the encephalitis group and others [4] and, because of this, is of interest as one of the few natural antiviral substances. As a result of the investigations described below, we have established that abikoviromycin has the structure (I).*

Abikoviromycin is a monoacid base with the composition $C_{10}H_{11}NO$. It is extremely unstable and rapidly polymerizes on isolation even at −50°C, but is only slowly inactivated in dilute solutions and is comparatively stable in the form of salts, among which the most convenient for working with have proved to be the picrate and the hydrogen sulfate.

Both the salts of abikoviromycin and the free base are readily reduced by complex metal hydrides or hydrogen in the presence of catalysts. The reduction products formed, being considerably more stable compounds, have served as key substances in the determination of the structure of the antibiotic. Thus, under the action of $NaBH_4$, abikoviromycin gives a high yield of a dihydro derivative which is a secondary amine readily acetylated by acetic anhydride. This dihydro derivative does not contain carbonyl groups and has only one hydrogen atom readily replaceable by deuterium, while the antibiotic itself does not deuterate when its sulfate is dissolved in D_2O. Consequently, in abikoviromycin the only oxygen atom is an ethereal atom, and the nitrogen atom is present in an imino group $>C=N-$.

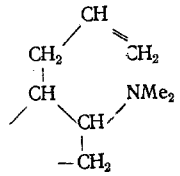
In the NMR spectrum of abikoviromycin there are signals of an ethylidene group (three-proton doublet at 2.10 and one-proton quartet at 6.18 ppm, J = 7 Hz) and a cis-disubstituted ethylene group (two one-proton doublets at 6.95 and 8.42 ppm, J = 6 Hz). According to the chemical shift of the olefinic protons and the UV spectra of the antibiotic in acidic and basic solutions, these groups are connected with one another and with the $>C=N-$ grouping to form a conjugated azomethine chromophore (A). The value of λ_{max} calculated for this chromophore of 291 nm and the expected value of the bathochromic shift of the long-wave absorption maximum in acid solution $\Delta\lambda_{N \rightarrow \overset{+}{N}H} \sim 60$ nm [7] agree well with the observed values (λ_{max}^{KOH} 289 nm, λ_{max}^{HCl} 341 nm).



A

Calculated:

C=C−C=N	215
additional C=C	30
exo-C=C	5
α-alkyl	5
δ- and ε-alkyl	2 × 18
λ_{max}	291 nm



B

*For preliminary communications, see [5, 6].

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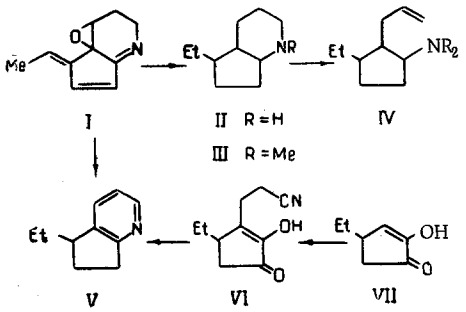
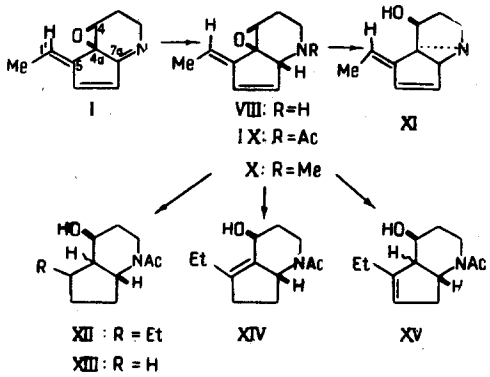
The empirical formula of abikoviromycin shows the presence in it of six double bonds and rings. On hydrogenation with PtO_2, abikoviromycin absorbs about 5 moles of H_2, forming a mixture of stereoisomeric perhydroabikoviromycins: saturated secondary amines, $C_{10}H_{19}N$. Since these amines contain no multiple bonds, their composition shows that they are bicyclic compounds. It follows from this that the antibiotic contains three double bonds (localized in the chromophore A) and three rings, of which one is an oxygen-containing heterocycle which undergoes hydrogenolysis in the presence of platinum.

Important information on the structure of the other two rings was obtained by exhaustive methylation and Hofmann degradation of the main stereoisomer of perhydroabikoviromycin. The NMR spectrum of the product of this reaction shows that in it the nitrogen atom is attached to a methine group connected with another methine group and a methylene group (sextet at 4.49 ppm with $J_1 = 5$, $J_2 = 10$, and $J_3 = 10$ Hz), and that the molecule contains a terminal double bond (signals of three olefinic protons at 5.0-5.4 and 6.07 ppm); at the same time the nature of the multiplet of the olefinic methine, having more than 12 lines, shows the presence of four vicinal protons, i.e., the presence of an unsubstituted allyl group. The only possible site of addition of this group is the second of the methine groups mentioned above, which leads to partial formula B. In combination with the structure of the chromophore of abikoviromycin A, this enables the product of the Hofmann degradation to be ascribed formula (IV), and the perhydroabikoviromycins themselves the structure of the ethyloctahydropyrindines (II).



On catalytic reduction in the presence of Pd black, abikoviromycin forms a tertiary base $C_{10}H_{13}N$. Its NMR spectrum shows the presence of an ethyl group and of a 2,3-disubstituted pyridine ring, and the UV spectrum practically coincides with that of the model substance 2,3-trimethylenepyridine [8, 9]; consequently the substance is the 5-ethylhydropyrindine (V). The structure of this compound was confirmed by independent synthesis from 4-ethylcyclopentane-1,2-diol (VII) [10] by condensing it with acrylonitrile and hydrogenation of the cyanoethyl derivative (VI) with subsequent dehydrogenation of the mixture of reduction products. In this way, the structure of the carbon skeleton of the antibiotic was definitively established.

The ethereal oxygen atom present in abikoviromycin must be attached on one side to an angular C atom, since the antibiotic contains only one proton on a carbon attached to oxygen. The signal of this proton in the NMR spectra of abikoviromycin and its dihydro derivative formed in the reduction of the antibiotic with $NaBH_4$ is poorly resolved (broadened singlet) and is therefore not indicative of its form. However, in the spectrum of the N-acetyl derivative of dihydroabikoviromycin this proton gives a clear quartet at 3.08 ppm ($J_1 = 5$ and $J_2 = 3$ Hz). It follows from this that the second point of attachment of the oxygen bridge is the C_4 atom. Thus, abikoviromycin possesses the structure (I) and its dihydro and its N-acetyldihydro derivatives structures (VIII) and (IX).

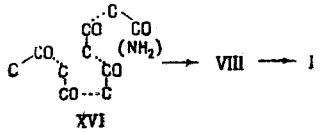


The configuration of the ethylidene group in the antibiotic was established on the basis of the difference of the NMR spectrum of dihydroabikoviromycin (VIII) from that of isodihydroabikoviromycin (XI). The latter compound is obtained by the reduction of the antibiotic (I) with lithium aluminum hydride, and also from dihydroabikoviromycin (VIII) by the action of $LiAlH_4$ or BuLi. It is formed as the result of the intramolecular opening of the epoxide ring by an anionoid N atom (after addition of a hydride ion in position 7a of abikoviromycin or the deprotonation of the NH group of dihydroabikoviromycin), which leads to the formation of a new, aziridine, ring with inversion of the 4a asymmetric center. These ideas on the mechanism of the formation of (XI) are confirmed by the stability of the N-methyl derivative (X) [obtained by the methylation of (VIII) by $CH_2O + NaBH_4$] under the conditions of the isomerization of (VIII) into (XI). It can be seen from a consideration of molecular models that in dihydroabikoviromycin (VIII) the substituent at C_1', which is present in the trans position with respect to C_6, is located above the plane of the epoxide ring and therefore undergoes diamagnetic shielding (see [11]), and the proton in position 4 is noncoplanar with the semicyclic hydrogen bond, and the anisotropic effect of this bond does not extend to it. In compound (XI), on the other hand, neither the methyl nor the H atom of the ethylidene group is shielded, since the epoxide ring has been opened; the proton at C_4 is located approximately in the plane of the ethylidene group and because of this it can be deshielded by the double bond. It was found that the isomerization of (VIII) into (XI) causes a considerable paramagnetic shift both of the 4-H proton (δ^{CCl_4} 2.94 → 4.92 ppm) and of the 1'-H proton (δ^{CCl_4} 4.99 → 5.79 ppm), affecting the position of the signal of the methyl group to a smaller extent ($\Delta\delta$ 0.13 ppm). This shows that in dihydroabikoviromycin (VIII) the exocyclic olefinic proton is located above the epoxide ring, i.e., according to the E–Z nomenclature [12], the ethylidene group has the E configuration.

Finally, the absolute configuration of the antibiotic was established by means of a study of the products of the further reduction of dihydroabikoviromycin (VIII). When this substance was hydrogenated in the presence of Ni_2B, the oxide ring and the diene system underwent reduction accompanied by migration of the double bond. After N-acetylation, the mixture of amino alcohols formed yielded a saturated acetylamino alcohol (XII) and also the Δ^{4a} and Δ^5 compounds (XIV) and (XV), the position of the double bond in which was shown by NMR. The mass spectrum of compound (XII) proved to be completely analogous to that of synthetic N-acetyloctahydropyrindin-4-ol (XIII), which confirmed the conclusion on the location of the oxygen function at the C_4 atom. Furthermore, in a polarimetric study of the unsaturated hydroxy compounds (XIV) and (XV) it was found that their conversion into the O-3,5-dinitrobenzoyl derivatives caused a negative change in the molecular rotation in the case of the α,β-unsaturated alcohol (XIV) ($[M]_D$ +288°; +182°) and a positive shift in the case of the β,γ- isomer (XV) ($[M]_D$ −208°; −145°), the optical rotatory dispersion curves of both dinitrobenzoates having a negative Cotton effect at 275 nm. According to Brewster's benzoate rule [13] and also according to Nakanishi's sector benzoate rule [14], this shows that both unsaturated alcohols (XIV) and (XV) have the S configuration of the C_4 asymmetric center.

Thus, abikoviromycin is (4S, 4aR, 5-1'E)-5-ethylidene-4,4a-epoxy-2,3,4,4a-tetrahydro-5H-1-pyrindine (I). It must be mentioned that the structure and relative configuration of (I) that we have established [5, 6] has recently been confirmed by an x-ray structural analysis of abikoviromycin selenate [17], although here the antibiotic was assigned the opposite absolute configuration.

So far as concerns the biogenesis of abikoviromycin, it may be assumed that the carbon skeleton of this compound is formed from five acetate units (XVI) the direct precursor of the antibiotic (I) being its dihydro derivative (VIII). In actual fact, we have found that some variants of the strain of Streptomyces abikoensis investigated produce dihydroabikoviromycin (VIII), as well as abikoviromycin, and that the former is readily dehydrogenated into the antibiotic (I), for example, by the action of picric acid.



XVI

EXPERIMENTAL

Wherever the solvent is not specified, the UV spectra were taken in 96% ethanol, the IR spectra in Nujol (i – inflection), the NMR spectra in $CDCl_3$ (s – singlet, d – doublet, t – triplet, q – quartet, sx – sextet, and m – multiplet), and the optical rotation in ethanol with c 0.05-0.1. The molecular weights were determined mass spectrometrically. The analytical results for all the compounds corresponded to the calculated figures.

1. Abikoviromycin (I). Streptomyces abikoensis was grown in a 100-liter stainless steel fermenter on a medium containing 1% of maize extract, 1.5% of starch, 1% of glucose, 0.4% of $(NH_4)_2SO_4$, 0.5% of NaCl, and 0.5% of chalk (pH 6.9-7.0) at 28°C with aeration at the rate of 1.1 liter/liter/min for 65-75 h. After separation from the mycelium, 60 liters of culture fluid was brought to pH 9 with a saturated solution of Na_2CO_3, cooled to 15°C, filtered, and extracted with ethyl acetate (3 × 20 liters). The extract was washed with conc. NaCl solution and the antibiotic was extracted with 0.1 N HCl saturated with NaCl (4 × 0.8 liter). The aqueous extract was washed with ether, brought to pH 9 with saturated Na_2CO_3 solution, and extracted with ether (4 × 0.8 liter). The ethereal extract was dried with Na_2SO_4 and mixed with 200 ml of a saturated benzene solution of picric acid; after 0.5 h, the precipitate of crude abikoviromycin picrate was filtered off, washed with ether, and dried in vacuum. Yield 20-30 g, decomposition temperature 135-138°C.

Abikoviromycin picrate (19.5 g) was dissolved in a mixture of 0.85 liter of acetone and 3.4 liters of ethyl acetate, the solution was filtered through 300 g of neutral Al_2O_3 (activity grade II), and the adsorbent was washed with 0.6 liter of ethyl acetate. The eluate contained 6-7 g of pure abikoviromycin (I) suitable for obtaining the salts described below.

Found: mol. wt. 161. $C_{10}H_{11}NO$. Calculated: mol. wt. 161.

Hydrogen sulfate (by the action of an ethereal solution of H_2SO_4): $C_{10}H_{13}NO_5S$, with decomposition temperature 140-141°C, $[\alpha]_D^{26}$ −232° (0.01 N HCl), +39° (0.01 N KOH); $\lambda_{max}^{0.01\,N\,HCl}$ 236, 341 nm (log ε 3.99; 4.05), $\lambda_{max}^{0.01\,N\,KOH}$ 218, 244, 289 nm (log ε 3.83; 3.99; 3.94); ν_{max} 1670, 1691 cm^{-1}; δ^{D_2O} 2.10 (3H, d, J 7), 2.3-2.9 (2H, m), 3.4-4.1 (2H, m), 4.54 (1H, broad, s), 6.18 (1H, q, J 7), 6.95 (1H, d, J 6), 8.42 (1H, d, J 6). Equiv. 259 (titration to phenolphthalein).

Picrate (by the action of a benzene solution of picric acid): $C_{16}H_{24}N_4O_8$, decomposition temperature 137-140°C; ν_{max} 1675 cm^{-1}.

Chloroplatinate (by the action of an ethanolic solution of chloroplatinic acid): decomposition temperature 180-186°C; ν_{max} 1670 cm^{-1}.

2. Perhydroabikoviromycin (II). To a suspension of Pt catalyst (from 259 mg of PtO_2) in 100 ml of water was added 2.59 g of the hydrogen sulfate of (I), and hydrogenation was carried out at 20°C until the absorption of hydrogen ceased. The solution was filtered, made alkaline with 50 g of K_2CO_3, and extracted with ether. The extract was dried with Na_2SO_4 and evaporated, and the residue was chromatographed in ether on a 1-mm layer of alkaline Al_2O_3 (400 g, activity grade IV). From the zones with R_f 0.71, 0.55, and 0.32 a mixture of methanol and ether (1 : 1) eluted the stereoisomeric perhydroabikoviromycins (IIA), (IIB), and (IIC). They were isolated in the form of the hydrochlorides (yields, respectively, 16%, 10%, and 39%) and were then converted in the usual way into the N-dinitrobenzoyl derivatives, which were purified by TLC on neutral Al_2O_3 (activity grade II) in the acetone−benzene−petroleum ether (1 : 1 : 1) system; all three isomers had R_f 0.80 in this system.

3,5-Dinitrobenzoate of (IIA): $C_{17}H_{21}N_3O_5$, mp 129-130°C (from ethanol), mol. wt. 347.

3,5-Dinitrobenzoate of (IIB): $C_{17}H_{21}N_3O_5$, mp 120-121°C (from ethanol), mol. wt. 347.

3,5-Dinitrobenzoate of (IIC): $C_{17}H_{21}N_3O_5$, mp 153-154°C (from ethanol), mol. wt. 347.

3. N-Methylperhydroabikoviromycin (III). To 1.33 g of the hydrochloride of (IIC) were added 10 ml of 35% formalin, 3.5 ml of 2 N KOH, and 20 ml of 85% formic acid. The mixture was boiled for 2 h and was then made alkaline with KOH and extracted with ether. The extract was dried with Na_2SO_4 and mixed with a saturated ethanolic solution of 1.6 g of picric acid. The yield of the picrate of (III) was 1.72 g (62%); $C_{17}H_{24}N_4O_7$, mp 167-168°C (decomp., from ethanol).

The base (III) was obtained from 0.8 g of the picrate by chromatography on alkaline Al_2O_3 (activity grade IV) in ethyl acetate and, without isolation, was converted into the methiodide $C_{12}H_{24}NI$ by the action of 5 g of CH_3I (1 h at 20°C). The yield of the methiodide of (III) was 0.55 g (88%); after reprecipitation from dichloroethane with ethyl acetate it had mp 186-187°C (decomp.).

4. 2-Allyl-1-dimethylamino-3-ethylcyclopentane (IV). A solution of 0.31 g of the methiodide of (III) in 5 ml of methanol was added to a suspension of Ag_2O (from 0.55 g of $AgNO_3$) in 5 ml of water. The mixture was shaken for 30 min in the dark, and was then filtered; the precipitate was washed with methanol and

the filtrate was evaporated in vacuum. The residue was distilled at 175-200°C/20 mm, the receiver being cooled to −70°C. The distillate was treated with 2 ml of 10 N NaOH and extracted with ether, and the extract was chromatographed on a 1-mm layer of alkaline Al_2O_3 (activity grade IV) in the ether−benzene (1:20) system. Compound (III) was eluted with ether from the zone with R_f 0.17 and was converted by the action of CH_3I into the initial methiodide of (III) with a yield of 31%. The methiodide of (IV) was obtained similarly from the fraction with R_f 0.76. Yield 52%; $C_{13}H_{27}NI$, mp 129-131°C; $\delta^{(CD_3)_2CO}$ 0.89 (3H, t, J 7), 1.2-1.7 (4H, m), 1.8-2.7 (6H, m), 3.52 (9H, s), 4.49 (1H, sx, J_1 5, J_2 10, J_3 10), 5.0-5.4 (2H, m), 6.07 (1H, m); m/e 181 (M − 142).

5. 5-Ethyl-6,7-dihydro-5H-1-pyrindine (V). The hydrogenation of 0.5 g of the hydrogen sulfate of (I) in 20 ml of water was performed at 20°C in the presence of 0.1 g of Pd black [15] until the absorption of H_2 ceased. The solution was made alkaline with K_2CO_3 and extracted with ether, and the extract was chromatographed in a 1-mm layer of Al_2O_3 (activity grade II) in the acetone−benzene−petroleum ether (1:1:1) system. Compound (V), $C_{10}H_{13}N$, was isolated from the zone with R_f 0.7-0.95, yield 13%, λ_{max} 268 i, 272, 279 i nm (log ε 3.64, 3.68, 3.56); $\lambda_{max}^{0.1\,N\,HCl\ in\ EtOH}$ 277 nm (log ε 3.86); δ^{CCl_4} 1.00 (3H, t, J 7); 1.03-2.00 (4H, m), 2.05-2.50 (1H, m), 2.8-3.1 (2H, m), 6.93 (1H, q, J_1 8, J_2 5), 7.37 (1H, d, J 8), 8.22 (1H, d, J 5), mol. wt. 147.

Picrate: $C_{16}H_{16}N_4O_7$, mp 108-109°C (from absolute ethanol).

6. Synthesis of (V). A. 3-(β-Cyanoethyl)-4-ethyl-2-hydroxycyclopent-2-enone (VI). The sodium derivative obtained from 3.2 g of (VII) [10] and 0.62 g of NaH in 50 ml of anhydrous tetrahydrofuran was treated with 3.4 ml of acrylonitrile. The mixture was boiled for 3 h and was then acidified with 2 ml of acetic acid and treated in the usual way by extraction with ethyl acetate. After TLC on silica gel (activity grade II) in the benzene−acetone (9:1) system, the zone with R_f 0.6-0.7 yielded 0.35 g (11%) of the initial (VII), and the zones with R_f 0.45-0.6 yielded 0.85 g (21%) of (VI), $C_{10}H_{13}NO_2$. mp 74-76°C (from benzene−heptane); λ_{max} 259 nm (log ε 4.02); ν_{max} 1650, 1700, 2250, 3320 cm^{-1}; δ 0.86 (3H, t, J 7), 1.0-2.0 (2H, m), 2.07 (1H, q, J_1 22, J_2 3), 2.59 (1H, q, J_1 22, J_2 6), 2.65 (2H, t, J 7), 2.69 (2H, t, J 7), 2.4-2.7 (1H, m), 6.44 (1H, broad, s), mol. wt. 179.

B. A solution of 1.1 g of (VI) in 15 ml of absolute ethanol was hydrogenated in the presence of 0.5 g of Raney Ni at 80°C and 80 atm. The solution was filtered, acidified with conc. HCl, and evaporated in vacuum. The residue was made alkaline with 1 N KOH and extracted with ether, and after the usual treatment the extract was evaporated. The substance obtained was mixed with 350 mg of 30% Pd/C and heated at 320-330°C for 4 h. After cooling, the reaction mixture was extracted with ether, the solvent was distilled off, and the residue was chromatographed on alumina (activity grade III) in the benzene−acetone (9:1) system. The zone with R_f 0.7-0.8 yielded 82 mg (11%) of (V), which has been described in experiment 5.

7. Dihydroabikoviromycin (VIII). At 20°C, 0.4 g of 85% $NaBH_4$ was added to 0.78 g of the hydrogen sulfate of (I) in 120 ml of water, and the mixture was stirred until the solid matter had dissolved. After 20 min, it was extracted with ether, the extract was dried with Na_2SO_4 and evaporated, and the residue was sublimed at 56°C/0.05 mm. This gave 0.36 g (85%) of (VIII), $C_{10}H_{13}NO$, mp 60-61°C; $[\alpha]_D^{26}$ +296°; λ_{max} 244 nm (log ε 4.11); ν_{max} 1502, 1675, 3200 cm^{-1}; δ^{CCl_4} 1.32 (1H, s), 1.73 (3H, d, J 7), 1.5-2.0 (3H, m), 2.6-2.9 (2H, m), 2.94 (1H, broad, s), 3.74 (1H, s), 4.99 (1H, q, J 7), 5.97 (1H, d, J 6), 6.55 (1H, d, J 6), mol. wt. 163.

N-Acetate of (IX), $C_{12}H_{15}NO_2$, mp 49-51°C (after sublimation at 47°C/0.02 mm); $[\alpha]_D^{26}$ +582°; λ_{max} 245 nm (log ε 4.18); ν_{max} 1630-1645 cm^{-1}; δ^{CCl_4} 1.75 (3H, d, J 7), 2.02 (3H, s), 1.7-3.5 (5H, m), 3.08 (1H, q, J_1 5, J_2 3), 4.93 (1H, s), 5.07 (1H, q, J 7), 6.25 (1H, d, J 6), 6.64 (1H, d, J 6), mol. wt. 205.

N-3,5-Dinitrobenzoate: $C_{16}H_{15}N_3O_5$, mp 165-167°C (from ethanol); $[\alpha]_D^{26}$ +244° ($CHCl_3$); λ_{max} 242 nm (log ε 4.63); ν_{max} 1543, 1573, 1625-1630 cm^{-1}; mol. wt. 357.

Dehydrogenation of (VIII) to (I): A solution of 165 mg of (VIII) in 20 ml of ether was mixed with 20 ml of saturated ethereal picric acid and the mixture was left at 20°C for 3 days. The precipitate of the picrate of (I) that had deposited was filtered off and washed with ether. Yield 82 mg (21%); mp 133-135°C (decomp.).

8. N-Methyldihydroabikoviromycin (X). At 5°C, 0.54 g of (VIII) in 10 ml of ethanol was treated with 0.7 ml of 40% formalin, and after 10 min, 150 mg of 85% $NaBH_4$ was gradually added. The mixture was stirred at 5°C for 30 min and was then left overnight, diluted with water, and extracted with ether. The extract was treated in the usual way and evaporated, and the residue was chromatographed on neutral alumina

(activity grade II), being eluted first with benzene and then with benzene–acetone (2:1). The benzene eluate yielded 0.24 g (41%) of (X), $C_{11}H_{15}NO$, mol. wt. 177, and the subsequent fractions gave 0.14 g (26%) of the initial (VIII). The N-methyl derivative (X) on Al_2O_3 (activity grade II) had R_f 0.83 in the benzene–acetone (1:1) system; λ_{max} 242 nm (log ε 4.07).

Methiodide: $C_{12}H_{18}NOI$, mp 236°C (decomp., from water); $[\alpha]_D^{26}$ +125° ($CHCl_3$); λ_{max} 194, 228 nm (log ε 4.24; 4.29); ν_{max} 1660 cm^{-1}; δ^{D_2O} 1.86 (3H, d, J 7), 2.88 (3H, s), 3.29 (3H, s), 1.3-3.8 (6H, m), 5.40 (1H, q, J 7), 6.38 (1H, d, J 6), 7.28 (1H, d, J 6).

9. Isodihydroabikoviromycin (XI). A solution of 210 mg of (VIII) in 5 ml of tetrahydrofuran was treated with 1.1 ml of a 0.76 M ethereal solution of $LiAlH_4$ and the mixture was stirred at 20°C for 1.5 h and was then boiled for 15 min; after cooling to 0°C the excess of $LiAlH_4$ was decomposed with 0.5 ml of water. The mixture was diluted with 50 ml of ethyl acetate, and the organic layer was separated off and dried with Na_2SO_4, and the solvent was distilled off in vacuum. The residue was triturated with a mixture of ethyl acetate and ether, and the precipitate of (XI) was filtered off and purified by TLC on neutral alumina (activity grade IV) in the benzene–acetone (1:1) system, the zone with R_f 0.4-0.5 being isolated. The yield of (XI) was 38 mg (18%), $C_{10}H_{13}NO$, mp 164-165°C (from ethanol); $[\alpha]_D^{26}$ −143° ($CHCl_3$); λ_{max} 245 nm (log ε 4.19); ν_{max} 1550, 3100-3200 cm^{-1}; δ 1.86 (3H, d, J 7), 1.5-2.2 (2H, m), 2.9-3.1 (3H, m), 3.18 (1H, s), 4.95 (1H, t, J 8), 5.83 (1H, q, J 7), 6.28 (1H, d, J 6), 6.48 (1H, d, J 6), mol. wt. 163.

10. 1-Acetyl-5-ethyl-4-hydroxyperhydropyrindine (XII) and Its 4a,5- and 5,6-Dehydro Derivatives (XIV) and (XV). In the presence of Ni_2B (from 1.75 g of $Ni(OAc)_2 \cdot 4H_2O$ [16]), 0.76 g of (VIII) in 15 ml of ethanol was hydrogenated until two moles of H_2 had been absorbed. The solution was filtered and evaporated and the residue was dissolved in 10 ml of Ac_2O; the solution was left at 20°C for 2 h and was then diluted with 150 ml of ether and 50 ml of ethyl acetate and worked up in the usual way. After TLC on neutral alumina (activity grade IV) in the benzene–acetone (1:1) system, the zone with R_f 0.6-0.7 yielded a mixture of (XII) and (XV), while the zone with R_f 0.4-0.5 furnished pure (XIV). The yield of (XIV) was 160 mg (16%); R_f 0.47 (in the same system); $C_{12}H_{19}NO_2$, mp 91-92°C (from benzene–heptane); $[\alpha]_D^{26}$ +138°; λ_{max} 201 nm; (log ε 4.25); ν_{max} 1627, 3300 cm^{-1}; δ 0.98 (3H, t, J 7), 2.03 (3H, s), 2.17 (2H, q, J 7), 1.7-2.5 (8H, m), 3.20 (1H, s), 4.65-5.00 (2H, m), mol. wt. 209.

The mixture of (XII) and (XV) was separated by rechromatography on Al_2O_3 (activity grade IV) with gradient elution (from benzene to ethyl acetate). The yield of (XII) was 20 mg (2%); R_f 0.66 in the benzene–acetone (1:1) system; $C_{12}H_{21}NO_2$, mp 126-127°C (from ethanol); $[\alpha]_{589}^{26}$ 0 ± 2°; $[\alpha]_{300}$ +132°; λ_{max} 205 nm, (log ε 4.23); ν_{max} 1627, 1632, 3280 cm^{-1}; mol. wt. 211.

The yield of (XV) was 160 mg (16%); R_f 0.64 (in the same system); $C_{12}H_{19}NO_2$, mp 124-125°C (from ethanol); $[\alpha]_D^{26}$ − 100°; λ_{max} 202 nm (log ε 4.33); ν_{max} 1590, 1660, 3300 cm^{-1}; δ 1.09 (3H, t, J 7), 2.10 (3H, s), 2.63 (1H, s), 1.5-3.0 (7H, m), 3.2-3.9 (2H, m), 3.4 (1H, m), 5.2-5.6 (2H, m), mol. wt. 209.

3,5-Dinitrobenzoate of (XIV): $[\alpha]_{589}^{26}$ +45°, $[\alpha]_{400}$ +280°, $[\alpha]_{368}$ +330°, $[\alpha]_{315}$ +30°, $[\alpha]_{280}$ +650°; λ_{max} 205, 227 i nm (log ε 4.58, 4.30); ν_{max} 1537, 1557, 1635, 1717 cm^{-1}; δ 1.06 (3H, t, J 7), 2.23 (3H, s), 2.37 (2H, q, J 7), 1.5-2.7 (8H, m), 5.1 (1H, m), 6.18 (1H, q, J_1 8, J_2 5).

3,5-Dinitrobenzoate of (XV): mp 208-209°C (from ethanol), $[\alpha]_{589}^{26}$ −37°, $[\alpha]_{400}$ − 170°, $[\alpha]_{380}$ − 145°, $[\alpha]_{310}$ − 750°, $[\alpha]_{280}$ 0°; λ_{max} 199, 227 i nm (log ε 4.79, 4.47); ν_{max} 1558, 1643-1665, 1727 cm^{-1}; δ 1.04 (3H, t, J 7), 2.17 (3H, s), 1.4-4.1 (9H, m), 5.25 (1H, m), 5.63 (1H, m), 5.87 (1H, m).

The selection of the strains of S. abikoensis was performed by V. D. Kuznetsov. The samples of N-acetyloctahydropyrindin-4-ols were provided by É. A. Mistryukov, The NMR spectra were taken by V. I. Sheichenko, the ORD were measured by G. A. Kogan, and the mass spectra by V. G. Zaikin.

SUMMARY

1. The reduction of the antibiotic abikoviromycin by complex metal hydrides and its hydrogenation in the presence of various catalysts have been studied.

2. It has been established that abikoviromycin is 5-ethylidene-4,4a-epoxy-2,3,4,4a-tetrahydro-5H-1-pyrindine and has the (4S, 4aR, 5-1'E) configuration.

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