Tetrahedron Vol 43, No. 3, pp. 631 to 641, 1987
Printed in Great Britain

0040-4020/87 $3.00 + .00
Pergamon Journals Ltd.

SYNTHESIS, CRYSTAL AND MOLECULAR STRUCTURE, AND HYPERCONJUGATION OF THE ISOMERIC 17,20-EPOXY-17-PICOLYL DERIVATIVES OF 5-ANDROSTENE AND 5α-ANDROSTANE

DUŠAN MILJKOVIĆ[1], KATARINA GAŠI[1], MARIJA KINDJER[1], SLOBODANKA STANKOVIĆ[2] AND GYULA ARGAY[3]

[1]Institute of Chemistry, Faculty of Sciences, V. Vlahovića 2, 21000 Novi Sad, Yugoslavia

[2]Institute of Physics, Faculty of Sciences, Ilije Djuričića 4, 21000 Novi Sad, Yugoslavia

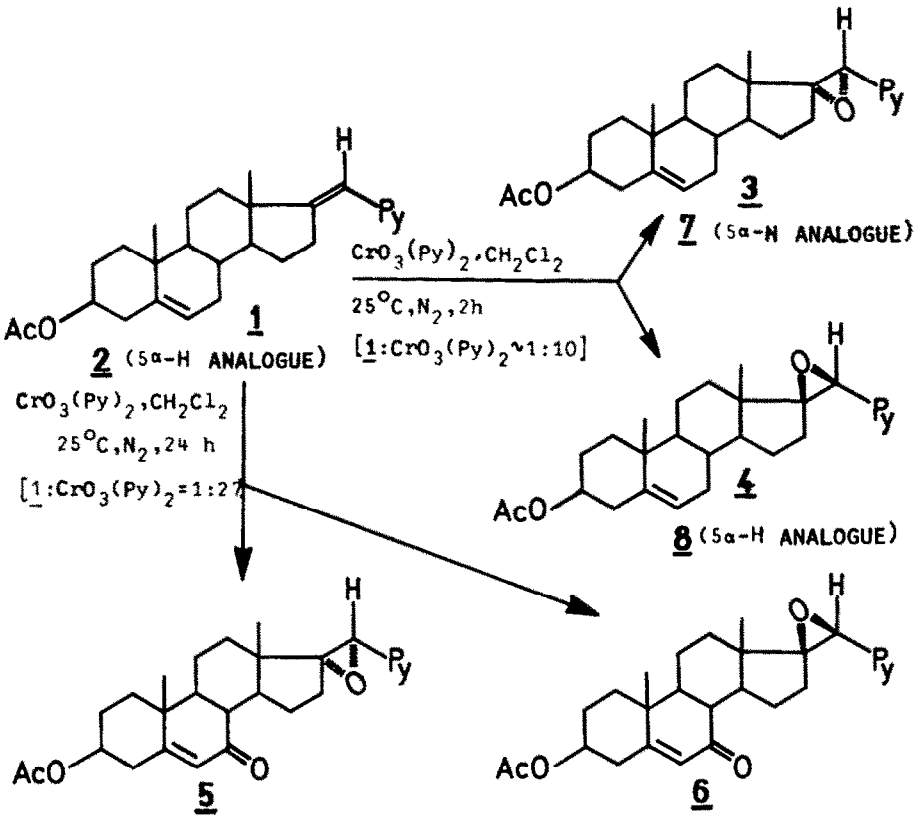
[3]Central Research Institute of Chemistry, Hungarian Academy of Sciences, Budapest 114, P.O. Box 17, H-1525 Hungary

(*Received in UK* 19 *December* 1986)

Abstract. Three pairs of isomeric 17,20-epoxy-17-picolyl-derivatives of 5-androstene and 5α-androstane (3 - 8) have been prepared by an oxidation of 3β-acetoxy-17-picolinylidene-androst-5-ene (2) and 3β-acetoxy-17-picolinylidene-5α-androstane (2) with in situ prepared Cr(VI) oxide-pyridine-complex in methylene chloride at room temperature. X-Ray structural analysis of the suitably crystalline epoxides 5 and 6 revealed the structure of 5 being 17α,20α-epoxide, while structure of 6 corresponded to 17β,20β-epoxide. It was proved that in both cases E-geometrical isomers were formed. Based on the deduced absolute stereochemistry of 5 and 6, the structures of other two pairs (3-4, 7-8) were readily worked out by NMR-spectroscopy. A mechanism of the oxidation reaction was proposed, and some other relevant chemical experiments were described. Finally, an explanation was offered for the observed differences of the relevant bond lengths and dihedral angles in 5 and 6 which indicated a slight σ - π conjugation between the epoxide and the pyridine rings, which might be coupled with long range effect of the C-7 carbonyl group.

PART I

In our previous works[1] three independant synthetic routes for obtaining 3β-acetoxy-17-picolinylidene-5-androsten-16-one, as well as its 5α-analogue, were described. These key-intermediates were successfully converted to the corresponding 21,27-bisnorsolanidine and 21,27-bisnordemissidine by catalytic hydrogenation[2]. The most difficult step in the mentioned multistep syntheses of either 21,27-bisnorsolanidine or 21,27-bisnoredemissidine was the introduction of 16-oxo-function next to 17-picolinylidine group in 5-androstene (1) series or in 5α-androstane (2) series. In this work we describe an unsuccessful attempt to functionalize the C-16 position into the corresponding oxo-function when 1 or 2 were treated with an excess of Cr(VI)-oxide-pyridine-complex in methylene chloride at room temperature. Our initial idea for attempting such a reaction was based on findings of Dauben, Lorber and Fullerton[3] that an allylic methylene group could be readily converted to an oxo-group by using Cr(VI)-oxide-pyridine reagent in methylene chloride. Indeed, in this work, we used a simplified procedure of preparing the Cr(VI)-oxide-pyridine reagent in situ according to the work Ratcliffe and Rodenhorst[4]. Obtained results of the oxidation of 1 and 2 with the mentioned reagent are summarized in the scheme 1.

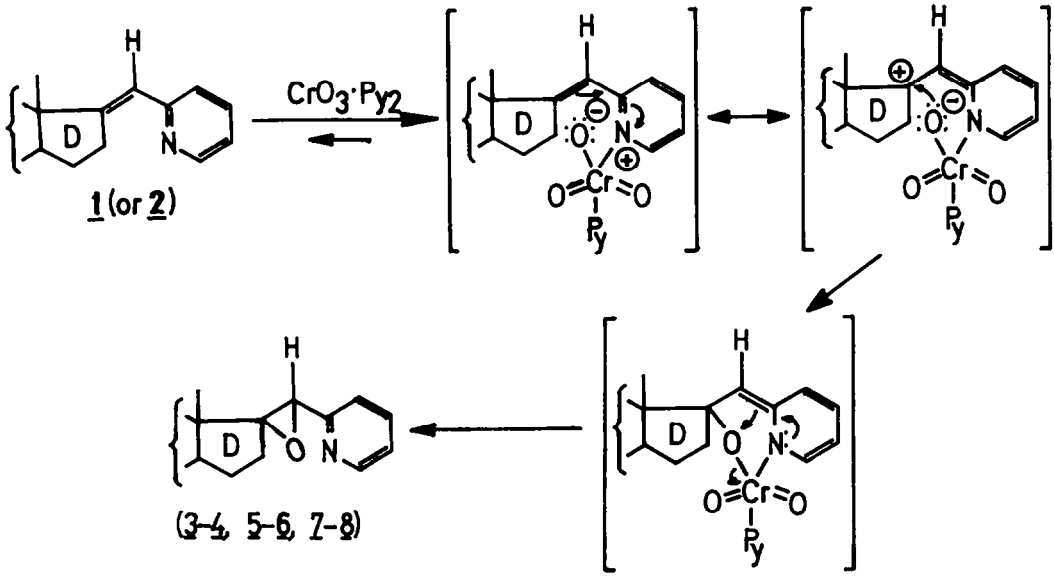


Scheme 1.

Starting with 1, and using a molar ratio of 1 to the reagent of 1:9, the main two reaction products were 3 and 4 (in an overall yield of 40%). If much greater molar excess of the reagent was used (1:27), the main two reaction products became 5 and 6. Obviously, in this case an allylic oxidation of the C-7 position occured at a later stage (after the epoxidation step). Starting with 2, a simpler reaction parthway was observed due to the lack of the 5,6-double bond. However, the overall yield of the obtained epoxides 7 and 8 remained essentially the same as in the case of the Δ-5 analogue (i.e., cca 40%). In all studied instances, under the conditions described, the ratio of α-and β-epoxide was essentionally the same, i.e. close to 1:1. The formation of the epoxides 3, 4, 5, 6, 7 and 8 could be partially explained by taking into account the works of some other authors who found that Cr(VI)--oxide derivatives could be of some value as epoxide forming reagents. Namely, chromic acid oxidations of olefins proceeds, generally speaking, in aqueous media with a cleavage of the double bond, while in anhydrous media (CrO_3 in anh. acetic acid or in acetic anhydride[5], t-butyl chromate in CCl_4-AcOH[6], or chromyl chloride in methylene chloride or CCl_4[7])oxidation of double bond may furnish corresponding diols, ketols or epoxides. Epoxide formation was specially noticed when the starting substrates were tetraphenyl ethylene derivatives (where, of course, an alternative allylic oxidation was impossible). For the above mentioned cases a mechanism was proposed which involves an intermediate formation of a carbonium ion (vicinal to the chromate ester grouping), a covalent capture of a H_2O molecule and a final epoxide closure[7]. As we could not find in the literature any case of Cr(VI)-oxidation of a double bond conjugated with a pyridine ring, we are now proposing a different mechanism for the observed epoxide formation reaction (scheme 2).

In addition, we attempted to prepare the mentioned epoxides (3, 4, 5, 6, 7 and 8) by using the other Cr(VI) reagents known to provide epoxides in other ca-

ses[5]. Thus, we tried to oxidize the compound 1 with chromic acid in AcOH, in a mixture of AcOH and its anhydride and in AcOH in presence of NaOAc. However, formation of epoxides was not even noticed in these cases; instead, 7-allylic oxidation, as well as the cleavage of the 17,20-double bond, was observed (see Experimental).



Scheme 2.

In order to provide some additional chemical evidence for the structure of the epoxides formed by CrO_3-Py_2 oxidation, their $LiAlH_4$-reduction was tried. Most probably, due to steric hindrance, epoxide rings remained unopened, so that the end-products were only 3β-alcohols (a trivial indirect hydrolysis of the corresponding 3β-acetates). However, the main evidence for the structure and absolute stereochemistry of the synthesized epoxides came from a detailed X-ray structural analysis of the nicely crystalline compounds 5 and 6 (see the second part of this work). From this analysis it became evident that the epoxide 5 was the α-isomer (oxygen of the epoxide ring was α-oriented according to commonly accepted α- and β-nomenclature in steroids), while the epoxide 6 was the β-isomer. At the same time, both 5 and 6 belong to the (E)-series. This fact needs an additional comment. Namely, it could be concluded that the starting olefins (1 and 2) were exlusively (E)-isomers. On the other hand, at least theoretically, the starting olefins might be mixtures of both possible geometrical isomers, whereupon the (Z)-isomers were unreactive due to some reasons we do not understand at the moment. However, according to our previous work[1] we strongly believe that the starting olefins were homogenious from the very begining belonging solely to the (E) series. Nevertheless, stereospecific formation of only (E)-olefins (1 and 2) must be considered separately and will be the subject of our future work.

The stereochemistry of other two pairs of isomeric epoxides (3-4, 7-8) was deduced indirectly by means of their NMR spectra. Namely, by comparing the chemical shifts for the H-C(20) in compounds 3 and 7 with the corresponding signal for the same atom in compound 5, it can be concluded that all three compounds have the same configuration at C-17 and C-20 atoms (all three relevant signals appear at 4,0 ppm). Similarly, the compounds 4, 6 and 8 are stereochemically identical at chiral centers C-17 and C-20 (H-C-20-signals appear, in these three compounds at 4,2 ppm). Interestingly enough, differences in NMR-signals of the C-18 angular methyl groups in all three epoxide pairs were not very striking so that no definite conclusions could

be drawn out about their corresponding stereochemistries on that basis.

One structural feature (observed in a detailed X-ray structural picture of 5 and 6) deserves a special comment. Namely, the most striking differences in bond lenghts of 5 and 6 (see Table 3.) appear at the following bonds: O(1)-C(17), O(1)-C(20), N(1)-C(20), N(1)-C(25), C(20)-C(21), C(22)-C(23), and C(24)-C(25). If we assume a hyperconjugation between the epoxide and the pyridine ring in 5 and 6, based on a simple resonance theory, one can postulate in both cases several resonating dipolar structures with N(1)-atom of the pyridine ring bearing a positive charge and O(1)-atom of the epoxide ring having a negative charge (this is just opposite to the simplest case,i.e. unsubstituted pyridine ring, where one usually assumes dipolar resonating structures with N-atom bearing a negative charge). If we take into a consideration such a simple model, the above observed bond distance pattern fits much better to a hyperconjugated model than to a non-conjugated one.

However, the β-epoxide (6) seems to be hyperconjugated to a greater extent than its α-isomer (5). This can be concluded from the fact that the relevant bonds in 6 (e.g., N(1)-C(25), C(22)-C(23), and C(20)-C(21)) are shorter than the corresponding ones in its isomer 5. This additional observation might be explained as follows: the N(1)-C(21)-C(20)-O(1)- dihedral angle (see Table 5.) in 6 is at +166.3°, while the same angle is at -174.8° for 5. Since the maximal hiperconjugation should take place between the adjacent epoxide and pyridine rings having a dihedral angle of approx. 120°, the observed dihedral angle of the β-isomer is closer to this optimal value.

Different optimal dihedral angles for 5 and 6 can be explained by taking into account non-bonding destabilizing interactions of the C(22)-H with $C(16)H_2$ - grouping.

There is an interesting example in the chemical literature[8] which is in accordance with an idea of α,β-unsaturated epoxide systems being hyperconjugated. Namely, Carruthers found that trans allylic alcohols were formed from α,β-unsaturated epoxides by 1,4-addition of lithium organocuprates.

Finally, still another effect could play an imporant role in the established hyperconjugation of 5 and 6, i.e., the observed differences in bond lenghts of C(8)-C(14), C(13)-C(14) and C(13)-C(17) which could be ascribed to a long range effect of the C-7 carbonyl group of the epoxide system of 5 and 6. However, this hypothesis needs additional chemical proves.

PART II

Figure 1 shows a perspective view of the structures together with the numbering scheme. The final relative coordinates given with their e.s.d's are listed in Tables 1 and 2. The bond lengths, valency angles and relevant torsion angles are listed in Tables 3, 4 and 5.

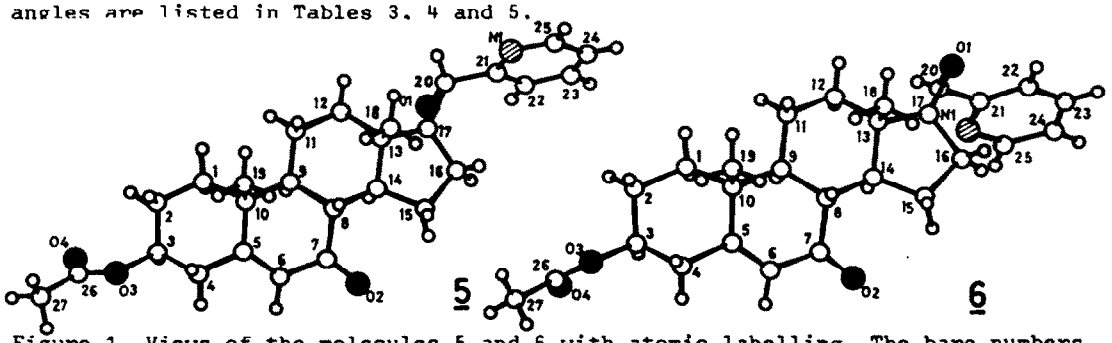


Figure 1. Views of the molecules 5 and 6 with atomic labelling. The bare numbers are carbon unless indicated otherwise. Hydrogen atoms are shown but not labelled.

Table 1. Final fractional coordinates ($x10^4$) and equivalent isotropic termal parameters for non-hydrogen atoms of compound 5. Estimated standard deviations are in parentheses. B_{eq} = 4/3* trace (B*G) where G is the direct metric tensor

	x/a	y/b	z/c	B_{eq} (A^2)
O(1)	0.7098(2)	0.5017(0)	0.2184(1)	4.4(1)
O(2)	0.6637(3)	-0.0565(3)	0.4692(1)	4.5(1)
O(3)	0.5343(2)	0.2666(3)	0.8909(1)	4.3(1)
O(4)	0.3379(3)	0.4044(5)	0.8943(2)	6.5(1)
N(1)	1.0404(3)	0.5469(5)	0.1236(2)	4.8(1)
C(1)	0.6113(3)	0.4939(5)	0.6796(2)	3.5(1)
C(2)	0.5920(3)	0.4723(5)	0.7782(2)	3.8(1)
C(3)	0.5359(3)	0.2971(5)	0.7956(2)	3.6(1)
C(4)	0.6257(3)	0.1574(5)	0.7624(2)	3.8(1)
C(5)	0.6581(3)	0.1835(4)	0.6669(2)	3.0(1)
C(6)	0.6467(3)	0.0553(4)	0.6105(2)	3.4(1)
C(7)	0.6862(3)	0.0628(4)	0.5190(2)	3.1(1)
C(8)	0.7580(3)	0.2234(4)	0.4925(2)	2.7(1)
C(9)	0.6982(3)	0.3789(4)	0.5391(2)	2.8(1)
C(10)	0.7067(3)	0.3594(4)	0.6418(2)	2.8(1)
C(11)	0.7605(4)	0.5484(5)	0.5097(2)	4.1(1)
C(12)	0.7587(4)	0.5693(4)	0.4088(2)	4.0(1)
C(13)	0.8256(3)	0.4167(4)	0.3682(2)	2.9(1)
C(14)	0.7505(3)	0.2515(4)	0.3920(2)	2.7(1)
C(15)	0.8052(3)	0.1177(4)	0.3300(2)	3.6(1)
C(16)	0.8259(4)	0.2151(5)	0.2439(2)	4.0(1)
C(17)	0.8149(3)	0.4054(5)	0.2676(2)	3.2(1)
C(18)	0.9782(3)	0.4084(6)	0.3961(2)	4.1(1)
C(19)	0.8522(3)	0.3831(6)	0.6836(2)	4.0(1)
C(20)	0.8503(3)	0.5462(5)	0.2111(2)	3.7(1)
C(21)	0.9086(3)	0.5163(5)	0.1234(2)	3.6(1)
C(22)	0.8321(4)	0.4605(7)	0.0501(2)	5.1(1)
C(23)	0.8972(5)	0.4322(7)	-0.0272(2)	6.0(2)
C(24)	1.0321(4)	0.4601(7)	-0.0277(2)	5.6(2)
C(25)	1.0981(4)	0.5182(8)	0.0477(3)	5.8(2)
C(26)	0.4279(4)	0.3275(5)	0.9313(2)	4.4(1)
C(27)	0.4397(5)	0.2864(7)	1.0286(2)	6.0(2)

Table 2. Final fractional coordinates ($x10^4$) and equivalent isotropic termal parameters for non-hydrogen atoms of compound 6

	x/a	y/b	z/c	B_{eq} (A^2)
O(1)	0.6958(3)	0.8209(0)	0.0037(4)	4.4(2)
O(2)	0.9636(3)	0.2795(7)	0.3648(5)	4.9(2)
O(3)	1.4038(3)	0.6531(11)	0.5739(5)	6.6(2)
O(4)	1.4045(3)	0.7070(10)	0.7779(5)	6.3(2)
N(1)	0.6058(4)	0.7270(11)	0.2899(5)	5.2(3)
C(1)	1.1790(5)	0.8597(11)	0.4132(7)	4.7(3)
C(2)	1.2820(5)	0.8442(13)	0.4676(8)	5.5(3)
C(3)	1.3046(5)	0.6726(16)	0.5402(7)	5.9(3)
C(4)	1.2675(5)	0.5123(13)	0.4626(7)	5.4(3)
C(5)	1.1673(5)	0.5281(11)	0.4000(6)	4.2(3)
C(6)	1.1102(5)	0.3971(11)	0.4072(7)	4.5(2)
C(7)	1.0143(4)	0.3935(10)	0.3419(6)	3.5(2)
C(8)	0.9851(4)	0.5427(9)	0.2459(6)	3.0(2)
C(9)	1.0321(4)	0.7198(10)	0.3012(6)	3.0(2)
C(10)	1.1383(4)	0.7010(10)	0.3283(6)	3.3(2)
C(11)	0.9967(4)	0.8839(9)	0.2218(8)	4.3(2)
C(12)	0.8926(5)	0.8944(9)	0.1869(7)	4.1(2)
C(13)	0.8535(4)	0.7241(9)	0.1185(6)	3.1(2)
C(14)	0.8826(4)	0.5651(9)	0.2081(6)	3.2(2)
C(15)	0.8228(5)	0.4095(10)	0.1418(7)	4.2(2)
C(16)	0.7332(5)	0.4993(10)	0.0769(7)	4.2(2)
C(17)	0.7516(4)	0.7018(11)	0.0920(6)	3.7(2)
C(18)	0.8832(4)	0.7058(11)	-0.0111(6)	4.2(2)
C(19)	1.1749(4)	0.7019(12)	0.2039(6)	4.1(2)
C(20)	0.6886(5)	0.8229(11)	0.1367(7)	4.1(2)
C(21)	0.6027(4)	0.7583(10)	0.1674(6)	3.9(2)
C(22)	0.5259(4)	0.7273(13)	0.0738(7)	4.9(3)
C(23)	0.4504(5)	0.6624(12)	0.1081(8)	5.6(3)
C(24)	0.4499(6)	0.6282(13)	0.2327(9)	5.9(3)
C(25)	0.5321(5)	0.6626(16)	0.3205(7)	6.2(4)
C(26)	1.4446(5)	0.6775(13)	0.6967(7)	5.1(3)
C(27)	1.5436(5)	0.6415(14)	0.7160(8)	6.1(3)

Table 3. Bond distances (Å) for compounds 5 and 6 with their e.s.d.'s in parentheses

	5	6
O(1)-C(17)	1.449(4)	1.432(8)
O(1)-C(20)	1.444(4)	1.447(8)
O(2)-C(7)	1.214(4)	1.203(8)
O(3)-C(3)	1.465(4)	1.466(7)
O(3)-C(26)	1.341(5)	1.337(9)
O(4)-C(26)	1.183(5)	1.177(8)
N(1)-C(21)	1.324(5)	1.320(9)
N(1)-C(25)	1.338(6)	1.312(9)
C(1)-C(2)	1.528(5)	1.538(8)
C(1)-C(10)	1.552(5)	1.540(10)
C(2)-C(3)	1.513(6)	1.502(14)
C(3)-C(4)	1.519(6)	1.498(14)
C(4)-C(5)	1.516(5)	1.516(9)
C(5)-C(6)	1.319(5)	1.317(10)
C(5)-C(10)	1.520(5)	1.521(11)
C(6)-C(7)	1.466(5)	1.463(8)
C(7)-C(8)	1.515(5)	1.517(9)
C(8)-C(9)	1.548(5)	1.559(9)
C(8)-C(14)	1.534(5)	1.517(7)
C(9)-C(10)	1.560(5)	1.566(6)
C(9)-C(11)	1.545(5)	1.524(10)
C(10)-C(19)	1.542(5)	1.542(8)
C(11)-C(12)	1.535(5)	1.532(7)
C(12)-C(13)	1.519(5)	1.524(10)
C(13)-C(14)	1.550(5)	1.532(9)
C(13)-C(17)	1.521(5)	1.506(7)
C(13)-C(18)	1.540(5)	1.548(9)
C(14)-C(15)	1.533(5)	1.548(9)
C(15)-C(16)	1.538(6)	1.533(9)
C(16)-C(17)	1.543(6)	1.544(11)
C(17)-C(20)	1.455(6)	1.462(9)
C(20)-C(21)	1.503(5)	1.480(8)
C(21)-C(22)	1.371(6)	1.377(9)
C(22)-C(23)	1.393(6)	1.354(9)
C(23)-C(24)	1.352(7)	1.357(12)
C(24)-C(25)	1.354(7)	1.406(11)
C(26)-C(27)	1.506(6)	1.483(8)

Table 4. Bond angles (°) for compounds 5 and 6 with their e.s.d.'s in parentheses

	5	6		5	6
C(17)-O(1)-C(20)	60.4(4)	61.0(7)	C(12)-C(13)-C(14)	109.7(5)	108.7(8)
C(3)-O(3)-C(26)	117.0(5)	117.2(11)	C(12)-C(13)-C(17)	116.7(5)	117.2(9)
C(21)-N(1)-C(25)	116.5(7)	117.2(12)	C(12)-C(13)-C(18)	111.6(5)	110.3(9)
C(2)-C(1)-C(10)	113.9(5)	114.0(10)	C(14)-C(13)-C(17)	100.6(4)	100.1(8)
C(1)-C(2)-C(3)	110.1(5)	111.0(11)	C(14)-C(13)-C(18)	112.1(5)	113.1(9)
O(3)-C(3)-C(2)	110.5(5)	108.6(11)	C(17)-C(13)-C(18)	105.7(5)	107.2(9)
O(3)-C(3)-C(4)	104.8(5)	107.1(11)	C(8)-C(14)-C(13)	111.1(5)	113.0(8)
C(2)-C(3)-C(4)	111.7(5)	112.5(12)	C(8)-C(14)-C(15)	121.0(5)	119.8(9)
C(3)-C(4)-C(5)	112.7(5)	113.5(12)	C(13)-C(14)-C(15)	103.6(5)	103.8(8)
C(4)-C(5)-C(6)	120.0(6)	121.0(11)	C(14)-C(15)-C(16)	104.6(5)	104.2(9)
C(4)-C(5)-C(10)	116.9(5)	116.1(10)	C(15)-C(16)-C(17)	105.5(5)	105.2(9)
C(6)-C(5)-C(10)	123.0(5)	122.9(11)	O(1)-C(17)-C(13)	118.8(5)	119.0(9)
C(5)-C(6)-C(7)	124.4(6)	125.1(11)	O(1)-C(17)-C(16)	116.4(5)	118.4(9)
O(2)-C(7)-C(6)	120.5(6)	121.2(10)	O(1)-C(17)-C(20)	59.6(4)	60.0(7)
O(2)-C(7)-C(8)	123.1(5)	123.8(10)	C(13)-C(17)-C(16)	106.8(5)	106.3(9)
C(6)-C(7)-C(8)	116.4(5)	115.0(10)	C(13)-C(17)-C(20)	122.8(5)	124.9(10)
C(7)-C(8)-C(9)	109.5(5)	109.1(8)	C(16)-C(17)-C(20)	125.1(5)	121.9(10)
C(7)-C(8)-C(14)	113.1(5)	113.1(9)	O(1)-C(20)-C(17)	60.0(4)	59.0(7)
C(9)-C(8)-C(14)	110.2(5)	111.1(8)	O(1)-C(20)-C(21)	117.4(5)	117.7(9)
C(8)-C(9)-C(10)	112.4(5)	110.8(8)	C(17)-C(20)-C(21)	121.6(6)	121.7(10)
C(8)-C(9)-C(11)	112.1(5)	113.5(9)	N(1)-C(21)-C(20)	114.0(6)	115.4(10)
C(10)-C(9)-C(11)	112.1(5)	113.4(9)	N(1)-C(21)-C(22)	123.2(7)	122.5(11)
C(1)-C(10)-C(5)	108.4(5)	108.9(9)	C(20)-C(21)-C(22)	122.8(6)	122.0(11)
C(1)-C(10)-C(9)	108.0(5)	107.5(9)	C(21)-C(22)-C(23)	118.1(7)	119.0(12)
C(1)-C(10)-C(19)	109.9(5)	109.5(9)	C(22)-C(23)-C(24)	119.5(8)	120.8(13)
C(5)-C(10)-C(9)	110.0(5)	110.0(9)	C(23)-C(24)-C(25)	117.9(8)	115.6(14)
C(5)-C(10)-C(19)	108.0(5)	108.7(9)	N(1)-C(25)-C(24)	124.9(8)	124.7(14)
C(9)-C(10)-C(19)	112.5(5)	112.1(9)	O(3)-C(26)-O(4)	123.7(7)	123.2(12)
C(9)-C(11)-C(12)	113.7(5)	113.3(9)	O(3)-C(26)-C(27)	111.1(6)	110.4(11)
C(11)-C(12)-C(13)	110.1(5)	110.1(9)	O(4)-C(26)-C(27)	125.2(7)	126.0(13)

Table 5. Relevant torsion angles (°) for compounds 5 and 6 with their e.s.d.'s in parentheses

	5	6
N(1)-C(21)-C(20)-O(1)	-174.8(7)	166.3(11)
C(1)-C(2)-C(3)-O(3)	172.4(6)	172.0(13)
C(4)-C(3)-C(2)-C(1)	56.1(5)	53.5(12)
C(4)-C(5)-C(10)-C(1)	-47.1(5)	-47.4(11)
C(5)-C(4)-C(3)-O(3)	-171.0(6)	-169.6(13)
C(5)-C(4)-C(3)-C(2)	-51.4(5)	-50.3(12)
C(5)-C(6)-C(7)-O(2)	-174.7(7)	-171.0(15)
C(5)-C(10)-C(1)-C(2)	51.8(5)	50.9(10)
C(6)-C(5)-C(10)-C(1)	134.7(7)	133.5(14)
C(8)-C(7)-C(6)-C(5)	6.8(5)	8.6(10)
C(8)-C(9)-C(10)-C(5)	-46.7(5)	-47.2(9)
C(9)-C(8)-C(7)-C(6)	-36.0(5)	-39.9(9)
C(9)-C(10)-C(5)-C(4)	-164.9(6)	-165.0(11)
C(9)-C(10)-C(5)-C(6)	16.8(5)	15.9(10)
C(10)-C(1)-C(2)-C(3)	-58.1(5)	-55.4(11)
C(10)-C(5)-C(6)-C(7)	3.6(5)	4.3(11)
C(10)-C(9)-C(8)-C(7)	56.6(5)	59.8(9)
C(11)-C(9)-C(8)-C(7)	-176.0(6)	-171.3(10)
C(12)-C(11)-C(9)-C(8)	50.3(5)	48.1(9)
C(12)-C(13)-C(14)-C(8)	-61.6(5)	-60.6(8)
C(13)-C(12)-C(11)-C(9)	-53.8(5)	-55.4(9)
C(13)-C(14)-C(8)-C(9)	57.2(5)	52.8(8)
C(14)-C(8)-C(9)-C(10)	-178.5(5)	-174.8(10)
C(14)-C(8)-C(9)-C(11)	-51.1(5)	-45.9(9)
C(14)-C(13)-C(12)-C(11)	58.3(5)	60.1(9)
C(14)-C(13)-C(17)-O(1)	98.7(4)	-176.6(8)
C(15)-C(14)-C(13)-C(12)	167.0(5)	168.1(10)
C(15)-C(16)-C(17)-O(1)	-121.0(5)	157.0(10)
C(15)-C(16)-C(17)-C(13)	14.4(5)	19.9(8)
C(16)-C(15)-C(14)-C(13)	-35.3(5)	-33.1(8)
C(16)-C(17)-C(13)-C(14)	-35.4(5)	-39.7(8)
C(16)-C(17)-C(20)-O(1)	102.6(6)	-106.7(11)
C(17)-C(13)-C(14)-C(8)	174.8(5)	176.0(9)
C(17)-C(13)-C(14)-C(15)	43.4(4)	44.7(8)
C(17)-C(16)-C(15)-C(14)	13.1(4)	8.3(8)
C(17)-C(20)-C(21)-N(1)	-104.9(7)	97.4(12)
C(18)-C(13)-C(14)-C(8)	62.9(5)	62.2(9)
C(18)-C(13)-C(14)-C(15)	-68.5(5)	-69.1(9)
C(18)-C(13)-C(17)-O(1)	-144.5(5)	-58.4(8)
C(19)-C(10)-C(5)-C(4)	71.9(5)	71.9(10)
C(19)-C(10)-C(5)-C(6)	-106.3(6)	-107.2(11)
C(20)-O(1)-C(17)-C(13)	113.2(5)	-115.8(8)
C(20)-O(1)-C(17)-C(16)	-116.9(5)	112.5(9)
C(20)-C(17)-C(13)-C(18)	-73.9(6)	-130.3(13)
C(21)-C(20)-O(1)-C(17)	112.5(6)	-112.2(12)
C(21)-C(20)-C(17)-O(1)	-105.5(6)	105.4(11)
C(21)-C(20)-C(17)-C(13)	147.8(7)	-148.4(13)
C(21)-C(20)-C(17)-C(16)	-2.9(6)	-1.3(10)
C(22)-C(21)-C(20)-O(1)	4.5(6)	-11.5(11)
C(22)-C(21)-C(20)-C(17)	74.4(7)	-80.4(12)

All bond distances and valency angles of steroid skeleton are in perfect agreement with the average values for 5-ene structures[9]. The significant difference apears in C(6) - C(7) bond length wich is 1.466(5) Å in compound 5 and 1.463(8) Å in 6 [the average value 1.508(10) Å]. The valency angles C(6) - C(7) - C(8) [116.4(5)° in 5 and 115.0(10)° in 6] and C(7) - C(8) - C(14) [113.1(5)° in 5 and 113.5(9)° in 6] also differ from the average values of 112.3(5)° and 110.4(5)°, respectively. The differences could be explained by an influence of doubly bonded O(2).

The conformation of steroid skeleton is similar in both compounds, as can be seen from Figure 2. According to the value of torsion angles [C(1) - C(2) - C(3) - O(3) = 172.4(6)° in 5 and 172.0(13)° in 6] acetoxy moiety assume β-*equatorial* position. C(18) and C(19)-methyl groups are, as usual, in β-axial position.

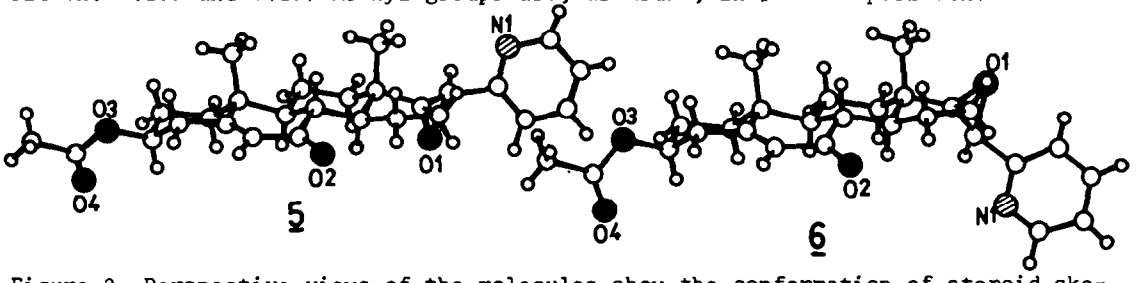


Figure 2. Perspective views of the molecules show the conformation of steroid skeleton and diferent postitions of picolyl moiety in compounds 5 and 6.

Ring-puckering coordinates[10] and asymetry parameters[9], listed in Table 6, define the conformation of rings A, B, C and D in compounds 5 and 6. Ring A is in a *chair* conformation in both compounds. Ring B exhibits a transition form between the 9α *envelop (sofa)* and 8β,9α *half-chair* conformation. Ring C, in general, adopt a *chair* conformation, but in compound 5 is distorted with considerable magnitude. This is due to the conformation of five-membered ring D. In compound 5 ring D is in an *envelope* conformation, while in 6 exhibits a transition form between *envelope* and *half-chair* conformation.

Table 6. Ring-puckering coordinates and asymmetry parameters

Ring	Comp.	Q(Å)	σ(Å)	(Å)	ΔC_s(Å)	ΔC_2(Å)
A:	5	0.532(4)	7.8(5)	51.9(3.5)	1.4(2)	4.3(1-2)
	6	0.515(11)	5.9(1.3)	41.7(12.7)	1.3(2)	2.8(1-2)
B:	5	0.469(4)	52.9(5)	222.1(6)	13.8(6)	10.3(5-6)
	6	0.498(8)	52.8(9)	218.5(1.2)	17.3(6)	7.3(5-6)
C:	5	0.576(4)	7.2(4)	262.4(3.5)	2.8(9)	5.0(8-9)
	6	0.558(7)	10.2(7)	231.3(4.2)	2.0(9)	5.0(8-9)
D:	5	0.427(4)	-	197.4(6)	15.8(13)	1.0(16)
	6	0.440(8)	-	190.9(1.0)	10.0(13)	9.4(16)

The considerable difference in conformation appears in position of picolyl moiety. Atom O(1) assums an α position in compound 5 [C(14) - C(13) - C(17) - O(1) = 98.7(4)°] and β position in 6 [C(14) - C(13) - C(17) - O(1) = -176.6(8)°]. The relative positions between O(1) and N(1) practically sustain [N(1) - C(21) - C(20) - O(1) = -174.8(7)° in 5 and 166.3(11)° in 6].

EXPERIMENTAL

PART I

IR spectra were recorded with Perkin-Elmer 457 spectrophotometer. NMR spectra were resorded with Varian FT-80 A instrument; chemical shifts are given in ppm values; symbols s, d, t and m denote singlet, doublet, triplet and multiplet respectively. Mass spectra were taken with VG-7035 spectrometer. Melting points were determined with a Büchi SMP-20 apparatus and are not corrected.

Oxidation of 1 and 2 with $CrO_3.Py_2$

a Preparation of chromium(VI)oxide-pyridine complex

Dry chromium(VI) oxide (4.5 g, 45 mmol) was added to a magnetically stirred solution of dry pyridine (7.2 ml, 90 mmol) in absolute methylene chloride (112 ml),at 5°C, in a nitrogen atmosphere. After the reaction mixture was stirred at 5°C for 15 min, the formed deep red solution of the reagent was allowed to warm up to room temperature.

b 3β-Acetoxy-17,20-epoxy-17-picolyl-5-androstene (3 and 4)

To the prepared solution of chromium(VI)oxide-pyridine complex (as described under a), a solution of compound 1 (2.02 g; 5 mmol) in CH_2Cl_2 (1 ml) was added, in a nitrogen atmosphere. Thus, the molar ratio of 1: $CrO_3.Py_2$ was 1:9. The reaction mixture was then let standing at room temperature for additional 2 hrs. The reaction mixture was first filtered and then CH_2Cl_2 was remuved in vacuum. The remained dark-colourd crude product was extracted with several portions of ether (200 ml). The combined ether extract was washed totally with 5% equeous $NaHCO_3$ solution (200 ml) and than with saturated aqueous NaCl solution (200 ml). The ether extract was dried over anhydrous Na_2SO_4, ether was then removed in vacuum, and the remained traces of pyridine were removed by co-distillation with toluene in vacuum. The obtained mixture of crude products (1.48 g) was chromatographed on a column of silica gel (150 g; benzene-ethylacetate, 15:1). Chromatography afforded compound 3 (0.336 g, 16%) m.p. 195-196°C (from EtOH), compound 4 (0.145 g, 6.9%) m.p. 194-195°C (from EtOH) and mixture of compounds 3 and 4 (0.355 g, 16.9%).

IR of 3: 3090, 1730, 1595, 1575, 1245, 1050 cm^{-1}; NMR ($CDCl_3$): 0.95 (s; 3H), 1.05 (s; 3H); 2.0 (s; 3H); 4.0 (s; 1H); 5.35 (d; 1H); 7.0-8.5 (m; 4H); MS: 421 (M^+; 52), 406 (27.7), 361 (82.8), 34.6 (16.7). Calculated for $C_{27}H_{35}O_3N$: C, 76.96; H, 8.31; N, 3.32. Found: C, 76.61; H, 8.48; N, 3.43.

IR of 4: 3090, 1730, 1595, 1575, 1245, 1050. NMR ($CDCl_3$): 1.0 (s; 3H); 1.05 (s; 3H); 2.0 (s; 3H); 4.2 (s; 1H); 5.35 (d; 1H); 7.0-8.5 (m; 4H). MS: 421 (M^+; 43.3). 406 (25.8), 361 (69.3), 346 (16.4). Calculated for $C_{27}H_{35}O_3N$: C: 76.96; H, 8.31;N,3.32.Found: C, 76.77; H, 8.17; N. 3.20.

c 3β-Acetoxy-17,20-epoxy-17-picolyl-5-androsten-7-ones (5 and 6)

Oxidation of compound 1 (1.01 g, 2.5 mmol) was carried out for 24 hrs in a solution of $CrO_3.Py_2$ (with a molar ratio of 1: $CrO_3.Py_2$ 1:27), at room temperature, in a nitrogen atmosphere. Reaction mixture was worked up as described under b. Crude products (0.566 g) were separated on a column of silica gel (60 g; benzene-ethylacetate, 9:1) affording compound 5 (0.156 g, 14,4%), m.p. 210-211°C (from EtOH) and compound 6 (0.172 g, 16.0%), m.p. 194°C (from EtOH).

IR of 5: 3060, 1730, 1665, 1630, 1590, 1245, 1030 cm^{-1}. NMR ($CDCl_3$): 0.95 (s; 3H); 1.25 (s; 3H); 2.05 (s; 3H); 4.0 (s; 1H); 4.4-4.9 (1H); 5.75 (s; 1H), 7.0-8.5 (m; 4H). MS: 435 (M^+, 27.8), 420 (24.3), 375 (13.0), 360 (6.6). Calculated for $C_{27}H_{33}O_4N$: C, 74.48; H, 7.58; N, 3.22. Found: C, 75.82; H, 7.60; N, 3.14.

IR of 6: 3060, 1750, 1680, 1640, 1600, 1250, 1040 cm^{-1}. NMR ($CDCl_3$): 1.0 (s; 3H); 1.25 (s; 3H); 2.0 (s; 3H); 4.2 (s; 1H); 4.45-4.95 (1H); 5.7 (s; 1H); 7.05-8.55 (m; 4H). MS: 435 (M^+, 95.1); 420 (17.9), 375 (7.9), 360 (3.6). Calculated for $C_{27}H_{33}O_4N \times 1/2\ H_2O$: C, 72.97; H, 7.66; N, 3.15. Found: C,72.82; H,7.54; N,3.54.

d 3β-Acetoxy-17,20-epoxy-picolyl-5α-androstanes (7 and 8)

Compound 2 (0.504 g, 1.26 mmol) was added to a solution of $CrO_3.Py_2$ complex in CH_2Cl_2 (molar ratio of 2 to $CrO_3.Py_2$ was 1:12) and reaction mixture was then let standing at room temperature for 2 hrs, in a nitrogen atmosphere. After usual work up, crude mixture of products (0.430 g) was separated on a column of silica gel (45 g; benzene-ethylacetate, 9:1) affording the 17α,20α-epoxide 7 (0.189 g, 17,2%), m.p. 191-192°C (from EtOH), the 17β,20β-epoxide 8 (0.100 g, 9.1%), m.p. 191°C (from EtOH), and a mixture of epoxide 7 and 8 (0.110, 9.9%).

IR of 7: 1730, 1590, 1245, 1020 cm^{-1}. NMR ($CDCl_3$): 0.8 (s; 3H); 0.9 (s; 3H); 2.0 (s; 3H); 4.0 (s; 1H); 4.5-5.0 (1H); 7,0-8.5 (m; 4H). MS: 423 (M^+; 70.2); 408 (32.7). Calculated for $C_{27}H_{37}O_3N$: C, 76.59; H, 8.75;N,3,31.Found:C,76.43;H,8.33; N, 3.52. IR of 8: 1740, 1600, 1250, 1030 cm^{-1}. NMR ($CDCl_3$): 0.8 (s; 3H); 0.9 (s; 3H); 2.0 (s; 3H); 4.2 (s; 1H); 4.5-5.0 (1H); 7.0-8.5 (m; 4H). MS 423 (M^+, 61.0); 408 (28.5). Calculated for $C_{27}H_{37}O_3N \times 1/4\ H_2O$: C, 75.79; H, 8.65; N, 3.27. Found: C, 75.69; H, 8.66; N, 3.42.

3β-Hydroxy-17α,20α-epoxy-17β-picolyl-5-androstene and

3β-hydroxy-17β,20β-epoxy-17α-picolyl-5-androstene

A solution of compound 3 (0.324 g, 0.76 mmol) in dry ether (50 ml) was added to a suspension of $LiAlH_4$ (0.14 g, 3.7 mmol) in dry ether (1.5 ml). Reaction mixture was magnetically stired at room temperature in a nitrogen atmosphere, for 1 hr. Methanol was then carefully added (to destroy an excess of $Li\ AlH_4$) followed by water (150 ml). The ether layer was separated while water layer was additionally

extracted with fresh ether (three times with 30 ml of ether). The combined ether extract was washed with water and dried over anhidrous Na_2SO_4. After removal of drying agent and solvent (in vacuum), the obtained crude product 9 (0.294 g) was purified on a column of silica gel (25 g; benzene-ethylacetate, 10:1) affording 3β-hydroxy-17α,20α-epoxy-17β-picolyl-5-androstene (9, 0.253 g, 86.3%) as a colourless oil. In an analogous was 3β-hydroxy-17β,20β-epoxy-17α-picolyl-5-androstene (10, 0.263 g, 89.5%), m.p. 102-103°C was prepared from the 17β,20β-epoxide 3 (0.324 g).

IR of 9: 3360, 1590, 1050 cm^{-1}. NMR ($CDCl_3$): 0.95 (s; 3H); 1.05 (s; 3H); 3.3-3.8 (1H); 4.0 (s; 1H); 5.35 (d; 1H); 7.0-8.5 (m, 4H). MS: 379 (M^+, 38.6).

IR of 10: 3430, 1605, 1060 cm^{-1}. NMR ($CDCl_3$): 1.0 (s; 3H); 1.05 (s; 3H); 3.3-3.8 (1H); 4.2 (s; 1H); 5.3 (d; 1H); 7.0-8.55 (m; 4H). MS: 379 (M^+, 69.8); 364 (60.1). Colculated for $C_{25}H_{33}O_2N \times 1/2\ H_2O$: C, 77.31; H, 8.50; N, 3.61. Found: C, 77.50; H, 8.73; N, 3,89.

Oxidation of 1 with chromium(VI)oxide in acetic acid

a 3β-Acetoxy-17-picolinylidene-5-androstene (3.03 g, 7.5 mmol) was dissolved in acetic acid (60 ml) and to thus obtained solution CrO_3 (4.5 g, 45 mmol) dissolved in aq. acetic acid(54 ml of AcOH and 6 ml of water) was added. Reaction mixture was heated at 90-95°C for 1 hr, then poured in water (1 l), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (totally with 500 ml). After drying the extract with anhydrous Na_2SO_4 and removal of $CHCl_3$ in vacuum, the residue (2.50 g) was chromatographed on silica gel column (180 g, benzene-ethylacetate, 9:1) affording: 3β-acetoxy-17-picolinylidene-5-androstene-7-one (11, 0.280 g, 8.9%), m.p. 165-167°C (from MeOH) and 3β-acetoxy-5-androstene-7,17-dione (12, 0.252 g, 9.8%) m.p. 200-201°C (from n-hexane-acetone).

b To a solution of 3β-acetoxy-17-picolinylidene-5-androstene (3.03 g 7.5 mmol) in AcOH (54 ml) CrO_3 (4.5 g, 45 mmol) dissolved in acetic acid (73 ml) and acetic acid anhydride (20 ml) at 90°C was added. Reaction mixture was heated at 90-95°C for 1 hr and then worked up as in the previous case. Crude mixture of products (2.336 g) was separated on silica gel column (180 g; benzene-ethylacetate, 15:1) affording compound 12 (0.273 g, 10.6%), m.p. 201-203°C (from n-hexane-acetone).

c To a solution of 3β-acetoxy-17-picolinylidene-5-androstene (3.03 g, 7.5 mmol) and sodium acetate (10.2 g) in AcOH (60 ml) CrO_3 (9 g, 90 mmol) dissolved in aq. acetic acid (75 ml of AcOH and 12 ml of H_2O) was added. Reaction mixture was heated at 90-95°C for 4 hrs, and worked up as described previously. After separation of reaction products (2.586 g) on a silica gel column (180 g, benzene-ethylacetate, 15:1), compound 11 (0.266 g, 8.5%), m.p. 166-167°C (from MeOH), and compound 12 (0.157 g, 6.1%), m.p. 200-202°C (from n-hexane-acetone) were obtained.

IR of 11: 3090, 1735, 1670, 1635, 1590, 1250, 1040 cm^{-1}.

IR of 12: 1740, 1730, 1675, 1630, 1240, 1030 cm^{-1}.

PART II

Crystal structure determination of the compounds 5 and 6

Crystals of both compounds belong to the monoclinic system, space group $P2_1$, Z = 2. The lattice parameters: (5) a = 9.885(3), b = 7.852(4), c = 15.146(5)Å, β = 93.99(2)°, V = 1172.73 Å^3, D_c = 1.23 Mgm^{-3}, D_m = 1.21 Mgm^{-3} (by flotation), $\mu(M_oK\alpha)$ = 0.76 cm^{-1}; (6) a = 15.029(5), b = 7.489(4), c = 10.681(3) Å, β = 102.26(3) V = 1174.75 Å^3, D_c = 1.23 Mgm^{-3}, D_m = 1.24 Mgm^{-3} (by flotation), $\mu(M_oK\alpha)$ = 0.76 cm^{-1}

Crystallographic data were measured on a fully automated Philips PW1100 single crystal diffractometer using graphit-monochromated $M_oK\alpha$ radiation at room temperature. Intensities for 2871 independent reflections for compound 5 and 2062 for 6 were measured by θ/2θ scan technique. 2524 of them for 5 and 1841 for 6 with $I > 3\sigma(I)$ were considered as observed. Only Lorentz and polarization corrections were applied.

The structures were solved using the MULTAN program[11]. All the heavy atoms were found in E-map. Full-matrix and block-diagonal least squares refinements of atomic positions and anisotropic vibrational parameters gave a final R of 0.045 for compound 5 and 0.061 for 6. The hydrogen positions were generated from assumed geometries. The scattering factors were taken from the *International Tables for X-ray Crystallography*[12]. All calculations were performed on a PDP 11/34 minicomputer with the Enraf-Nonius SDP-34 system in Budapest.

Acknowledgment: The authors are grateful to Löki Attila and Jakob Beáta, "Kossuth Lajos" University, Hungary, for recording mass and NMR spectra. The authors are also grateful to prof. A. Kálmán, Central Research Institute of Chemistry, Hungarian Academy of Sciences Budapest, for useful discusions.

REFERENCES

1. a) D. Miljković, K. Gaši, Bull. Chem. Soc., Beograd 46, 263 (1981); b). D. Miljković, K. Gaši, ibid. 47, 19 (1982); c) D. Miljković, K. Gaši, ibid. 47, 173 (1982); d) K. Gaši, K. Bajin, J. Jovanović-Vlaović, D. Miljković, Review of Research, Faculty of Science, University of Novi Sad, 13, 19 (1983).
2. a) D. Miljković, K. Gaši, Chemica Chronika, New Series, 9, 325-335 (1980); b) D. Miljković, K. Gaši, M. Kindjer, S. Stanković, B. Ribár, G. Argay, Croatica Chemica Acta, 58(4)721 (1985).
3. W.G. Dauben, M. Lorber, D.S. Fullerton, J. Org. Chem., 34, 3587 (1969).
4. R. Ratcliffe, R. Rodenhorst, J. Org. Chem., 35, 4000 (1970).
5. M. Schildknecht, W. Föttinger, Justus Liebigs Ann. Chem., 659, 20 (1962).
6. T. Matsura, T. Suga, J. Org. Chem., 30, 518 (1965).
7. H.O. House, "Modern synthetic reactions", W.A. Benjamin, INC. Menlo Park, California, p. 281 (1972)., and references cited therein.
8. W. Carruthers, Chem. Ind. (London), 931 (1973).
9. W.L. Duax, C.M. Weeks and D.C. Rohrer, in Topics in Stereochemistry, Vol. 9, pp 271-383. J. Wiley and Sons, New York (1976).
10. D. Cremer and J.A. Pople, JACS, 97, 1354 (1975).
11. G. Germain, P. Main and M.M. Woolfson, Acta Cryst., A27, 368 (1971).
12. International Tables for X-ray Crystallography, Vol. III. Kynoch Press, Birmingham (1962).