Quantitative analysis of the monosaccharides of cycloaraloside E with the aid of GLC [4] in the presence of D-xylose as standard showed that the compound contained two D-glucose residues.

Cyclosieversigenin (II) and Cycloaraloside A (III) from (I). Glycoside (I) (70 mg) was hydrolyzed with 20 ml of 0.25% methanolic sulfuric acid at 50°C for 2 h. The reaction mixture was diluted with water, and the methanol was evaporated off. The precipitate that had deposited was filtered off and was chromatographed on a column with elution by system 3. This led to the isolation of 10 mg of cyclosieversigenin (II), mp 239-241°C (from methanol), $[\alpha]_D^{27}$ +51 ± 2° (c 1.0; methanol).

Continued elution of the column with system 1 gave 33 mg of a progenin (III), mp 240-242°C (from system 1), $[\alpha]_D^{27}$ +33 ± 2° (c 1.0; methanol). The PMR spectrum of glycoside (III) also coincided with that of cycloaraloside A.

LITERATURE CITED

1. M. I. Isaev, M. B. Gorovits, and N. K. Abubakirov, Khim. Prir. Soedin., 806 (1989).
2. M. I. Isaev, M. B. Gorovits, and N. K. Abubakirov, Khim. Prir. Soedin., 431 (1985).
3. M. I. Isaev, M. B. Gorovits, and N. K. Abubakirov, Khim. Prir. Soedin., 156 (1989).
4. M. A Agzamova, M. I. Isaev, M. B. Gorovits, and N. K. Abubakirov, Khim. Prir. Soedin. 719 (1986).
5. H. K. Wang, K. He, L. Ji, Y. Tezuka, T. Kikuchi, and I. Kitagawa, Chem. Pharm. Bull. 37, 2041 (1989).

SYNTHESIS, METHYLATION, AND ACYLATION OF 1,2-DIHYDRODEOXY-VASICINONES AND THEIR HOMOLOGS

Kh. M. Shakhidoyatov and G. A. Belova

UDC 547.944/945+547.856.1

2,3-Trimethylene- and 2,3-pentamethylene-1,2,3,4-tetrahydro-4-quinazolones and their 6-methyl and 6-bromo derivatives have been obtained by the reduction of deoxyvasicinone and its 6-methyl and 6-bromo derivatives and also their seven-membered homologs at the cycloalkane ring with sodium tetrahydroborate in ethanol. The alkylation and acylation reactions of the above-mentioned reducing compounds have been studied.

The results of a study of the products of the reduction of deoxyvasicinone at the C=O bond (3,4-dihydroquinazolines) are widely represented in the literature. Hitherto, inadequate attention has been devoted to derivatives of 1,2-dihydrodeoxyvasicinone, although there is information on their synthesis by sodium tetrahydroborate reduction [1].

In order to find biologically active compounds in this series, we have performed the regiospecific reduction of deoxyvasicinone and its substituted and seven-membered homologs at the cycloalkane ring. The reaction took place smoothly under the conditions described for certain substituted 4-quinazolones in [2]. As the starting materials we used deoxyvasicinone and its 6-methyl and 6-bromo derivatives (Ia-c).

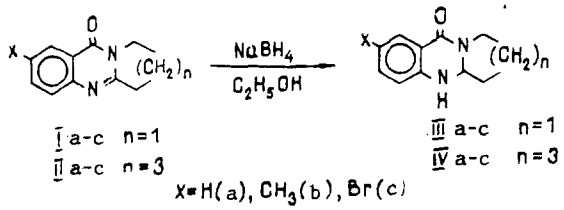
The application of this reaction to the seven-membered homologs of deoxyvasicinone (IIa-c) likewise gave the products of the reduction of the C=N bond (scheme 1).

The 1,2-dihydrodeoxyvasicinones (IIIa-c) and their homologs (IVa-c) that were synthesized are well crystallizing substances soluble in many polar organic solvents (chloroform, DMFA, DMSO, and acetone) and sparingly soluble in water and neutral solvents (hexane, petroleum ether, diethyl ether).

Institute of Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent.

Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 659-663, September-October, 1990. Original article submitted December 25, 1989; revision submitted February 5, 1990.

0009-3130/90/2605-0561$12.50



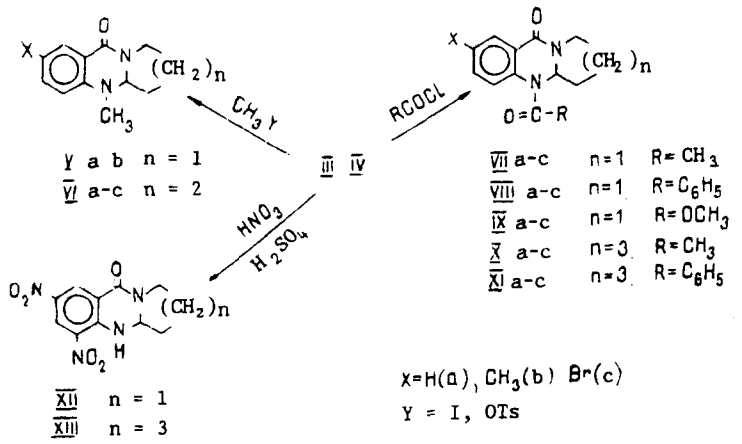
Scheme 1

We have studied the methylation of the 1,2-dihydrodeoxyvasicinones and their homologs. The reaction was performed with the use of methyl iodide or methyl tosylate in the presence of a salt-forming agent – sodium hydride (or K_2CO_3) in solution in DMFA (or acetone).

The 1-methyl products (Va, b; VIa-c) were formed in 45-50% yields. It must be mentioned that in all cases, together with methylation, dehydrogenation took place.

1-Methyl-1,2-dihydrodeoxyvasicinones were also formed in the reduction of deoxyvasicinone methiodides with sodium tetrahydroborate. The reduction of the methiodides of their seven-membered homologs took place anomalously, since the methyl group at the N-1 atom was split out with the formation of 2,3-pentamethylene-1,2,3,4-tetrahydro-4-quinazolones.

The acylation of compounds (IIIa-c) and (IVa-c) took place on heating under the action of acid chlorides (benzoyl chloride, methyl chloroformate) in the presence of triethylamine (or NaH) in benzene (or DMFA) solution. The benzoylation of compounds (IVa-c) took place smoothly in chloroform solution under the action of an excess of acid chloride. Acetic anhydride was used to obtain the 1-acetyl derivatives The 1-acyl-1,2-dihydrodeoxyvasicinones obtained (VII-XI) were substances crystallizing well from hexane and petroleum ether.



Scheme 2

We have investigated some electrophilic substitution reactions of compounds (IIIa) and (IVa). Thus, the nitration of 1,2-dihydrodeoxyvasicinone (IIIa) and its seven-membered homolog (IVa) gave the products of nitration in positions 6 and 8 of the quinazoline ring (scheme 2). As has been shown previously, on the nitration of deoxyvasicinone (Ia) and homolog (IIa), the substitution of one hydrogen atom at C-6 takes place and it is impossible to introduce a second nitro group.

Such a marked difference between deoxyvasicinone and its 1,2-dihydro derivative is due to the possibility of the formation of a quaternary salt in the case of the former, which leads to a sharp decrease in the nucleophilicity of the benzene ring, particularly after the introduction of one nitro group into position 6. In the case of 1,2-dihydrodeoxyvasicinone, however, such salt formation is difficult in view of the absence of a cyclic amidine system. Furthermore, because of the absence of conjugation, the N-1 nitrogen atom donates its free electron pair to the benzene ring, increasing its nucleophilicity and thereby favoring electrophilic substitution in position 8.

The structures of the compounds obtained were shown on the basis of the results of IR, mass, and PMR spectra, and their individuality by thin-layer chromatography (Silufol).

TABLE 1. Characteristics of the Compounds Synthesized

Initial compound	Reaction product	Yield, %	mp, °C	R_f^*	mol. mass (mass spectrum)
Ia	III a	85	181—183	0,23	188
Ib	III b	60	235—237	0,19	202
Ic	III c	56	218—220	0,25	267
IIa	IV a	80	176—178	0,56	216
IIb	IV b	70	171—173	0,48	230
IIc	IV c	74	166—168	0,51	295
IIIa	V a	48	136—138	0,38	202
IIIb	V b	45	139—141	0,35	216
IVa	VI a	47	95—96	0,67	230
IVb	VI b	52	122—124	0,54	244
IVc	VI c	45	131—133	0,57	309
IIIa	VII a	60	120—122	0,29	230
IIIa	VIII a	55	128—130	0,55	292
IIIa	IX a	60	90—93	0,45	246
IIIb	VII b	54	144—146	0,31	244
IIIb	VIII b	68	147—148	0,65	306
IIIb	IX b	70	106—108	0,40	260
IIIc	VII c	35	149—151	0,34	309
IIIc	VIII c	43	143—145	0,59	371
IIIc	IX c	40	146—148	0,46	325
IVa	X a	58	118—120	0,52	258
IVa	XI a	91	187—189	0,66	320
IVb	X b	60	12 —127	0,45	272
IVb	XI b	93	124—125	0,70	334
IVc	X c	44	95—96	0,56	337
IVc	XI c	86	174—176	0,77	399
IIIa	XII	75	216—218	0,36	278
IIIb	XIII	53	175—177	0,41	309

*The values were determined in the solvent system chloroform—diethyl ether (1:1) (Silufol).

In the IR spectra of compounds (IIIa-c) and (IVa-c), the absorption bands of the carbonyl group had shifted into the 1635-1640 cm^{-1} region in place of 1655-1680 cm^{-1} for the initial compounds (Ia-c) and (IIa-c). The IR spectra of (IIIa-c) were also characterized by the presence of an absorption band in the 3270-3285 cm^{-1} region, showing the presence of a NH group. Fro compounds (IVa-c), these bands appeared at from 3105 to 3220 cm^{-1}. The initial substances had no absorption in this region.

The IR spectra of compounds (Va and b) and (VIa-c) lacked the absorption bands of NH groups that were characteristic for the initial compounds (IIIa-c) and (IVa-c). The carbonyl group was revealed in the 1650-1665 cm^{-1} region. In the PMR spectra of the compounds, the methyl groups at the N-1 atoms appeared in the form of singlets in the 2.7-2.8 ppm region.

For compounds (VII-XI), the absorption bands of the carbonyl group were shifted in comparison with those of the initial 1,2-dihydrodeoxyvasicinones and their seven-membered homologs into the 1640-1650 cm^{-1} ($\nu_{C=O}$) and 1684-1730 cm^{-1} ($\nu_{N-1-C=O}$) regions.

The mass spectra of these compounds had intense peaks of the molecular ions (90-100%) and of $M^+ - 1$ (30-92%) and $M^+ - 2$, and also the peaks of ions characterizing their fragmentation.

The yields and some physicochemical properties of the compounds obtained are given in Table 1.

A study of the biological activities of the compounds synthesized, carried out in the phytotoxicology laboratory of the Institute of the Chemistry of Plant Substances of the Uzbek SSR Academy of Sciences, showed that some of them posssessed weak defoliant or stimulating activities.

EXPERIMENTAL

2,3-Pentamethylene-1,2,3,4-tetrahydro-4-quinazolone (IVa). A mixture of 1 g (0.005 mole) of 2,3-pentamethylene-3,4-dihydro-4-quinazolone (IIa) and 1 g (0.026 mole) of $NaBH_4$ was treated with 50 ml of ethanol and was then heated in the water bath for 6 h. Water was added to the reaction mixture to dissolve the precipitate, and it was extracted wtih chloroform (3 × 100 ml). The chloroform extracts were dried with anhydrous Na_2SO_4 and filtered.

The chloroform was distilled off. This gave 0.86 g (86%) of (IVa) with mp 176-178°C (acetone). Compounds (IIIa-c) and (IVb and c) were obtained similarly.

1-Methyl-2,3-pentamethylene-1,2,3,4-tetrahydro-4-quinazolone (VIa). A solution of 1 g(0.005 mole) of (IVa) in 50 ml of absolute DMFA was treated with 0.12 g (0.005 mole) of NaH, and the mixture was stirred for 20 min. Then 0.31 ml (0.005 mole) of CH_3I was added and the resulting mixture was heated with stirring in the boiling water bath for 8 h. After this the DMFA was distilled off and the residue was recrystallized from petroleum ether. This gave 0.5 g (47%) of (VIa) with mp 95-96°C. (Va and b) and (VIb and c) were synthesized similarly.

2,3-Pentamethylene-3,4-dihydro-4-quinazolone methiodide. An ampul was charged with 1 g(0.005 mole) of (IVa), 1 ml (0.016 mole) of CH_3I, and 10 ml of ethanol. The sealed ampul was heated in the boiling water bath for 6 h. Then the precipitate that had deposited was filtered off and was carefully washed with diethyl ether. This gave 1.16 g (70%) of the methiodide, with mp 228-230°C. The methiodides of the 6-substituted derivatives of 2,3-trimethylene- and 2,3-pentamethylene-2,4-dihydro-4-quinazolones were obtained in the same way.

1-Benzoyl-2,3-pentamethylene-1,2,3,4-tetrahydro-4-quinazolone (XIa). a) A solution of 2 g (0.009 mole) of (IVa) in 100 ml of benzene was treated with 1.26 ml (0.009 mole) of triethylamine and 0.99 ml (0.009 mole) of benzoyl chloride. The reaction mixture was heated with stirring on the boiling water bath for 6 h. Then it was treated with 10% NaOH solution and the benzene was distilled off. This gave 1.77 g (60%) of (XIa) having mp 187-189°C (petroleum ether). Compounds (VIIa-c) and (XIb and c) were obtained similarly.

b) A solution of 2 g (0.009 mole) of (IVa) in 50 ml of chloroform was treated with 1.98 ml (0.018 mole) of benzoyl chloride. The mixture was boiled on the water bath with stirring for 3 h. Then it was treated with 10% NaOH solution and the chloroform was distilled off. This gave 2.66 g (90%) of (XIa) having mp 187-189°C (petroleum ether). Compounds (XIb and c) were obtained similarly.

1-Acetyl-2,3-pentamethylene-1,2,3,4-tetrahydro-4-quinazolone (Xa). To 20 ml of acetic anhydride was added 2 g (0.009 mole) of (IVa). The reaction mixture was boiled for 3 h and was then treated with 20% $NaHCO_3$ solutions. It was extracted with chloroform (3 × 100 ml), and the chloroform was distilled off. This gave 1.39 g (58%) of (Xa) with mp 118-120°C (petroleum ether). Compounds (VIIa-c) and (Xb and c) were synthesized similarly.

6,8-Dinitro-2,3,-pentamethylene-1,2,3,4-tyetrahydro-4-quinazolone (XIII). With stirring and cooling to 0°C, 2.8 g (0.013 mole) of (IVa) was dissolved in 21 ml of concentrated H_2SO_4. Then, with vigorous stirring, a nitrating mixture (1.25 ml of HNO_3 (d = 1.5) + 1.75 ml of H_2SO_4 (d = 1.84)) was added to the reaction mixture at such a rate that its temperature did not rise above 2°C. Then it was stirred at 5-10°C for 1 h and was poured onto ice, and the precipitate was filtered off and washed with water. This gave 2.10 g (53%) of (XIII) with mp 175-177°C (methanol). Compound (XII) was obtained in the same way.

LITERATURE CITED

1. B. Kh. Zharekeev, M. V. Telezhenetskaya, Kh. N. Khashimov, and S. Yu. Yunusov, Khim. Prir. Soedin., 679 (1974).
2. S. C. Pakrashi and A. K. Chakravarty, J. Org. Chem., 37, 3143 (1972).
3. Kh. M. Shakhidoyatov, A. Irisbaev, É. Oripov, and Ch. Sh. Kadyrov, Khim. Prir. Soedin., 557 (1976).