mercial solasodine as marker. The plates were dried and were sprayed with one of three revealing agents – antimony trichloride in chloroform, the Dragendorff reagent, and iodine vapor, as described in the literature [8].

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ALKALOIDS OF Peganum harmala.

UNUSUAL REACTION OF PEGANINE AND VASICINONE

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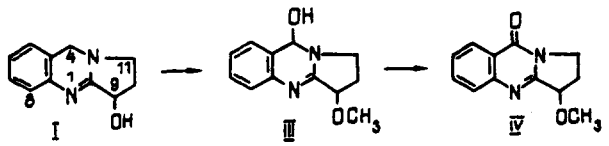
A number of derivatives of peganine and vasicinone have been obtained: 4-hydroxy-9-O-methylpeganine, isodihydrovasicinone, and 9-methoxy-, 9-phenoxy-, and 9,9-dichlorodeoxyvasicinones. An unusual ease of reduction of vasicinone and of 9-chlorodeoxyvasicinone has been found. An introduction of a hydroxy group into position 4 of a dihydroquinazoline alkaloid with the aid of sodium hydride has been detected.

Continuing a search for physiologically active compounds among the quinazoline alkaloids, we have obtained derivatives of peganine (I) and vasicinone (II) and have found an unusual behavior of them in some cases.



Scheme 1

When (I) was methylated with methyl iodide in the presence of NaH we isolated product (III) (Scheme 1), the molecular mass of which was 16 a.m.u. greater than for the expected O-methylpeganine, and which had the elementary composition $C_{12}H_{14}N_2O_2$. In the mass spectrum of (III) the most intense ion was $(M - 17)^+$, corresponding to the ejection of an OH group from the molecular ion. The PMR spectrum of (III), as compared with (I) had a signal from an OCH_3 group at 3.20 ppm, a one-proton singlet at 5.75 ppm, and a broadened one-proton signal at 7.60 ppm which disappeared on deuteration, showing the presence of a –CH–OH grouping. The ready ejection of the OH group under electron impact showed that it was possibly present at C-4 or C-11. The absence of a two-proton singlet in the 4.5 ppm region caused by C-4

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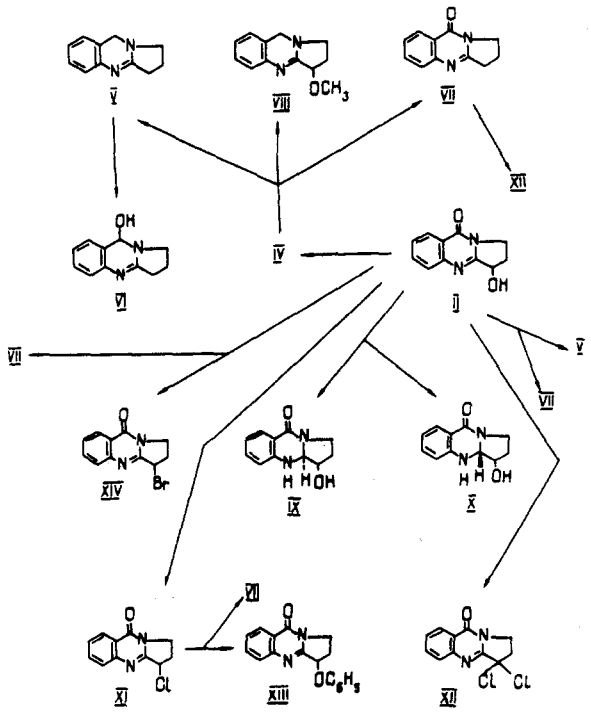
methylene protons showed that the newly formed hydroxy group was present at C-4. In actual fact, when the product was oxidized we obtained O-methylvasicinone (IV). On the basis of these facts, structure (III) must be ascribed to the compound obtained. It may be assumed that the appearance of a hydroxy group in this reaction takes place through the formation of a 4-sodio derivative which is oxidized by atmospheric oxygen to a peroxide compound. The latter is reduced by the sodium hydride to 4-hydroxy-O-methylpeganine (III). The similar formation of a CH–OH group has been observed [1] in the $LiAlH_4$ reduction of 2-benzyl-4-quinazolone.

The interaction of (I) with NaH led to resinification, while under these conditions deoxypeganine (DOP, V) formed peganol (VI, Scheme 2).



Scheme 2

When vasicinone (II) was methylated with methyliodide in the presence of sodium hydride, we obtained O-methylvasicinone (IV). The PMR spectrum, as compared with the spectrum of (II), showed an additional three-proton singlet at 3.48 ppm, and the signal of the proton geminal to the OCH_3 group, C-9–N, was shifted upfield. The reduction of (IV) with Zn/HCl yielded (V), deoxyvasicinone (DOV, VII), and O-methylpeganine (VIII) in amounts of 83, 10, and 1%, respectively. In the mass spectrum of (VIII) the main peak was that of an ion with m/z 171, $C_{11}H_{11}N_2$, the M^+ peak was very insignificant, and the $(M-1)^+$ peak, with a low intensity, had the composition $C_{12}H_{13}N_2O$, which confirmed structure (VIII). When vasicinone was reduced under the same conditions, equal amounts (~30% each) of DOP (V) and DOV (VII) were formed.

Earlier [2], by the $NaBH_4$ reduction of vasicinone we had obtained dihydrovasicinone (IX). When it was purified on a column of SiO_2 a second base (X), with mp 207-210°C was obtained. The mass spectra of (IX) and (X) practically coincided, but a mixture gave a depression of the melting point. Compounds (X) and (IX) are probably diastereoisomers. In the PMR spectrum of (IX) the C-2–H signal was observed in the form of a doublet at 4.85 ppm, and the C-9–H signal in a form of a quartet with approximately equal SSCCs, which showed their similar orientations. The α-orientation has been established for C-9–H [3], and therefore the C-2–H in dihydrovasicinone (IX) must also be α-oriented. Corresondingly, C-2–H in isodihydrovasicinone (X) has the β-orientation, the C-9–H signal being a multiplet with small SSCC values.

9-Chlorodeoxyvasicinone (XI) has been obtained from (II) under the action of $SOCl_2$ [4] with a yield of 48%. We have increased the yield of (XI) to 75% by using $POCl_3$. If, however, vasicinone was subjected to the action of $POCl_3$ + PCl_5 then not only C-9–OH but also C-9–H was replaced by chlorine with the formation of 9,9-dichlorodeoxyvasicinone (XII). It may be mentioned that in analogous reaction DOV likewise gave compound (XII), although with a lower yield. On being fused with phenol, (XI) formed the phenoxy derivative (XIII). In an attempt at the alkylation or aminoalkylation of chloro-DOV (XI) with butanol or aniline under the conditions of phase-transfer catalysts, DOV (VII) was unexpectedly obtained as the main product. Reckoning on obtaining 9-bromodoxyvasicinone (XIV), we performed the reaction of vasicinone with PBr_3. However, (XIV) was isolated only in trace amounts, the main product proving to be deoxyvasicinone (VII). It is likely that a phosphoric acid ester is first formed at the alcohol group and this is extremely readily reduced with the aid of PBr. We have been unable to find any analogies in the literature.

EXPERIMENTAL

Methylation of Peganine. A suspension of 1 g of (I) in 30 ml of dry dioxane was treated with 0.3 g of NaH. The mixture was heated with stirring at 30°C for 2 h. Then, 0.4 ml of CH_3I in 4 ml of dioxane was added. Heating and stirring were continued for another 4 h. The solid matter was filtered off with suction, washed with dioxane, and discarded. The filtrate was evaporated and the residue was dissolved in 10% H_2SO_4 solution. The acid solution was washed with chloroform and was then made alkaline with NH_4OH, and the reaction product was extracted with chloroform. After drying and the elimination of the solvent by distillation, 0.48 g of a semicrystalline mass was obtained. When this was treated with a mixture of acetone and hexane (1:6), 0.16 g of (III) separated out, with mp 158-160°C. UV spectrum, $\lambda_{max}^{C_3H_5OH}$ (nm): 210, 280. PMR (100 MHz, $CDCl_3$): 7.60 (1H, s, C-4–OH); 7.17 (4H, m, Ar–H); 5.75 (1H, br.s, H-4); 3.70 (1H, m, H-9); 3.30 (1H, m, H-11); 3.20 (3H, s, OCH_3); 1.82 (3H, m, 2H-10, H-11). It was impossible to isolate individual compounds from the residual reaction mixture.

Preparation of Peganol. To 1 g of DOP (V) in 30 ml of dioxane was added 0.4 g of NaH, and the mixture was heated with stirring at 60-70°C for 2 h. The solvent was distilled off. The residue was treated in the way described above. The semicrystalline mass was treated with C_6H_6, which led to the separation of 0.07 g of a product with mp 165°C. A mixed sample gave no depression of the melting point with an authentic sample of peganol, and their R_f values in TLC were identical. Their mother solutions yielded 0.3 g of the initial (V) and 0.3 g of (VII).

O-Methylvasicinone (IV). a) Vasicinone (1 g) was methylated in the similar way to the methylation of peganine. The hydrochloride was obtained from the residue after the dioxane had been distilled off: mp 212-213°C (decomp., acetone–alcohol), yield 54%. The base regenerated from the salt had mp 58-60°C (petroleum ether). Mass spectrum, m/z: 216 (M^+), 186 (100%).

b) With stirring, a solution of 0.07 g of $KMnO_4$ in 30 ml of aqueous acetone was added dropwise to a solution of 0.14 g of (III) in 25 ml of aqueous acetone (1:1). The precipitate of MnO_2 was filtered off and washed with acetone, and the washing acetone was combined with the filtrate and evaporated. The residue was treated with chloroform. From the mixture remaining after the elimination of the chloroform was obtained 0.08 g of a hydrochloride which, after recrystallization from a mixture of acetone and ethanol, had mp 214°C. The spot on TLC [Al_2O_3, chlf–C_6H_6 (1.5:85)] coincided with the spot of the hydrochloride of (IV) obtained by method a).

9-Chlorodeoxyvasicinone (XI). A mixture of 2 g of vasicinone (II), 15 ml of C_6H_6, and 4 ml of $POCl_3$ was heated in the water bath with stirring for 4 h. It was then evaporated and the residue was treated with NH_4OH and $CHCl_3$. The residue from the distillation of the chloroform extract was transferred to a column containing Al_2O_3 and was eluted with C_6H_6. The substance obtained after the C_6H_6 had been driven off was crystallized from a mixture of petroleum ether and alcohol, giving 1.7 g of a product with mp 107-108°C.

9,9-Dichlorodeoxyvasicinone (XII). With cooling, 3 ml of $POCl_3$ was added dropwise to a mixture of 1 g of (II) and 4.12 g of PCl_5. The reaction mixture was heated at 110°C for 4.5 h, and its treatment with acetone then yielded 0.25 g of (XII), mp 179°C, M^+ 256/254. UV spectrum, $\lambda_{max}^{C_2H_5OH}$ (nm): 227, 240 (shoulder), 285. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1690

(N–C=O), 1540, 1615, 1480. PMR spectrum ($CDCl_3$), ppm: 8.16 (1H, d, H-5); 7.30-7.90 (3H, m, Ar–H); 4.15 (2H, t, H-11); 3.05 (2H, t, H-10). The residual mother solution, consisting of a mixture of eight substances, was not separated further. None of the initial (II) was detected.

9-Phenoxydeoxyvasicinone (XIII). A mixture of 0.77 g of (XI), 3.29 g of phenol, and 0.39 g of KOH was heated at 120-150°C for 7 h. After cooling, the reaction mixture was distributed between 20% NaOH solution and chloroform. The chloroform solution was carefully washed with water and dried with Na_2SO_4, and the solvent was distilled off to give 0.58 g of a product with mp 146-147°C (ethanol); hydrochloride with mp 187-190°C, M^+ 278. The mother solution was separated on a column of SiO_2, yielding 0.02 g of (VII).

Interaction of (XI) with $NH_2C_6H_5$. A mixture of 0.11 g of (XI), 0.046 g of NH_2–C_6H_5, 0.6 ml of CH_2Cl_2, 0.6 ml of 20% NaoH solution, and 0.01 g of triethylbenzylammonium chloride (TEBAC) was heated for 1 h. The mixture was acidified with 10% H_2SO_4 solution and was then made alkaline with NH_4OH and the reaction products were extracted with chloroform. The residue after elimination of the solvent was crystallized from petroleum ether. This gave 0.04 g of (VII) with mp 110°C, M^+ 186, a mixture with deoxyvasicinone giving no depression of the melting point.

Interaction of (XI) with BuOH. A mixture of 0.11 g of (XI), 0.06 ml of BuOH, 1.2 ml of CH_2Cl_2, 0.5 g of NaOH, 0.5 ml of H_2O, and 0.006 g of TEBAC was heated with stirring for 1 h, and the organic layer was separated off; the aqueous phase was washed with CH_2Cl_2, and the combined extracts were evaporated, diluted with water, and extracted with ether. The ethereal solution was washed with 2 N NaOH and then with saturated NaCl solution and was dried with Na_2SO_4 and evaporated. This gave 0.09 g of (VII) (mixed melting point, TLC, mass spectrum).

Interaction of (II) with PBr_3. With stirring, 1.5 ml of PBr_3 in 20 ml of C_6H_6 was added dropwise to a suspension of 1 g of vasicinone in 30 ml of dry C_6H_6. Stirring was continued with heating on the water bath for 5 h. The solvent was evaporated off, the residue was made alkaline and the reaction products were extracted with chloroform, the extract was evaporated, and the residue was separated on a column of SiO_2 with elution by C_6H_6–$CHCl_3$ (1:1). Similar fractions were combined and the products that they contained were recrystallized from a mixture of hexane and acetone. This gave 0.56 g of compound (VII), mp 110°C, showing no depression of the melting point with an authentic sample of DOV and having the same TLC characteristics. The mother liquors were reseparated on a column of SiO_2. The benzene fractions, after recrystallization from hexane–acetone (1:1), yielded 0.05 g of (XIV), mp 146°C, a mixture with an authentic sample of 9-bromodeoxyvasicinone showing no separation in TLC and giving no depression of the melting point.

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