SYNTHETIC ANALOGS OF Peganum ALKALOIDS

VI. PHOTOCHEMICAL OXIDATION OF 2,3-POLYMETHYLENE-QUINAZOLINE DERIVATIVES

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The rates of the photochemical oxidation of quinazoline alkaloids – deoxypeganine, peganine, pentamethylenequinazoline, and peganol – to the corresponding oxo derivatives have been studied. It has been shown by HPLC that the oxidation of deoxypeganine proceeds through a stage of the formation of a carbinolamine (peganol); in the case of its hydrochloride, the reaction takes place by the same scheme but four times more slowly. Tetra- and pentamethylenequinazolines have been synthesized and information on their melting points in the literature has been corrected. In the series trimethylenequinazoline–pentamethylenequinazoline–tetramethylenequinazoline the stability falls from left to right.

Continuing a study of the preparation of analogs of quinazoline alkaloids, we have synthesized 2,3-tetra- and -pentamethylenequinazolones and have then reduced them to the corresponding quinazoline compounds. Attention was attracted to the fact that the reduction products spontaneously oxidized to the initial quinazolone with extreme rapidity. Cases of autooxidation of peganine to vasicinone in sunlight [1, 2], and also during its isolation and purification (countercurrent distribution, chromatograph) [3] have been frequently reported in the literature. Similar transformations are also undergone by other quinazoline alkaloids. Thus, for example, deoxypeganine is oxidized to deoxyvasicinone [2, 4], vasicoline to vasicolinone [5, 6], adhatodine to anisotine [5], and tetramethylenequinazoline to tetramethylenequinazolone [7]. These processes relate to the above-mentioned alkaloids in the form of bases. According to the literature [4] and to our own observations [8], the salts of the quinazoline bases are stable. However, other authors have reported the conversion of a 0.1% aqueous solution of peganine hydrochloride into vasicinone on storage [9].

Starting from what has been said above, we decided to compare the rates of photochemical oxidation of 2,3-polymethylenequinazolines with different sizes of ring C and to evaluate the stability of their hydrochlorides.

On the photochemical oxidation of a chloroform solution of deoxypeganine as the free base it was found that it was converted almost completely into deoxyvasicinone in 5 h. At intermediate stages of the reaction, a spot of a substance with a R_f value close to that of the alkaloid peganol was detected. When deoxypeganine hydrochloride was used, the concentration of the intermediate product increased. However, attempts to isolate the substance in the pure form with the aid of column chromatography and preparative TLC were unsuccessful. On each occasion we obtained a mixture of the intermediate product with deoxyvasicinone, which could not be eliminated. To analyze the reaction mixture formed on the photochemical oxidation of deoxypeganine, therefore, we decided to use high-performance liquid chromatography (HPLC).

Conditions for separating the alkaloids deoxypeganine (I), peganol (II), and deoxyvasicinone (III) have been described in the literature [10]. When an aqueous solution of deoxypeganine hydrochloride was subjected to HPLC analysis, the following facts were revealed. After irradiation on the chromatogram for only one hour, in addition to the peak of the initial alkaloid a peak was detected with a retention time coinciding with that of a standard sample of the alkaloid peganol. After continuous irradiation for 4 h, the pattern had changed appreciably. In addition to the peaks of deoxypeganine and peganol, the peak of a third component (deoxyvasicinone) appeared on the chromatogram. When the process of

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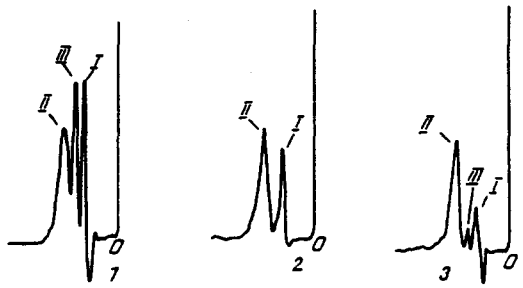
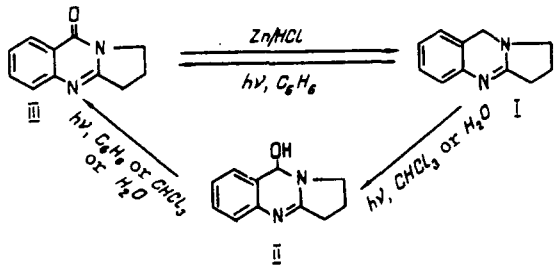


Fig. 1. Chromatograms: 1) model mixture of alkaloids deoxypeganine (I), peganol (II), and deoxyvasicinone (III); 2) reaction mixture after irradiation for 1 h; 3) reaction mixture after irradiation for 4 h.

photochemical oxidation was lengthened, the ratio between the three alkaloids in the reaction mixture changed in the direction of an increase in the amount of deoxyvasicinone and, correspondingly, the amounts of the other two components decreased. Finally, deoxyvasicinone remained the only reaction product. The results of the HPLC analysis are given in Fig. 1.

Thus, deoxypeganine hydrochloride is not stable to the action of the radiation of a quartz mercury lamp and is gradually oxidized to deoxyvasicinone. As in the case of the free alkaloid, the process takes place through intermediate stage of the formation of a carbinolamine and its completion requires a far greater time. A scheme of the transformation of the three alkaloids investigated is given below.



Some other quinazoline alkaloids were subjected to photochemical oxidation. The results of these experiments are given in Table 1. As can be seen from Table 1, among the bases with quinazoline structure that were studied peganine was the most stable. A substance with a seven-membered ring C – pentamethylenequinazoline – was the least stable. When peganine was oxidized, a compound was formed in an intermediate stage the R_f values of which was close to that for 4-hydroxypeganine. It may be assumed that the appearance of substance with the carbinolamine structure is characteristic for the photochemical oxidation of quinazoline systems. In other words, the reaction probably takes place in the following sequence: methylene group → carbinol → carbonyl. When deoxypeganine and its dimethoxy analogs were oxidized in sunlight, Chowdhury et al. [11] likewise detected minor additional peaks in HPLC analysis. We consider that they may correspond to carbinolamines. In the case of pentamethylenequinazoline no additional spot could be observed, obviously because of its high rate of oxidation.

In the treatment of literature information, we directed attention to the fact that the melting points given by some authors for quinazolones and quinazolines are close but according to others the constants differ considerably [12-16]. In view of this we entertained a suspicion that the melting points given in a number of cases for quinazoline did in actual fact relate to their oxo derivatives. To check this hypothesis, the quinazolines synthesized were isolated and were purified in the form of salts which were then converted as rapidly as possible into the free bases using cooled reagents and protection from light. The tetra- and pentamethylenequinazolines obtained melted at 52-53°C and 81-82°C, respectively.

In an attempt to crystallize tetramethylenequinazoline from hexane, we obtained a substance with mp 98°C, which coincides with the melting point of the oxo derivatives that we

TABLE 1. Photochemical Oxidation of Quinazoline Alkaloids

Experiment No.	Initial compound	Solvent	Reaction time	Intermediate product	Final product
1	Deoxypeganine	$CHCl_3$	5	Peganol	Deoxyvasicinone
2	Deoxypeganine	C_6H_6	3	—	Deoxyvasicinone
3	Deoxypeganine	H_2O	20	Peganol	Deoxyvasicinone
4	Peganine	$CHCl_3$	13	Hydroxypeganine	Vasicinone
5	Peganol	$CHCl_3$	8	—	Deoxyvasicinone
6	Peganol	C_6H_6	8	—	Deoxyvasicinone
7	Pentamethylene-quinazoline	$CHCl_3$	2	—	Pentamethylene-quinazoline

had obtained and with literature information [12]. It is obvious that complete oxidation of the initial quinazoline had taken place. A similar process was observed when the reaction product was chromatographed on silica gel plates, and also in an attempt to perform HPLC analysis.

Pentamethylenequinazoline behaved similarly, giving on alumina a mixture of spots of two substances (the quinazoline and the quinazolone). However, when pentamethylenequinazoline was chromatographed on silica gel it gave a single spot, unlike its tetramethylene analog. This showed a lower stability of the latter. On comparing these experimental results with literature information it may be assumed that a number of authors were probably dealing either with pure quinazolone bases or with mixtures of quinazolines and quinazolone with a predominance of the latter components.

Thus, in the series trimethylenequinazoline–pentamethylenequinazoline–tetramethylenequinazoline the stability decreases from left to right. The oxidation of these compounds to the corresponding quinazolone derivatives takes place both under the action of natural and artificial irradiation and also in heat treatment and in chromatography on sorbents of different types.

EXPERIMENTAL

Photochemical Oxidation of 2,3-Polymethylenequinazolines (general procedure). A quinazoline alkaloid (deoxypeganine, peganine, pentamethylenequinazoline, peganol) (0.05 g) freshly prepared from the corresponding hydrochloride was dissolved in cold chloroform or benzene (10 ml). This solution was placed in a quartz glass flask and irradiated with the light of a DRT-400 quartz mercury lamp with constant stirring. The distance from the source of irradiation in all the experiments was 18 cm. The reaction mixture was subjected to TLC analysis every 30 min. After the end of the reaction, the solvent was evaporated off, and the solid residues were recrystallized and were compared with control samples of alkaloids with respect to R_f values and melting points.

As a result of the reactions, deoxypeganine and peganol gave deoxyvasicinone (mp 107-108°C), peganine gave vasicinone (200-201°C), and pentamethylenequinazoline gave pentamethylenequinazolone (mp 96-98°C). TLC analysis was performed on Silufol UV 254 plates, using benzene–chloroform–methanol (3.5:5:1.5) as the mobile phase.

HPLC Analysis of an Aqueous Solution of Deoxypeganine Hydrochloride. A Milikhrom microcolumn liquid chromatograph was used. Chromatographic conditions: Silasorb C 18 column (2 × 80 m), particle size 5 μm, rate of elution 0.1 ml/min. UV detection at 296 nm. Mobile phase: methanol–water–acetic acid (70:30:0.0033).

An aqueous solution of deoxypeganine hydrochloride (0.1%) was irradiated by the procedure described above. Chromatographic samples were taken every 30 min.

Isolation of Tetramethylenequinazoline. The reduction of tetramethylenequinazolone was carried out by the procedure of [14]. After the end of heating, the cooled solution was extracted with chloroform. The solid residue after the evaporation of the extract was recrystallized from hexane–acetone (4:1). This led to the isolation of 0.14 g of unchanged tetramethylene quinazolone (from 0.53 g initially). Then the acid solution was made alkaline with cold concentrated ammonia and was treated with cold ether. The combined ethereal extracts were dried over potassium hydroxide, filtered, and acidified with an alcoholic solution of hydrochloric acid. The white precipitate that deposited was separated off, washed with ether, and recrystallized from acetone methanol (1.2:1). The yield of hydrochloride was 0.35 g (59%), mp 150-155°C (decomp.).

Part of the hydrochloride was converted into the base, which was washed several times with hexane (mp 49-50°C) and was recrystallized from ether (mp 52-53°C). The sulfate was also obtained from the hydrochloride, and this was washed with acetone and recrystallized from ethanol; mp 209-210°C. All the operations on the isolation and purification of the free tetramethylenequinazoline were carried out with protection from the light.

Isolation of Pentamethylenequinazoline. Pentamethylenequinazoline hydrochloride was obtained by the method described above with a yield of 49%. Its mp was 202-204°C (from acetonitrile). The hydrochloride (0.1 g) was made alkaline with cooled ammonia to pH 9, and the base was extracted with three portions of cold ether, the ethereal extract was dried over potassium hydroxide and filtered, and the solvent was distilled off under vacuum. The solid residue formed on cooling at 0°C was recrystallized from petroleum ether (50-60°C)–benzene (28:1). The mp of the base was 81-82°C.

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