SYNTHETIC ANALOGUES OF Peganum ALKALOIDS.

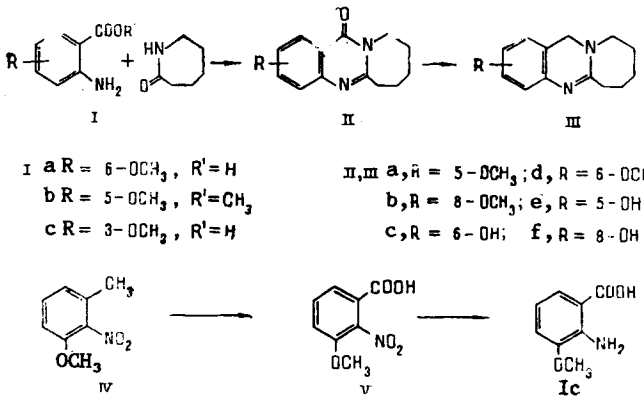
III. PENTAMETHYLENEQUINAZOLONES

A. L. D'yakonov, M. V. Telezhenetskaya, and L. Yu. Yunusov

UDC 547.944/945+547.856.1

Monosubstituted 5-, 6-, and 8-methoxy-3,4-dihydro-2,3-pentamethylenequinazolones (1-3) have been syntehsized by the condensation of monosubstituted methoxyanthranilic acids with caprolactam. Demethylation with hydrobromic acid gave the corresponding hydroxy compounds [4-6]. When the 6- and 8-methoxy- and 6- and 8-hydroxy-3,4-dihydro-2,3-pentamethylenequinazolones (2, 3, 5, and 6) were reduced with zinc in hydrochloric acid, the corresponding quinazoline derivatives (7-10) were obtained. The melting points of the basis and their hydrochlorides are given. Some features of their UV, mass, and PMR spectra are reported.

Continuing work on the production of analogues of Peganum L. alkaloids [1, 2], we have synthesized pentamethylenequinazolones (II) and pentamethylenequinazolines (III). The quinazolones (II) were synthesized by condensing substituted anthranilic acids (I, R' = H) with caprolactam in the presence of phosphorus oxychloride [3]. The use of toluene as solvent in this reaction permits the amount of phosphorus oxychloride to be decreased and the heterogeneity of the reaction mixture to be lowered.



6-Methoxyanthranilic acid (Ia) was obtained from m-dinitrobenzene in three stages by the scheme given in a preceding paper [2].

For the synthesis of 6-methoxy-3,4-dihydro-2,3-pentamethylenequinazolone (IIb) we used not 5-methoxyanthranilic acid (Ib, R' = H) but its methyl ester (Ib, R' = CH_3). The latter was obtained from 5-methoxyisatin [1] by oxidation with hydrogen peroxide in the presence of sodium methanolate [4]. The use of methyl 5-methoxyanthranilate in the condensation reaction in place of 5-methoxyanthranilic acid permitted the yield of the quinazalone (IIb) to be doubled in comparison with the scheme adopted previously [1]. In the preparation of 3-methanthranilic acid (Ic) we changed the sequence of operations in the scheme of synthesis given in [1], which permitted the stage of acylating the amino group followed by the saponification of the acyl residue to be eliminated. 3-Methoxy-2-nitrotoluene (IV) [1] was oxidized to the corresponding benzoic acid (V), and then the 3-methoxy-2-nitrobenzoic acid (V) was reduced to 3-methoxyanthranilic acid (Ic) under the conditions given in [5]. These modifications doubled the yield of 3-methoxyanthranilic acid (Ic) in comparison with the scheme of synthesis used previously [1].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 465-469, July-August, 1986. Original article submitted February 10, 1986.

0009-3130/86/2204-0435$12.50

TABLE 1. PMR Spectra of the 3,4-Dihydro-2,3-pentamethylenequinazolones

Compound	Aromatic protons				Methylene protons			OCH_3
	5	6	7	8	9	13	10-12	
VI	8.25		7.00 m		3,00 m	4.32 m	1,8 bs	—
IIa	—	6,38 d	7.63 t	7,18 d	3,02 m	4.37 m	1,87 bs	3.97 s
IIb	7,52 s	—	7,32 d	7,55 d	3,01 m	4,35 m	1,79 bs	3,86 s
IIc	7,75 d	7.24 t	7,05 d	—	3,10 m	4,34 m	1.79 bs	3,95 s

s — singlet; d — doublet; t — triplet; m — multiplet; bs — broadened singlet.

The reduction of the pentamethylenequinazolones (II) to the corresponding pentamethylenequinazolines (III) took place less smoothly than in the case of the trimethylenequinazolones [1]. The yields of (III) did not exceed 30-50% because of the formation of a number of by-products, and we were unable to obtain the corresponding quinazolones (III) from 5-methoxy-3,4-dihydro-2,3-pentamethylenequinazolone (IIa) and 5-hydroxy-3,4-dihydro-2,3-pentamethylenequinazolone (IId). Similarly, we did not obtain a 5-hydroxytrimethylenequinazoline from 5-hydroxy-3,4-dihydro-2,3-trimethylenequinazolone [2]. This is apparently prevented by a strong hydrogen bond between the substituent in the C-5 position and the carbonyl group at C-4, and also by steric hindrance.

The hydroxypentamethylenequinazolnes (IId-f) and the hydroxypentamethylenequinazolines (IIIe, f) were synthesized in a similar manner to the hydroxytrimethylenequinazolones described in [1, 2].

In the UV spectra of the quinazolones (IIa-c), five absorption bands were observed in the 237, 276-280, 287-289, 319-322, and 332-335 nm regions which had undergone a bathochromic shift in comparison with quinazolones unsubstituted in the benzene ring [6].

For the hydroxy compounds (IIe and f), the bathochromic shift was even more considerable (342-343 nm), while for the 5-methoxy- and 5-hydroxypentamethylenequinazolones (IIa and d), and the UV spectra coincided. The spectra of the weakly phenolic compounds (IId and f) did not change on the addition of alkali, in contrast to the phenol (IIe), in the spectrum of which there was only one maximum in the 300 nm region. Similar changes on the addition of alkali are undergone by the UV spectrum of 6-hydroxytrimethylenequinazolone. In the quinazolines (III), two absorption maxima characteristic for 3,4-dihydroquinazolines were observed in the 215 and 290 nm region [6].

In the mass spectra of substances (IIa-c) the characteristics established for the corresponding trimethylenequinazolones and for a pentamethylenequinazolone unsubstituted in the benzene ring [2, 7] were observed. The strongest peak was that of the molecular ion. Subsequent fragmentation took place through the cleavage of ring C. Processes leading to the breakdown of the methoxy group raised the intensity of the $(M - 15)^+$ ion in the quinazolone (IIb) and of the $(M - 29)^+$ ion in compound (IIa), where this process was the dominating one. In the hydroxyquinazolones (IId-f), the difference in the intensities of the ions was not so considerable, although one must note an increased intensity of the $(M - 29)^+$ ion for (IId) and for the $(M - 17)^+$ ion for (IIe). In the mass spectra of the quinazolines (III), regardless of the nature and position of the substituents, the main peak was that of the $(M - 1)^+$ ion.

The PMR spectra of the quinazolones (II) (Table 1), were similar to the spectra of the trimethylquinazolones [1]. The signals of the methylene protons in positions 10, 11, and 12 were very close and appeared in the form of broadened six-proton singlets. In compounds (IIb and c), as a result of the influence of the methoxy group, no downfield shift of the signal of the C-5 proton was observed as in the case in the unsubstituted pentamethylenequinazolone (VI) (see Table 1).

EXPERIMENTAL

For general remarks see [1].

6-Methoxy-2-nitrobenzonitrile was obtained by the procedure described in [8].

6-Methoxy-2-aminobenzonitrile. A mixture of 4.41 g of the nitro compound, 5 g of iron, 33 ml of methanol, and 40 ml of conc. hydrochloric acid was heated in the water bath for 6.5 h. The crystals that deposited on cooling were filtered off with suction and washed with acetone: 3.24 g, mp 210-212°C (decomp.); the melting point of the base obtained from the hydrochloride was 139-140°C. According to the literature [9]: 125-138°C.

6-Methoxyanthranilic Acid (Ia). A mixture of 3.24 g of 2-amino-6-methoxybenzonitrile hydrochlroide and 20 ml of 20% NaOH was heated in the boiling water bath for 27 h. Then the reaction mixture was cooled and filtered, and the filtrate was acidified by pH 4 with conc. HCl. The precipitate that deposited (1.09 g) was filtered off with suction. It was used without further purification.

Methyl 5-Methoxyanthranilate (Ib). With cooling and stirring, to a suspension of 6.5 g of 5-methoxyisatin in 55 ml of methanol was added 20 ml of 30% methanolic sodium methanolate and then, dropwise, 10 ml of 35% H_2O_2 in such a way that the temperature of the reaction mixture remained between 0 and 10°C. After the mixture had been stirred for 30 min at room temperature, the methanol was driven off. Water was added to the residue and the reaction product was extracted with dichloromethane. After the solvent had been eliminated, a red-brown oil remained which was used without further purification.

3-Methoxy-2-nitrobenzoic Acid (V). With vigorous stirring, 20 g of potassium permanganate was added in small portions to a suspension of 5 g of 3-methoxy-2-nitrotoluene [1] in 215 ml of hot water. The reaction mixture was heated in the boiling water bath for 2 h, and then the hot mixture was filtered and the residue was carefully washed with hot water. The filtrate and the washwaters were combined and were evaporated to 50 ml, and, with ice cooling, they were acidified with conc. HCl. The voluminous white precipitate that deposited was filtered off with suction, dried in the air, and recrystallized from absolute ethanol; yield 3.4 g, mp 249-250°C. According to the literature [10]: mp 251°C.

3-Methoxyanthranilic Acid (Ic). A solution of 4.5 g of the acid (V) in 50 ml of ethanol was treated with 4.5 ml of 95% hydrazine hydrate. The reaction mixture was heated to 50°C and 0.7 g of freshly prepared Raney nickel was added and it was then boiled for an hour, at the end of which a further small amount of Raney nickel was added to decompose the excess of hydrazine hydrate. The ethanol was distilled off, and, with cooling, the residue was treated with conc HCl. The 3-methoxyanthranilic acid hydrochloride that deposited was filtered off with suction, and dried in the air; 3.23 g, mp 202-203°C (glacial acetic acid); mp of the acid 170-171°C, which agrees with the results obtained previously [1].

5-Methoxy-3,4-dihydro-2,3-pentamethylenequinazolone (IIa). With stirring 0.69 g of caprolactam and then 0.83 g of the hydrochlroide of the acid (Ia) were added to a solution of 2 ml of phosphorus oxychloride in 5 ml of toluene. The mixture was heated at 100-140°C for 2 h. The toluene and the excess of $POCl_3$ were evaporated off. A concentrated solution of NH_4OH was added to the residue and it was treated with chloroform. The oil remaining after the chloroform had been driven off was transferred to a column containing 20 g of Al_2O_3. On elution with benzene the first fractions gave 0.4 g of (IIa) with mp 135°C (hexane–acetone (4:1)), and the subsequent fractions gave 0.25 g of the hydrochloride of (IIa) with mp 212°C (decomp.).

IR spectrum (ν, cm^{-1}): 1570, 1600, 1675.

Mass spectrum (m/z, %): 244 (92), 243 (37), 215 (100).

6-Methoxy-3,4-dihydro-2,3-pentamethylenequinazolone (IIb). A. To a solution of 1.31 g of caprolactam in 33 ml of toluene was added, in drops, 3.8 ml of phosphorus oxychloride and then a solution of 1.4 g of methyl 5-methoxyanthranilate. The reaction mixture was stirred and heated at 100°C for 3 h. After cooling, the liquid layer was decanted off. Concentrated NH_4OH was carefully added to the residue, and it was treated with chloroform. The chloroform extract was dried with Na_2SO_4 and filtered, and the chloroform was evaporated off. The semicrystalline reddish brown residue was passed through a column of Al_2O_3 with benzene as eluent. This gave 1.53 g (81%) of (IIb) with mp 118-119°C. According to the literature [11]: mp 116-117°C; melting point of the hydrochloride 225-226°C.

IR spectrum (ν, cm^{-1}): 1575, 1595, 1620, 1670.

Mass spectrum (m/z, %): 244 (100), 243 (23), 229 (67), 215 (68), 190 (87).

B. The condensation of 0.59 g of caprolactam with 0.71 g of 5-methoxyanthranilic acid under the conditions described above yielded 0.56 g (66%) of (IIb).

8-Methoxy-2,3-dihydro-2,3-pentamethylenequinazolone (IIc). This was synthesized in a similar manner to (IIa) from 2.55 g of 3-methoxyanthranilic acid hydrochloride. The yield of (IIc) was 1.5 g, mp 139°C (hexane–acetone (4:1)). According to the literature [3]: mp 138-139°C; hydrochloride, mp 198°C (decomp.).

IR spectrum (ν, cm^{-1}): 1575, 1600, 1675.

Mass spectrum (m/z, %): 244 (100), 243 (24), 229 (24), 215 (33), 190 (38).

The Hydroxy-3,4-dihydro-2,3-pentamethylenequinazolones (IId, e, and f). There were obtained from the corresponding methoxy-3,4-dihydro-2,3-pentamethylenequinazolones (IIa, b, and c) by heating them with 47% hydrobromic acid [1]. Compound (IId), mp 140-141°C (hexane); hydrochloride, mp 201-202°C; M^+ 230; yield 74%; compound (IIe): mp 231-232°C (Al_2O_3 column, eluent benzene); hydrochloride, mp 247-248°C; M^+ 230; yield 83%; compound (IIf): mp 156°C (hexane–acetone (1:1)); hydrochloride, mp 235-237°C (decomp.);M^+ 230; yield 80%.

The Methoxy and Hydroxy-3,4-dihydro-2,3-pentamethylenequinazolines (IIIb, c, e, and f) were synthesized from the corresponding quinazolones (IIb, c, e, and f) by reduction with zinc in hydrochloric acid, according to [1]. After the usual working-up procedure, in each case an oily residue remained which consisted of a mixture of 6-8 substances. To this mixture was added an ethanolic solution of hydrochloric acid, the ethanol was evaporated off, and the residue was treated with acetonitrile. The crystalline hydrochloride that separated out was filtered off with suction and was recrystallized from a 1:1 mixture of acetone and ethanol. Compound (IIIb): hydrochloride, mp 249-250°C; base,mp 113-114°C; yield 40%; compound (IIIc): hydrochloride, mp 197-199°C (decomp.), yield 51%; compound (IIIe): hydrochloride, mp 212-213°C, yield 50%; compound (IIIf): hydrochloride, mp 223-227°C; yield 33%.

SUMMARY

1. 3,4-Dihydro-2,3-pentamethylene-4-quinazolones monosubstituted in the benzene ring with methoxy groups in positions 5, 6, and 8, respectively, have been synthesized.

2. A modification of the schemes of synthesis used previously has permitted the yields of 6- and 8-methoxy-3,4-dihydro-2,3-pentamethylenequinazolones to be doubled.

3. The reduction of the pentamethylenequinazolones to the corresponding quinazolines has been studied.

4. It has been shown that a methoxy group in a pentamethylenequinazolone is smoothly demethylated.

5. Some characteristic features of the spectra of the compounds obtained have been reported.

LITERATURE CITED

1. A. Karimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prir. Soedin., 498 (1982).
2. A. Karimov, V. N. Plugar', M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prir. Soedin., 396 (1983).
3. Kh. M. Shakhidoyatov, A. Irisbaev, L. M. Yun, E. Oripov, and Ch. Sh. Kadyrov, Khim. Geterotsikl. Soedin., 11, 1564 (1976).
4. J. Reissenweber and D. Mangold, Angew. Chem., 20, 822 (1981).
5. D. Balcom and A. Furst, J. Am. Chem. Soc., 73, 4334 (1953).
6. M. V. Telezhenetskaya and S. Yu. Yunusov, Khim. Prir. Soedin., 731 (1977).
7. V. N. Plugar', Ya. V. Rashkes, and Kh. M. Shakhidoyatov, Khim. Prir. Soedin., 180 (1979); V. N. Plugar', Ya. V. Rashkes, A. Karimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prir. Soedin., 68 (1983).
8. Organic Syntheses [Russian translation], Moscow, Coll. 3, 201 (1952).
9. R. A. Snow, D. M. Cottrell, and L. A. Paquette, J. Am. Chem. Soc., 99, 3734 (1977).
10. Beilstein's Handbuch der organischen Chemie, Berlin, Vol. 10, p. 146.
11. J. Devi, R. S. Kapil, and S. P. Popil, Indian J. Chem., 14B, 354 (1976).