Some Derivatives of Indeno[2,1-*g*]pteridine

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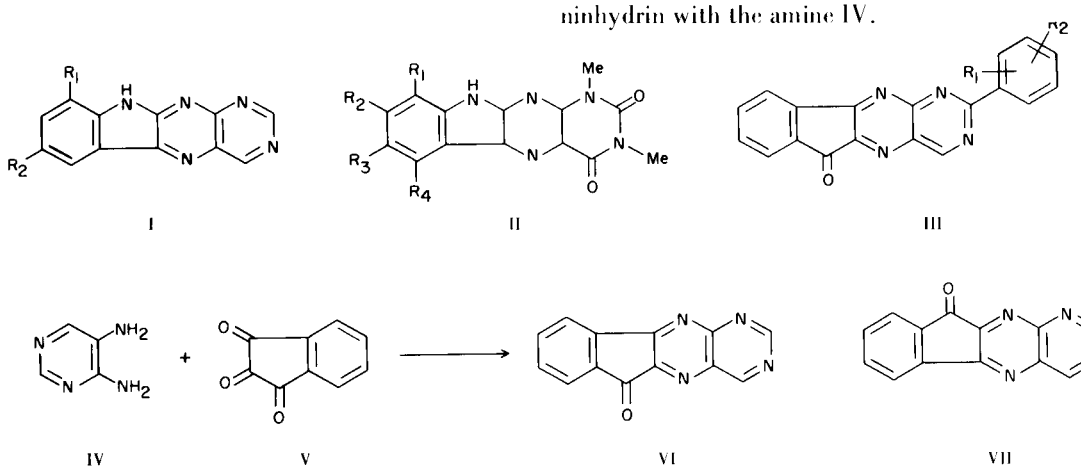
The condensation of indantrione monohydrate (ninhydrin) with *ortho*-diamines derived from pyridine and pyrimidine led to the synthesis of several new indeno[2,1-*g*]pteridine derivatives. The structure of these compounds is discussed and their physical properties described.

The pteridine nucleus is present in the molecule of a great number of natural substances (pigments, vitamine B, alloxazines, etc.), and nearly all of its derivatives are endowed with important biological properties. Thus, over the past ten years pteridine derivatives have aroused considerable interest among chemists and pharmacologists (1,2,3). The fact that a number of polycyclic nitrogen heterocycles, as for instance the "tricycloquinazolines" (4) or certain purines bases (5), exhibit carcinogenic properties, prompted us to investigate the condensation of aromatic or heterocyclic *ortho*-diamines (6) with a series of *ortho*-quinones, isatins or phthalonimides, and in this context we have already described (7) the synthesis and properties of several derivatives of 10*H*-indolo[3,2-*g*]-pteridine (I and II).

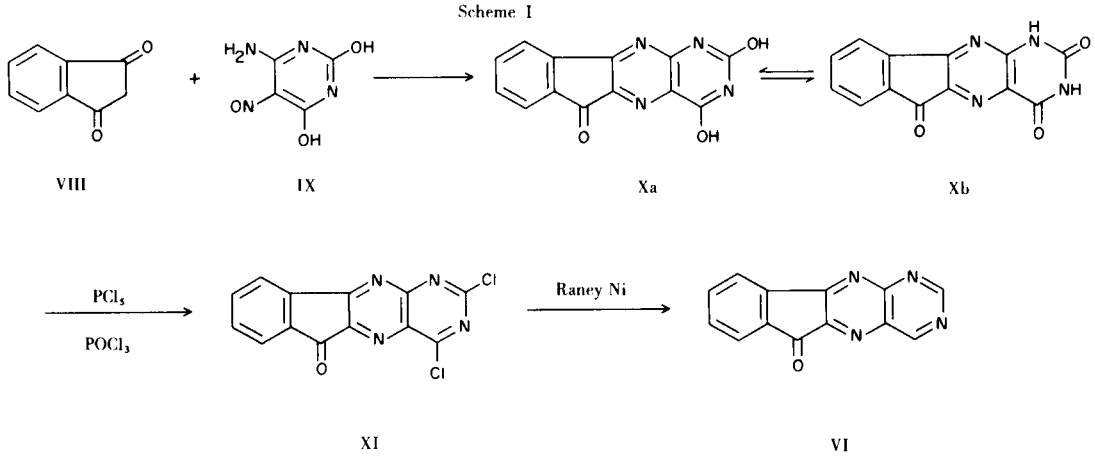
The present paper reports the synthesis and properties of several derivatives of 6*H*-indeno[2,1-*g*]pteridine obtained by the reaction of ninhydrin (indantrione monohydrate) with various *ortho*-diamines derived from pyridine or pyrimidine. Hitherto, only the 4-amino-2-phenyl-6*H*-indeno[2,1-*g*]pteridin-6-one (III) derivatives obtained from the reaction of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 1,3-indandione had been recorded in the literature (8).

When ninhydrin was reacted with an unsymmetrical *ortho*-diamine such as 4,5-diaminopyrimidine (IV), the condensation can lead *a priori* either to a mixture of two compounds (VI and VII), or to a single compound whose structure could correspond to one or other of the two possible formulas. Bearing in mind that the $-NH_2$ function in position 5 of the diamine IV has a greater basicity than the $-NH_2$ in position 4 (7), it can be expected that it is the former group that reacts preferentially with the most reactive carbonyl of indantrione, *i.e.* the carbonyl in position 2 (9).

Reaction of ninhydrin with 4,5-diaminopyrimidine furnished a single, homogenous product to which we assign structure IV rather than VII, for reasons described above. This structure was verified following the pathway elaborated in Scheme I. Timmis synthesis (11) applied to 1,3-indandione and 6-amino-2,4-dihydroxy-5-nitrosopyrimidine (IX) gives in an unequivocal way the compound Xa, which can of course exist in another tautomeric form Xb. The latter, on treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride, gives the dichloro derivative XI, which on hydrogenolysis in the presence of Raney nickel, gives 6*H*-indeno[2,1-*g*]pteridin-6-one, the same compound obtained by condensation of ninhydrin with the amine IV.



Scheme I



Similary, condensation of the triketone with, respectively, 2,3-diaminopyrimidine and 3,4-diaminopyrimidine resulted in deazapteridines to which we assign structures XII and XIII, since given the possibility of XIVa ⇋ XIVb and XVa ⇋ XVb resonance, the -NH_2 group in position 3 has a lower pK_a than the -NH_2 groups in position 2 or 4, hence a greater reactivity. Under the same conditions, 4,5,6-triamino-, 2,4,5,6-tetramino-, and 4,5,6-triamino-2-hydroxypyrimidine afforded compounds XVI, XVII, and XVIII, respectively.

With 4,5-diamino-6-hydroxy-2-mercaptopyrimidine, we obtained a compound crystallizing from a mixture of benzene-pyridine as brick red microprisms which, on heating toward 300°, lost the crystallization solvent and turned yellow. The absence of absorption bands towards the 3700-3500 cm^{-1} and 2600-2550 cm^{-1} regions (the absorption regions of hydroxyl and SH groups) in the infrared spectrum (potassium bromide disks) of this last compound and, in contrast, the presence of a fairly intense band at 3300 cm^{-1} and of another at 1700 cm^{-1}, corresponding to the -NH- and amide carbonyl group respectively, led us to formulate it as XIXa rather than the tautomeric XIXb.

Lastly, the reaction of ninhydrin with 4,5-diamino-1,3-dimethyluracil likewise afforded a single product to which, on similar grounds, we assign structure XX, for there again, it is the amino group in position 5 of 4,5-diaminouracil that displays the greatest activity (10).

All the compounds obtained showed similar characteristics; all were yellow or orange colored, and all had relatively high melting points.

EXPERIMENTAL

6*H*-Indeno[2,1-*g*]pteridin-6-one (VI).

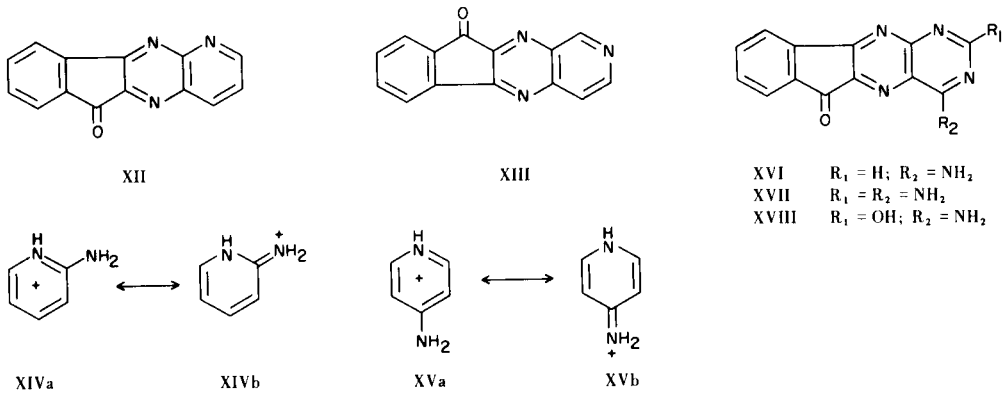
Method a.

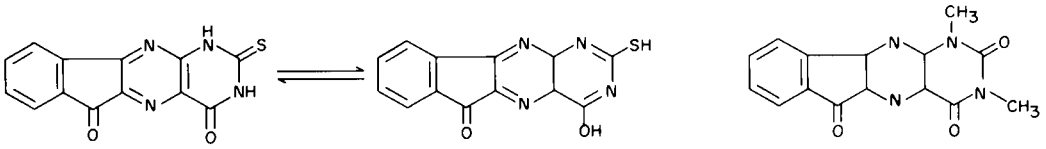
A solution of ninhydrin (1.78 g., 0.01 mole) and 4,5-diaminopyrimidine (1 g., 0.01 mole) in isobutyl alcohol (50 ml.) in the presence of a drop of glacial acetic acid was heated under reflux for 2 hours; on cooling, the precipitate obtained was dried, washed in alcohol, and recrystallized from ethanol, to give golden platelets (1.78 g.), m.p. 238°.

Anal. Calcd. for $C_{13}H_6N_4O$: C, 66.6; H, 2.5; N, 23.9. Found: C, 66.5; H, 2.7; N, 23.8.

Method b.

A mixture of XI (3.5 g.), potassium hydroxide (3.5 g.) and Raney nickel (3 g.) was suspended in absolute alcohol (150 ml.).





XIXa XIXb XX

Hydrogen was bubbled through the suspension under constant stirring for 6 hours at room temperature. After discarding a solid product, the filtrate was concentrated and chromatographed over alumina. Compound VI was obtained by elution with benzene-cyclohexane (1:1) and recrystallized from ethanol, golden platelets (0.6 g.), m.p. 238°.

6*H*-2,4-Dihydroxyindeno[2,1-*g*]pteridin-6-one (X).

A mixture of 6-amino-2,4-dihydroxy-5-nitrosopyrimidine (7.8 g.) and 1,3-indandione (6.6 g.) in glacial acetic acid (150 ml.) was heated for 24 hours at a temperature of 150-160° in the presence of a drop of concentrated hydrochloric acid. The precipitate formed after cooling was filtered, washed with water and crystallized from ethanol, to give scarlet crystals (5 g.), m.p. > 330°.

Anal. Calcd. for $C_{13}H_6N_4O_3$: C, 58.7; H, 2.3; N, 21.0. Found: C, 58.5; H, 2.1; N, 20.9.

6*H*-2,4-Dichloroindeno[2,1-*g*]pteridin-6-one (XI).

A mixture of X (5 g., 0.02 mole), phosphorus pentachloride (4.5 g., 0.022 mole) and phosphorus oxychloride (20 ml.) was refluxed for 24 hours. After cooling, the reaction mixture was added to ammonia in presence of crushed ice. The precipitate was filtered and recrystallized from ethanol to give maroon microcrystals (3.5 g.), m.p. >330°.

Anal. Calcd. for $C_{13}H_4Cl_2N_4O$: C, 51.5; H, 1.3; N, 18.5. Found: C, 51.3; H, 1.2; N, 18.3.

10*H*-Indeno[2,1-*b*]pyrido[4,3-*e*]pyrazin-10-one (XIII).

This compound was obtained by the same technique as for VI (method a) from 3,4-diaminopyridine, this compound crystallized as cream-yellow platelets from ethanol-benzene, m.p. 275° (sublimation >200°), yield, 80%.

Anal. Calcd. for $C_{14}H_7N_3O$: C, 72.1; H, 3.0; N, 18.0. Found: C, 71.9; H, 3.0; N, 17.9.

6*H*-Indeno[1,2-*b*]pyrido[4,3-*e*]pyrazin-6-one (XII).

This compound was obtained from 2,3-diaminopyridine and crystallized from xylene as bright yellow microcrystals, m.p. 305°, yield, 80%.

Anal. Calcd. for $C_{14}H_7N_3O$: C, 72.1; H, 3.0; N, 18.0. Found: C, 71.9; H, 3.1; N, 17.8.

6*H*-4-Aminoindeno[2,1-*g*]pteridin-6-one (XVI).

The ninhydrin and 4,5,6-triaminopyrimidine dissolved in pyridine in the presence of a drop of glacial acetic acid was heated under reflux for 3 hours; XVI crystallized from pyridine as orange microcrystals, m.p. >360°, yield, 65%.

Anal. Calcd. for $C_{13}H_7N_5O$: C, 62.7; H, 2.8; N, 28.1. Found: C, 62.5; H, 2.7; N, 27.9.

6*H*-2,4-Diaminoindeno[2,1-*g*]pteridin-6-one (XVII).

This compound was prepared from 2,4,5,6-tetraaminopyrimidine sulfate, which was sparingly soluble in the usual solvents (alcohols, pyridine, nitrobenzene, or acetic acid) even at the boiling point, was purified by sublimation *in vacuo* and formed orange-red microcrystals, m.p. >360°, yield 60%.

Anal. Calcd. for $C_{13}H_8N_6O$: C, 59.1; H, 3.1; N, 31.8. Found: C, 58.9; H, 3.3; N, 31.7.

6*H*-4-Amino-2-hydroxyindeno[2,1-*g*]pteridin-6-one (XVIII).

This compound was obtained from 4,5,6-triamino-2-hydroxypyrimidine sulfate. It crystallized from pyridine as orange microcrystals, m.p. >360°, yield, 50%.

Anal. Calcd. for $C_{13}H_7N_5O_2$: C, 58.9; H, 2.7; N, 26.5. Found: C, 58.7; H, 2.6; N, 26.3.

4,6-Dioxo-2-thio-1,2,3,4-tetrahydro-6*H*-indeno[2,1-*g*]pteridine (XIXa).

This compound was obtained from 4,5-diamino-6-hydroxy-2-mercaptopyrimidine. It crystallized from benzene-pyridine as brick red microprisms, which, on heating, lost the solvent and turned yellow, m.p. >360°, yield, 40%.

Anal. (yellow form) Calcd. for $C_{13}H_6N_4O_2S$: C, 55.3; H, 2.1; N, 19.8. Found: C, 55.3; H, 2.2; N, 19.5.

1,3-Dimethyl-2,4,5-trioxo-1,2,3,4-tetrahydro-6*H*-indeno[2,1-*g*]-pteridine (XX).

This compound was obtained from 4,5-diaminouracil and crystallized from ethanol-benzene in buttercup yellow microcrystals, m.p. 338°, yield, 50%.

Anal. Calcd. for $C_{15}H_{10}N_4O_3$: C, 61.0; H, 3.4; N, 19.0. Found: C, 60.8; H, 3.5; N, 19.2.

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