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THE SYNTHESIS OF UNSUBSTITUTED PHENANTHRO [2, 1-d] THIAZOLE

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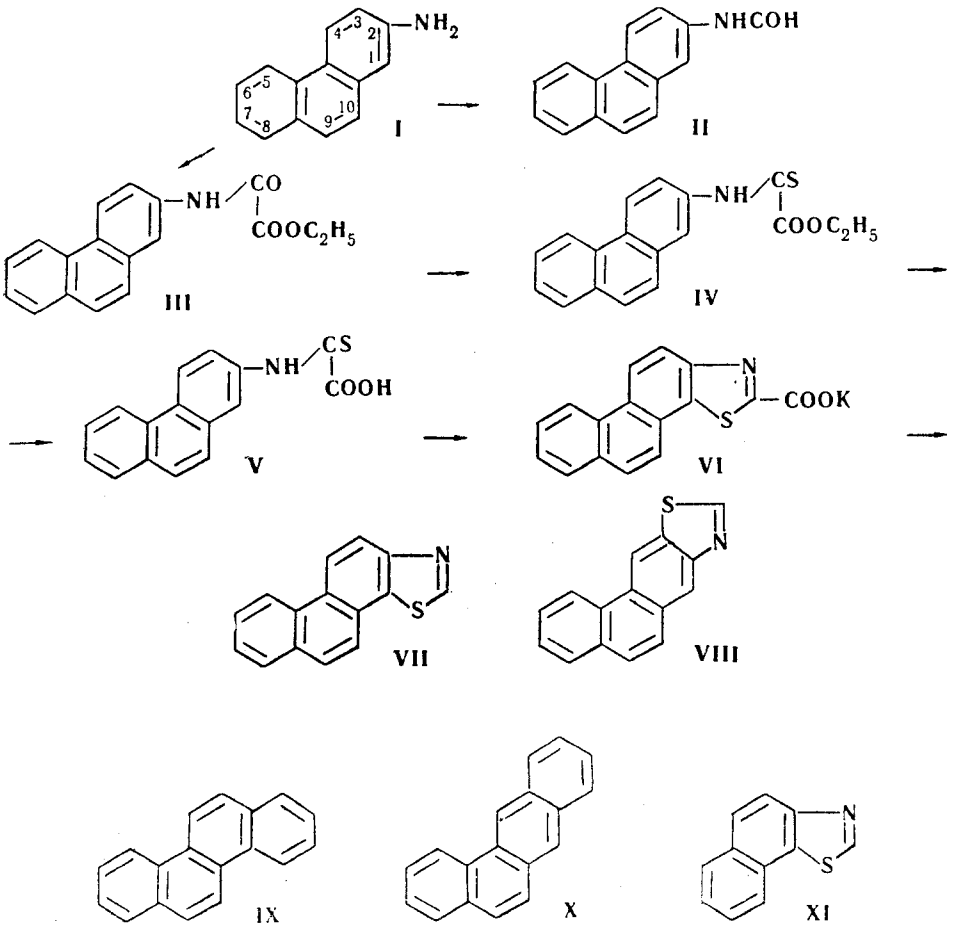
Phenanthro [2, 1-d] thiazole was obtained by the oxidative ring-closure of 2-phenanthrylthiooxamic acid to the corresponding phenanthrothiazole-2-carboxylic acid, which was then decarboxylated.

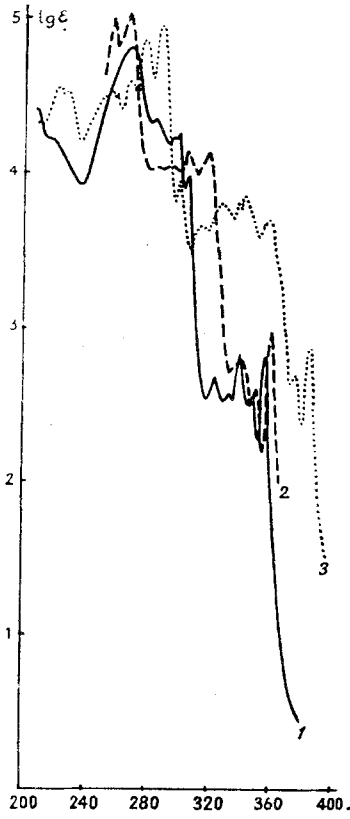
Among the polycyclic carcinogenic compounds, those with condensed aromatic and heterocyclic rings are of interest. It is known that some compounds of this type, for example those containing a thiophene ring, possess considerable carcinogenic activity [1]. Having decided to prepare some new compounds of this type in order to compare their chemical structure with their carcinogenic activity, we undertook the preparation of some phenanthrothiazoles and their derivatives.

The literature contains descriptions of the syntheses of phenanthrothiazoles with the thiazole ring in the 9, 10 position [2], or in positions 1, 2 and 3, 4, but containing additional acetoxy or hydroxy substituents in the phenanthrene nucleus [3]. We did not use these methods of synthesis, since it is known that the introduction of substituents into positions 9 and 10 of the phenanthrene nucleus results in a marked reduction in the carcinogenic activity of these derivatives, and that a similar effect is produced by the introduction of a hydroxyl group [1].

The starting material for the preparation of the unsubstituted phenanthrothiazole was 2-aminophenanthrene (I), which was obtained by known methods [4]. We intended originally to make use of the Jacobson procedure [5], which consists in cyclizing thioacylamino-compounds with potassium ferricyanide in alkaline solution. The requisite 2-formamidophenanthrene (II) was obtained by heating 2-aminophenanthrene with formic acid. However, attempts to convert compound II to the corresponding thioformyl derivative, either by boiling with phosphorus pentasulfude in toluene or xylene solution, or by heating a mixture of these reagents at 200° in absence of a solvent, were unsuccessful. This route was therefore abandoned, and we made use of a variant which had been used previously in the synthesis of naph-



thothiazoles [6]. Diethyl oxalate reacted with amine I to give ethyl 2-phenanthryloxamate (III), which was converted by phosphorus pentasulfide in ether to the ethyl thiooxamate (IV). The free acid (V) was submitted to oxidative cyclization by alkaline potassium ferricyanide to give potassium phenanthro [2,1-d] thiazole-2-carboxylate (VI), which on decarboxylation give phenanthro-[2,1-d] thiazole (VII). It will be realized that the cyclization of the thioacid V might also be expected to give the isomeric phenanthro [2,3-d] thiazole (VIII). However, only one product having the composition of a phenanthrothiazole was isolated from this reaction, and the given structure was supported by comparison of its absorption spectrum with those of chrysene (IX) and 1,2-benzanthracene (X). It will be seen from the figure that the spectral curve of our pehnanthrothiazole is much closer to the curve for chrysene than to that for benzanthracene, which suggests an angular structure such as that possessed by compound VII. In addition, cyclization of 2-naphthylthioxamic acid under the same conditions is known to result only in the formation of the angular naphtho [2,1-d] thiazole (XI). This close analogy makes it certain that in the present case the cyclization leads to the formation of the angular structure VII, and not the linear compound VIII. We hope to provide chemical evidence in support of this conclusion, in a forthcoming publication.



Absorption Spectra: 1) phenanthro [2, 1-d] thiazole; 2) chrysene; 3) 1,2-benzanthracene.

Microanalyses were carried out in the analytical laboratory of the Institute, under the supervision of A. D. Chinaeva. Spectrographic measurements were carried out in alcoholic solution, on an SF-4 instrument in the Peresleni laboratory of the Ordzhonikidze All-Union Scientific Research Chemical and Pharmaceutical Institute.

Experimental

2-Formamidophenanthrene (II). A mixture of 0.2 g of 2-aminophenanthrene and 1.5 ml of formic acid was boiled for 45 min, then water and formic acid were vacuum-distilled off on a water bath. A further 1.5 ml of formic acid was added to the residue, and again vacuum-distilled, to give 91% of colorless crystals, mp 191°–192° (from xylene). Found: C 80.97; H 5.32; N 6.85%. Calculated for $C_{15}H_{11}NO$: C 81.40; H 4.98; N 6.33%.

Ethyl-2-phenanthryloxamate (III). A mixture of 2.0 g (0.01 mole) of 2-aminophenanthrene and 4.0 g (0.027 mole) of dry diethyl oxalate was boiled under reflux for 1 hr. The reaction product, which began to separate while the mixture was being heated, was extracted from the cooled reaction mixture with boiling ethanol. The compound separated from the cooled ethanolic solution as colorless, lustrous plates, mp 164°–165°, yield 82%. Found: C 73.39; H 5.26; N 4.76%. Calculated for $C_{18}H_{15}NO_2$: C 73.72; H 5.12; N 4.77%.

Ethyl 2-phenanthrylthiooxamate (IV). Powdered phosphorus pentasulfide (0.8 g, 0.0036 mole) was added slowly with mechanical stirring to a solution of the ethyl ester III (0.8 g, 0.0027 mole) in dry xylene (150 ml) at the boil, and the reaction mixture boiled for 1.5 hr. The hot xylene solution was decanted from a small quantity of tar which was formed, the solvent vacuum-distilled off and the residue treated with hot chloroform. The compound separated on cooling as transparent orange rhombs with one molecule of solvent of crystallization, mp 148°–149° (in an open capillary). Found: C 56.29; H 3.90; S 7.42%. Calculated for $C_{18}H_{15}NO_2S \cdot CHCl_3$: C 56.01; H 3.73; S 7.47%.

Recrystallization from benzene gave transparent orange plates free from solvent of crystallization, mp 149°–150°, yield 56%. Found: C 69.67; H 4.88; S 10.30%. Calculated for $C_{18}H_{15}NO_2S$: C 69.90; H 4.85; S 10.35%.

2-Phenanthrylthiooxamic acid (V). Ester IV (0.15 g) was shaken for 2 hr with 60 ml of 10% NaOH. The solution was filtered from insoluble impurities, the filtrate acidified with hydrochloric acid, and the yellow precipitate which separated was extracted with ether. Removal of the solvent left the acid III in quantitative yield. Golden-yellow needles from benzene-petroleum ether, mp 196°–198°. Found: C 68.11; H 3.91; N 5.30; S 11.20%. Calculated for $C_{16}H_{11}NO_2S$: C 68.32; H 3.91; N 4.98; S 11.03%.

Phenanthro [2, 1-d] thiazole (VII). The crude ether IV (0.55 g) was shaken with 150 ml of 10% NaOH for 2 hr, the alkaline solution filtered and the filtrate treated gradually with stirring with a solution of potassium ferricyanide (3.25 g) in water (15 ml). After standing for 1 hr at room temperature, the salt VI which separated was filtered off,

washed with a small quantity of water, and boiled for 2 hr with 40 ml of 15% hydrochloric acid. The hot acid solution was filtered, the filtrate cooled, and neutralized with aqueous ammonia. The base which separated was dissolved in ether and the ethereal extract dried over Na_2SO_4. The residue after removal of the solvent was recrystallized from petroleum ether (bp 60°–80°) to give lustrous, colorless plates which coalesced to form needles, mp 192°–193°, yield 69%. Found: C 76.53; H 3.77; S 13.89%. Calculated for $C_{15}H_9NS$: C 76.59; H 3.83; S 13.61%. Picrate—yellow needles from ethanol, mp 229°–230°. Found: C 54.49; H 2.68; N 12.21%. Calculated for $C_{21}H_{12}N_4O_7S$: C 54.31; H 2.58; N 12.08%.

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