SOME SUBSTITUTED 4-AMINOTHIONAPHTHENO [3, 2-d] PYRIMIDINES

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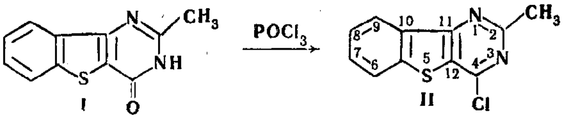
Boiling 2-methyl-4-oxo-3, 4-dihydrothionaphtheno[3, 2-d]-pyrimidine with phosphorus oxychloride gives 2-methyl-4-chlorothionaphtheno [3, 2-d]pyrimidine (II), in which the chlorine atom is mobile. Nucleophilic substitution of the mobile chlorine atom in compound II gives the 4-ethoxy, 4-(N-piperidino), 4-(N^4-methyl-N'-piperazino), 4-[2'-(diethylamino)ethylamino], 4-3'-(diethylamino)-2-hydroxypropylamino]substituted derivatives.

The thionaphtheno [3, 2-d] pyrimidine system can be regarded as consisting of benzothiophene and pyrimidine condensed together. Since benzothiophene possesses considerable biological activity, and pyrimidine derivatives enter into the composition of nucleic acids and other substances important to life, we were interested in the possibility of discovering biologically active compounds among derivatives of thionaphtheno [3, 2-d] pyrimidine, the more so since the latter is a thia-aza isostere of β-carboline, on which biologically active alkaloids, gramine, reserpine, and aimalitsin, etc., are based. As far as we have been able to ascertain, the literature describes only one compound with the thionaphtheno [3, 2-d] pyrimidine skeleton, 2-methyl-4-oxo-3, 4-dihydrothionaphtheno [3, 2-d] pyrimidine (I) [1].

As the basis of our work we took compound I, containing the group —CO—NH—, which we could convert to —CCl═N—, and transform to a fully aromatized system. Actually boiling I with phosphorus oxychloride gives a 56% yield of 2-methyl-4-chlorothionaphtheno [3, 2-d] pyrimidine (II):



The chlorine at position 4 has considerable mobility, and undergoes nucleophilic replacement when II is treated with sodium ethoxide, piperidine, piperazine, N-benzoyl- and N-methylpiperazine, 2-(diethylamino)-ethylamine, 3-(diethylamino)-1-hydroxypropylamine. The compounds prepared are being submitted for biological study, the results of which will be published later.

EXPERIMENTAL

2-Methyl-4-chlorothionaphtheno[3, 2-d]pyrimidine (II). A mixture of 19.5 g (0.09 mole) 2-methyl-4-oxo-3, 4-dihydrothionaphtheno [3, 2-d]pyrimidine [1], 195 ml $POCl_3$, and 19.5 ml diethylaniline was refluxed for 1 hr, almost all the $POCl_3$ vacuum-distilled off, the residue decomposed with ice, the yellowish-brown precipitate filtered off, washed first with Na_2CO_3 solution, then with water, and dried in a desiccator over H_2SO_4. Recrystallization from $CHCl_3$ using decolorizing charcoal gave 11.4 g (56%) II. Colorless crystals, insoluble in water, EtOH, acetone, but soluble in hot $CHCl_3$, mp 173°–175°. Found: C 56.3; H 3.1; Cl 15.4; N 12.0; S 13.7%. Calculated for $C_{11}H_7ClN_2S$: C 56.3; H 3.0; Cl 15.1; N 11.9; S 13.7%.

2-Methyl-4-ethoxythionaphtheno[3, 2-d]pyrimidine. 0.5 g (2.1 mole) II was introduced into 2.4 ml NaOEt solution (0.5 g Na and 20 ml EtOH), a further 10 ml EtOH added, and the whole refluxed for 4 hr. The precipitate of NaCl was removed by filtration, the filtrate diluted with water, and the resultant precipitate recrystallized from 25 ml EtOH, using decolorizing charcoal, to give 0.2 g (42.5%), of well-formed long acicular crystals, insoluble in water, soluble in EtOH, ether, acetone, and $CHCl_3$, mp 112°–114°. Found: N 12.0%. Calculated for $C_{13}H_{12}N_2OS$: N 11.5%.

2-Methyl-4-(N-piperidino)thionaphtheno[3, 2-d]pyrimidine. 0.5 g (2.1 mmole) II, 0.4 g (4.7 mmole) piperidine, and 10 ml EtOH were heated together for 1 hr 30 min at 60°–65°, when everything dissolved. The EtOH was distilled off, the residue treated with water, filtered off, washed with water, and air-dried, yield 0.63 g, recrystallized from 3 ml 90% EtOH, using decolorizing charcoal, to give 0.46 g (69.5%) finely crystalline powder, insoluble in water, but soluble in EtOH, ether, and acetone, mp 113°–114°, (swells). Found: N 14.6; H_2O 3.4%. Calculated for $C_{16}H_{17}N_3 \cdot 0.5H_2O$: N 14.8; H_2O 3.1%.

2-Methyl-4-(4'-benzoylpiperazine)thionaphtheno[3, 2-d]pyrimidine (III). 2.8 g (12 mmole) II was condensed with 5 g (26 mmole) benzoylpiperidine in 84 ml boiling EtOH, reaction time 1 hr. Everything dissolved, half the EtOH was distilled off, the residue diluted with water, the crystalline precipitate filtered off, and washed with water, then with ether, and air-dried. Weight 4.15 g (90%), mp 146°–149°.

2-Methyl-4-(N-piperazino)thionaphtheno[3, 2-d]pyrimidine (IV). 5.67 g of the crude III prepared above was refluxed for 4 hr 30 min with 300 ml 2 N HCl, i. e. until everything dissolved. The products were decolorized with charcoal, cooled, benzoic acid extracted with ether (1.14 g benzoic acid was recovered from the ether solution), the aqueous layer vacuum-evaporated off, and the residue recyrstallized from 90% EtOH, using decolorizing charcoal. Yield of IV hydrochloride 3.25 g (57%), mp 253°–256° (decomp). Found: Cl 17.5; H_2O 9.1%. Calculated for $C_{15}H_{16}N_4S \cdot 2HCl \cdot 2H_2O$: Cl 18.0; H_2O 9.2%.

Base IV. 0.5 g (1.2 mmole) IV dihydrochloride was dissolved in 2 ml water, and 0.5 ml ammonia solution added. On standing the oil which separated out crystallized, it was removed, washed with water, and dried, weight 0.35 g (96%), mp 138°–141°; picrate fine yellow needles, mp 258°–260° (ex 50% EtOH; decomp). Found: N 19.2%. Calculated for $C_{15}H_{16}N_4S \cdot C_6H_3N_3O_7$: N 19.1%.

2-Methyl-4-(4'-methylpiperazino)thionaphtheno[3, 2-d]pyrimidine. 1.5 g (15 mmole) N-methylpiperazine was refluxed with 2.5 g (11 mmole) II and 2.5 g (25 mmole) Et_3N in 50 ml EtOH, for 1 hr, after which 100 ml hot water was added, and after keeping in a refrigerator, the precipitate was filtered off, washed with water, dried, and recrystallized from 24 ml of 50% EtOH. Yield 1.5 g mp 111°–112°, readily soluble in EtOH, ether, and $CHCl_3$. Found: C 61.4; H 6.2; S 10.3%. Calculated for $C_{16}H_{18}N_4S \cdot H_2O$: C 61.0; H 5.8; S 10.0%.

Dihydrochloride. 3 g of the crude base in 25 ml EtOH was treated with 4 ml concentrated HCl, the viscous precipitate formed separated off, washed with EtOH, and recrystallized from 120 ml 90% EtOH, to give 3 g compound mp 272°–280° (decomp). Found: Cl 17.3%. Calculated for $C_{16}H_{18}N_4S \cdot 2HCl \cdot 2H_2O$: Cl 17.4%. Colorless minute crystals, readily soluble in water, sparingly soluble in water, sparingly soluble in EtOH.

2-Methyl-4-[2'-(diethylamino)ethylamino]thionaphtheno[3, 2-d] pyrimidine. Similarly to the above, 2.5 g (11 mmole) II and 3 g

(26 mmole) 2-(diethylamino)ethylamine in 50 ml EtOH gave 3.25 g crude base, 0.5 g of which after recrystallizing from 4 ml EtOAc+ +petrol ether (1:1) gave 0.3 g (60%) mp 112°-114° (Kofler). Found: C 64.8; H 6.9; S 10.2%. Calculated for $C_{17}H_{22}N_4S$: C 65.0; H 6.9; S 10.5%. White well-defined prisms, readily soluble in EtOH, $CHCl_3$, less soluble in ether and EtOAC.

Dihydrochloride. 2.75 g crude base was dissolved in 40 ml EtOH, decolorized with charcoal, filtered, and the filtrate made acid to Congo Red with HCl. A flaky precipitate was formed, filtered off, washed with EtOH, and dried. Yield 2.86 g mp 258°-260°, after recrystallizing from 25 ml 75% EtOH it had mp 268°-270°. Found: Cl 17.7; H_2O 4.2%. Calculated for $C_{17}H_{22}N_4S \cdot 2HCl \cdot H_2O$: Cl 17.6; H_2O 4.5%.

2-Methyl-4-[3'-(diethylamino)-2-hydroxypropylamino]thionaphtheno[3,2-d]-pyrimidine. Proceeding in a way similar to that described above, 3-diethylamino-2-hydroxypropylamine was condensed with II in ethanol. Mp 113°-116° (ex EtOAc+petrol ether, then from petrol ether). Found: C 62.9; H 6.7; S 9.2%. Calculated for C_1 H_2 N $C_{18}H_{24}N_4OS$: C 62.8; H 7.0; S 9.3%. White crystalline powder, readily soluble in EtOH, ether, and $CHCl_3$, slightly soluble in petrol ether. Dihydrochloride. This was prepared similarly to that described above. The precipitate of dihydrochloride was dissolved in MeOH, treated with decolorizing charcoal, the filtrate diluted with acetone, the crystalline precipitate filtered off, and dried in a desiccator. Mp 256°-260°. Found: Cl 16.6%. Calculated for $C_{18}H_{24}N_4OS \cdot 2HCl \cdot 0.5H_2O$: Cl 16.6%.

REFERENCE

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