[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XVIII. DERIVATIVES OF 4-PYRIMIDONE

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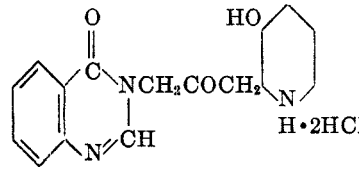
Received August 4, 1952

4-Quinazolone, the aromatic moiety of the Hydrangea alkaloid (I), may be regarded as a 4-pyrimidone substituted on the 5 and 6 positions. In order to



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investigate whether or not other 5,6-substituted pyrimidones, such as XI, would have desirable properties as antimalarials, the syntheses of a series of compounds of this type were initiated. As a class these compounds were unsatisfactory since the most active member of the series, the 5-phenyl derivative, XIa, had a low quinine coefficient of about 3 and the general method of synthesis (1) failed in many cases.[1]

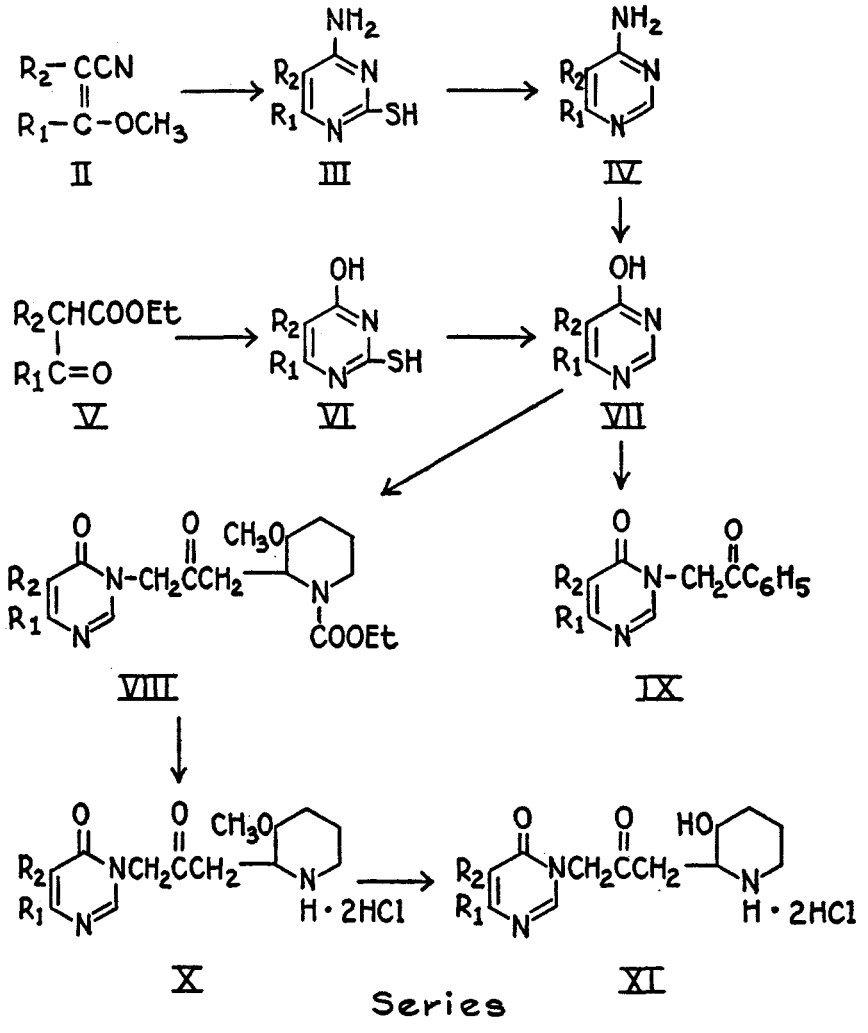
Two types of substituents have been placed on the 5-position, aryl and alkyl. The aryl derivatives were synthesized from α-aryl-β-alkyl-β-methoxyacrylonitriles (II), readily obtainable from the appropriate benzyl cyanide (2), by condensation with thiourea to the 2-mercapto-4-aminopyrimidines (III). Desulfurization with hydrogen peroxide proceeded smoothly to the 4-aminopyrimidines (IV) and hydrochloric acid hydrolysis gave the desired 4-pyrimidols (VIIa, b, and c). The intermediate, IVa, was prepared from benzyl cyanide, formamide, and ammonia at 170° according to a method recently described (3).

The 5-alkyl derivatives were synthesized by condensation of an appropriately substituted β-keto ester (V) with thiourea to the 2-mercapto-4-pyrimidols (VI) followed by hydrogen peroxide desulfurization to the pyrimidols (VIId, e, and f), a method of synthesis described for 5,6-dimethyl-4-pyrimidol (4). Both 5-aryl- and 5-alkyl-4-pyrimidols could be alkylated by treatment of their sodium salts with phenacyl bromide as shown by the formation of IXa and IXf[2] from 5-phenyl-4-pyrimidol (VIIa) and 5,6,7,8-tetrahydro-4-quinazolone (VIIf), respectively.

Alkylation of the 4-pyrimidols (VII) with the blocked alkaloid side chain, 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine (5), gave non-crystalline condensation products (VIII). Hydrolysis of these crude products with hydro-

[1] The biological data will be reported elsewhere by Dr. R. Hewitt and co-workers of these Laboratories.

[2] It is possible, though unlikely, that the phenacyl group entered the 1-position of the 4-pyrimidol. No second alkylation product could be isolated, contrasting to the products obtained by methylation of 5-phenyl-4-pyrimidol (VIIa) (3).



chloric acid (1) gave crystalline dihydrochlorides only in two cases, Xa and Xb. These were further hydrolyzed with 48% hydrobromic acid to give the desired analogs, XIa and b, of the Hydrangea alkaloid. Thus the method of synthesis was successful only when R_2 was an aryl group and failed in every case when R_2 was an alkyl group.

Acknowledgement: The authors wish to thank Mr. L. Brancone and staff for the microanalyses and Messers W. McEwen, J. Poletto, and L. Binovi for large scale preparation of some of the intermediates.

EXPERIMENTAL

2-Mercapto-4-amino-5-p-chlorophenyl-6-methylpyrimidine (IIIb). A solution of 11.8 g. of 2-*p*-chlorophenyl-3-methoxycrotononitrile (IIb) (2), 6.6 g. of thiourea, and 4.6 g. of sodium methoxide in 100 cc. of absolute alcohol was refluxed on the steam-bath for two hours, then diluted with 300 cc. of water. The solution, clarified by filtration, was acidified with acetic acid to give 11.9 g. (84%) of product, m.p. 325° dec. In a pilot run the yield was 95% (2.3 g.), m.p. 325° dec. Recrystallization of a sample from Methyl Cellosolve with the aid of Norit gave white crystals, m.p. 334° dec.

Anal. Calc'd for $C_{11}H_{10}ClN_3S$: C, 52.5; H, 3.98; N, 16.7.

Found: C, 52.6; H, 4.24; N, 16.6.

In the same manner condensation of 13.5 g. of IIc with 7.1 g. of thiourea gave 13.2 g. (82%) of *2-mercapto-4-amino-5-p-chlorophenyl-6-ethylpyrimidine* (IIIc), m.p. 320° dec. Recrystallization as above gave white crystals, m.p. 330° dec.

Anal. Calc'd for $C_{12}H_{12}ClN_3S$: C, 54.3; H, 4.53; N, 15.8.

Found: C, 54.0; H, 4.70; N, 15.5.

2-Mercapto-5,6,7,8-tetrahydro-4-quinazolone (VIf). A solution of 20 g. of 2-carbethoxycyclohexanone and 14.5 g. of thiourea in 100 cc. of absolute alcohol containing 10 g. of sodium methoxide was refluxed and stirred on the steam-bath for two hours during which the sodium salt of the product separated. The reaction mixture was worked up as described for IIIb; yield, 15.3 g. (67%), m.p. 314–317° dec. Recrystallization of a sample from methanol afforded white crystals, m.p. 315–317° dec.

Anal. Calc'd for $C_8H_{10}N_2OS$: C, 52.7; H, 5.50; N, 15.4.

Found: C, 52.6; H, 5.65; N, 15.4.

Similarly, 27.5 g. of ethyl benzylacetoacetate and 14.5 g. of thiourea gave 19.5 g. (67%) of *2-mercapto-5-benzyl-6-methyl-4-pyrimidol* (VIe), m.p. 254–255°. Recrystallization from methanol afforded white crystals, m.p. 256–257°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: C, 62.1; H, 5.17; N, 12.1.

Found: C, 62.1; H, 5.34; N, 12.2.

From 24.6 g. of ethyl *n*-propylacetoacetate and 16.6 g. of thiourea in the same fashion was obtained 17.1 g. (65%) of *2-mercapto-5-n-propyl-6-methyl-4-pyrimidol* (VId), m.p. 206–208°. Chi and Chang (6) recorded a yield of 56% and m.p. 209°.

4-Amino-5-p-chlorophenyl-6-methylpyrimidine (IVb). To 85 cc. of 12% hydrogen peroxide heated to 90° was added with stirring 10 g. of IIIb in portions over a period of ten minutes. The mixture was stirred at 90° for one hour when most of the material had dissolved. The cooled solution was decanted from some insoluble gum, then made basic with 10% sodium hydroxide with cooling. The hydrated product was collected and washed with water; yield, 8.0 g. (91%), m.p. 121° (gas). After being dried *in vacuo* at 80°, a sample melted at 131–133°. Recrystallization of a sample from 50% methanol gave hydrated white crystals, m.p. 122–123° (gas), which melted at 141–142° when dried at 80° (1 mm.).

Anal. Calc'd for $C_{11}H_{10}ClN_3$: C, 60.2; H, 4.56; N, 19.1.

Found: C, 60.0; H, 4.78; N, 19.2.

Similarly, peroxide oxidation of 10.5 g. of IIIc gave 8.4 g. (91%) of crude *4-amino-5-p-chlorophenyl-6-ethylpyrimidine* (IVc), as hydrated crystals, m.p. 98–99° (gas). For analysis the compound was best purified by conversion to the hydrochloride by solution in absolute alcoholic hydrogen chloride and addition of ether; white crystals, m.p. 299–300° dec. Recrystallization in the same fashion raised the m.p. to 310° dec.

Anal. Calc'd for $C_{12}H_{12}ClN_3 \cdot HCl$: N, 15.5. Found: N, 15.4.

The hydrochloride was quantitatively converted to the *free base*, m.p. 140–142°, by solution in water and addition of sodium carbonate. Recrystallization from dilute methanol gave white crystals, m.p. 141–142°.

Anal. Calc'd for $C_{12}H_{12}ClN_3$: C, 61.6; H, 5.18; N, 18.0.

Found: C, 61.1; H, 5.45; N, 18.0.

5-p-Chlorophenyl-6-methyl-4-pyrimidol (VIIb). A solution of 6.8 g. of IVb in 35 cc. of

12 *N* hydrochloric acid was refluxed 22 hours, then evaporated to dryness *in vacuo*. The residue was dissolved in 50 cc. of water by the addition of 10% aqueous sodium hydroxide. The solution was clarified with Norit and acidified to *p*H 4 with acetic acid. The product was collected and washed with water; yield, 4.2 g. (62%), m.p. 220–222°. Recrystallization from 50% methanol with the aid of Norit gave white crystals, m.p. 236–237°.

Anal. Calc'd for $C_{11}H_9N_2O$: C, 59.8; H, 4.08; N, 12.7.

Found: C, 59.5; H, 4.19; N, 12.9.

5-p-Chlorophenyl-6-ethyl-4-pyrimidol (VIIc). A solution of 6.0 g. of crude IVc (m.p. 98–99°) in 35 cc. of 12 *N* hydrochloric acid was refluxed for 18 hours during which the hydrochloride of the product separated. This salt was removed by filtration on a glass filter from the cooled mixture and washed with 12 *N* hydrochloric acid. No additional crystalline product could be isolated from the filtrate. A solution of the hydrochloride in 30 cc. of 10% sodium hydroxide was clarified with Norit, then acidified with acetic acid; yield, 3.2 g. (53%), m.p. 262–264°. Recrystallization of a sample from methanol with the aid of Norit gave white crystals, m.p. 271–271.5°.

Anal. Calc'd for $C_{12}H_{11}ClN_2O$: C, 61.4; H, 4.73; N, 11.9.

Found: C, 61.5; H, 4.80; N, 11.9.

5,6,7,8-Tetrahydro-4-quinazolone (VIIf). To 16.3 cc. of 12% hydrogen peroxide heated to 80° was added portionwise with stirring 15.3 g. of VIf at such a rate that the temperature was 80–90°. After being stirred an additional 15 minutes at 85°, the solution was concentrated to about one-third *in vacuo*, made just alkaline with sodium carbonate, saturated with salt, and extracted with three 100-cc. portions of chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo* leaving 10 g. (79%) of white solid, m.p. 150–153° with softening at 143°. Two recrystallizations from ethyl acetate raised the m.p. to 162–164°.

Anal. Calc'd for $C_8H_{10}N_2O$: C, 64.0; H, 6.66; N, 18.7.

Found: C, 64.1; H, 7.00; N, 18.9.

Similarly, oxidation of 3.8 g. of VIe with 32 cc. of 12% hydrogen peroxide at 90–95° (there was no reaction at 80°) gave 2.7 g. of *5-benzyl-6-methyl-4-pyrimidol* (VIIe), m.p. 142–145°. Recrystallization from ethyl acetate afforded white crystals, m.p. 157–158°.

Anal. Calc'd for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.00; N, 14.0.

Found: C, 72.0; H, 6.15; N, 14.1.

Oxidation of 6.0 g. of VId with 65 cc. of 12% hydrogen peroxide at 70–85° gave 4.1 g. of crude *5-n-propyl-6-methyl-4-pyrimidol* (VIId). Recrystallization from heptane by decanting the hot solution from some insoluble gum gave 3.1 g. (63%) of product, m.p. 106–109°. Further recrystallization from petroleum ether (20–40°) containing a little ethyl acetate formed white crystals, m.p. 115–116°.

Anal. Calc'd for $C_8H_{12}N_2O$: C, 63.1; H, 7.90; N, 18.4.

Found: C, 63.3; H, 7.74; N, 18.3.

3-Phenacyl-5,6,7,8-tetrahydro-4-quinazolone (IXf). To a solution of 2.0 g. of VIIf in 13.5 cc. of 1 *N* methanolic sodium methoxide was added a solution of 2.92 g. of phenacyl bromide in 29 cc. of methanol. After one hour the solution was diluted with 120 cc. of iced water and 30 cc. of 10% sodium hydroxide. A gum separated from the solution and the whole was extracted with three 50-cc. portions of chloroform. The combined dried extracts were evaporated to dryness *in vacuo*. Trituration of the nearly solid residue with 20 cc. of methanol afforded 2.2 g. (62%) of product, m.p. 171–173°. Recrystallization from 66% methanol afforded white crystals of unchanged m.p.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 5.97; N, 10.5.

Found: C, 71.7; H, 6.25; N, 10.6.

Similarly, reaction of 2.29 g. of 5-phenyl-4-pyrimidol (3) with phenacyl bromide gave 2.6 g. (67%) of *3-phenacyl-5-phenyl-4-pyrimidone* (IXa)[2], m.p. 137–139°. Recrystallization from methanol afforded white crystals, m.p. 142–144°.

Anal. Calc'd for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.83; N, 9.65.

Found: C, 74.7; H, 4.97; N, 9.67.

3-[β-Keto-γ-(3-methoxy-2-piperidyl)propyl]-5-phenyl-4-pyrimidone dihydrochloride (Xa). Condensation of 5.8 g. of 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine (5) with the sodium salt of 2.94 g. of VIIa in methanol as described for 4-quinazolone (5) gave 5.2 g. of crude VIIIa as a gum. Hydrochloric acid hydrolysis (1, 5) gave 0.23 g. (3.2%) of the desired product as white crystals, m.p. 210–211° dec.

Anal. Calc'd for $C_{19}H_{23}N_3O_3 \cdot 2HCl$: C, 55.0; H, 6.04; N, 10.1.
Found: C, 54.8; H, 6.49; N, 10.2.

Similarly, 2.82 g. of VIIb gave 0.52 g. (8.8%) of *3-[β-keto-γ-(3-methoxy-2-piperidyl)propyl]-5-p-chlorophenyl-6-methyl-4-pyrimidone dihydrochloride* (Xb) as white crystals, m.p. 214°dec.

Anal. Calc'd for $C_{20}H_{24}ClN_3O_3 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 50.9; H, 5.76; N, 8.90.
Found: C, 51.0; H, 5.92; N, 8.67.

The respective derivatives of VII failed to give crystalline Xc, d, e, or f by the above conditions.

3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-5-phenyl-4-pyrimidone dihydrochloride (XIa). Hydrobromic acid hydrolysis (5) of 745 mg. of Xa gave 190 mg. (26%) of product, m.p. 190° dec.

Anal. Calc'd for $C_{18}H_{21}N_3O_3 \cdot 2HCl$: C, 54.0; H, 5.75; N, 10.5.
Found: C, 53.7; H, 6.14; N, 10.6.

3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-5-p-chlorophenyl-6-methyl-4-pyrimidone dihydrochloride (XIb). Hydrobromic acid hydrolysis (5) of 500 mg. of Xb gave 220 mg. (45%) of white crystals from absolute alcoholic hydrogen chloride and ether, m.p. 135° dec.

Anal. Calc'd for $C_{19}H_{22}ClN_3O_3 \cdot 2HCl \cdot 1\frac{1}{2}H_2O$: C, 48.0; H, 5.71; N, 8.81.
Found: C, 48.1; H, 5.71; N, 8.29.

SUMMARY

The syntheses of two analogs of the Hydrangea alkaloid with the 4-quinazolone moiety replaced by 5-aryl-4-pyrimidones have been described.

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