

Inhibitors of Platelet Aggregation. 4. [1,2,5]Thiadiazolo[3,4-c]acridines, 7,8,9,10-Tetrahydro[1,2,5]thiadiazolo[3,4-c]acridines, and 8,9-Dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinolines (I)

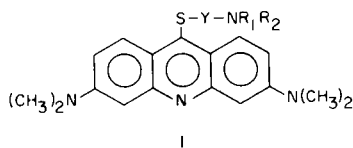
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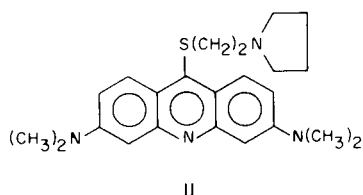
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The condensation of 4-amino-2,1,3-benzothiadiazole (IV) with diphenyliodonium-2-carboxylate gave *N*-(2,1,3-benzothiadiazol-4-yl)anthranilic acid (V) (28%), which was cyclized with phosphorus oxychloride to 6-chloro[1,2,5]thiadiazolo[3,4-c]acridine (VI) (84%). Treatment of VI with 3-(dimethylamino)-1-propanethiol hydrochloride in phenol afforded 6-[[3-(dimethylamino)propyl]thio][1,2,5]thiadiazolo[3,4-c]acridine (VII) (65%). The reaction of IV with a mixture of methyl and ethyl 2-oxocyclohexanecarboxylate gave the adduct, which was ring closed in Dowtherm to 7,9,10,11-tetrahydro[1,2,5]thiadiazolo[3,4-c]acridin-6(8*H*)one (VIII) (70%). Chlorination of VIII with phosphorus oxychloride gave 6-chloro-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-c]acridine (IX) (84%), which was condensed with 3-(dimethylamino)-1-propanethiol hydrochloride in phenol yielding 6-[[3-(dimethylamino)propyl]thio]-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-c]acridine (X) (27%). 6-[[3-(dimethylamino)propyl]thio]-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline (XIII) (25%) was prepared similarly from IV and a mixture of methyl and ethyl 2-oxocyclopentanecarboxylate *via* 7,8,9,10-tetrahydro-6*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinolin-6-one (XI) (85%) and 6-chloro-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline (XII) (56%). The effects of compounds VII-XIII as inhibitors of platelet aggregation are discussed.

Adenosine diphosphate (ADP) plays a key role in platelet aggregation and thrombosis (2-8), and it has been proposed that compounds active against ADP-induced platelet aggregation may prove to be useful for the prevention and treatment of thrombosis and embolism. In a recent communication from these laboratories (8), it was reported that certain 3,6-bis(dimethylamino)-9-[[di(alkylamino)alkyl]thio]acridines (I) and related sub-

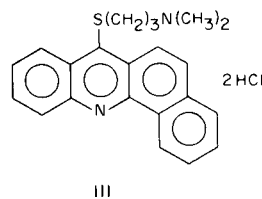


stances were potent inhibitors of ADP-induced platelet aggregation *in vitro* and in plasma from rabbits that had been treated with these substances. Moreover, 3,6-bis-



(dimethylamino)-9-[[2-(1-pyrrolidiny)ethyl]thio]acridine (II) also caused a significant increase in both primary and secondary bleeding time from a micropuncture wound in the mouse mesentery 4 and 24 hours after a single intravenous 10 mg./kg. dose (8).

To enable an assessment of the importance of the [(dialkylamino)alkyl]thio side-chain and the (dialkylamino)acridine moieties relative to the antithrombotic effects of the 9-[[di(alkylamino)alkyl]thio]-2- and 3-(dialkylamino)acridines (8), a variety of other [[di(alkylamino)alkyl]thio]heterocyclic compounds were subsequently prepared and evaluated as potential inhibitors of platelet aggregation (1). Although the overall results of the latter study suggest that a dialkylamino substituent on the heterocyclic moiety has a significant part in conferring optimal antithrombotic activity among various [[di(alkylamino)alkyl]thio]hetero-



cyclic compounds, it is noteworthy that 7-[[3-(dimethylamino)propyl]thio]benz[*c*]acridine dihydrochloride (III), which lacks a dialkylamino ring substituent, is nevertheless a fairly potent inhibitor of ADP-induced platelet aggregation *in vitro* and in plasma taken from rabbits treated with the drug.

The present communication, therefore, describes the synthesis of [1,2,5]thiadiazolo[3,4-*c*]acridine, 7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-*c*]acridine, and 8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline analogs of III. These ring systems are unknown based on a search of *Chemical Abstracts* and "The Ring Index" (9), and thus constitute novel heterocyclic nuclei.

Chemistry.

The synthetic approach utilized for the preparation of the [1,2,5]thiadiazolo[3,4-*c*]acridines and cyclopenta[*b*]-[1,2,5]thiadiazolo[3,4-*h*]quinolines is outlined in Scheme 1. The condensation of 4-amino-2,1,3-benzothiadiazole (IV) with diphenyliodonium-2-carboxylate in 2-propanol in the presence of cupric acetate gave *N*-(2,1,3-benzothiadiazol-4-yl)anthranilic acid (V) in 28% yield. Cyclization with phosphorus oxychloride afforded 6-chloro[1,2,5]thiadiazolo[3,4-*c*]acridine (VI) (84%), which upon heating with 3-(dimethylamino)propanethiol hydrochloride in phenol gave 6-[[3-(dimethylamino)propyl]thio][1,2,5]thiadiazolo[3,4-*c*]acridine (VII) in 65% yield.

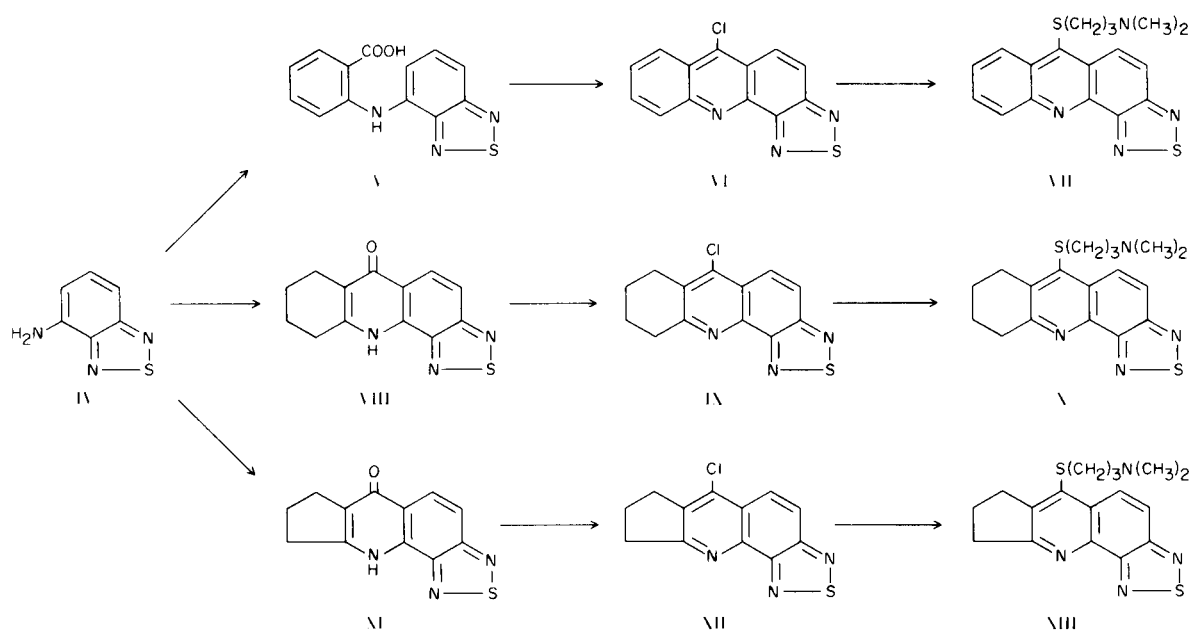
The condensation of 4-amino-2,1,3-benzothiadiazole (IV) with a mixture of methyl and ethyl 2-oxocyclohexanecarboxylate *in vacuo* provided the crystalline adduct,

which was ring-closed in refluxing Dowtherm A to give 7,9,10,11-tetrahydro[1,2,5]thiadiazolo[3,4-*c*]acridin-6(8*H*)one (VIII) (70%). Chlorination of VIII with phosphorus oxychloride yielded 6-chloro-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-*c*]acridine (IX) (84%), which was allowed to react with 3-(dimethylamino)-1-propanethiol hydrochloride to give 6-[[3-(dimethylamino)propyl]thio]-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-*c*]acridine (X) (27%). In like manner, IV was condensed with a mixture of methyl and ethyl 2-oxocyclopentanecarboxylate to give the crystalline adduct, which was ring closed to 7,8,9,10-tetrahydro-6*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinolin-6-one (XI) (85%). Chlorination of XI with phosphorus oxychloride then afforded 6-chloro-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline (XII) (56%), which was converted to 6-[[3-(dimethylamino)propyl]thio]-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline (XIII) in 25% yield by treatment with 3-(dimethylamino)-1-propanethiol hydrochloride. Spectral data (ir, uv, nmr) were in agreement with the structures shown for each of the fused thiadiazole derivatives.

Biological Results.

The [1,2,5]thiadiazolo[3,4-*c*]acridines, 7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-*c*]acridines, and 8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinolines VII through XIII were tested as inhibitors of ADP-induced platelet aggregation *in vitro* utilizing a modification (8) of the method of Born and Cross (5). Briefly, when ADP

SCHEME 1



is added to rabbit platelet-rich plasma (PRP) and the PRP is gently agitated, the individual platelets aggregate, or stick together, to form clumps. Each clump contains a large number of platelets. The consequent decrease in the number of particles in suspension causes a decrease in the optical density of the PRP. Compounds that inhibit platelet aggregation minimize or prevent this decrease in the optical density. Colorimetric measurements afford a quantitative measure of the amount of the platelets (5,8).

6-[[3-(Dimethylamino)propyl]thio][1,2,5]thiadiazolo[3,4-c]acridine (VII) produced 35% inhibition of platelet aggregation *in vitro* at a concentration of 10^{-5} M, but was less active than the 3,6-bis(dimethylamino)-9-[[dialkylamino]alkyl]thio]acridines (I, II) or 7-[[3-(dimethylamino)propyl]thio]benz[c]acridine dihydrochloride (III) reported previously (1,8). The drug lacked appreciable antithrombotic effects in rabbits at a dose of 25 mg./kg., intravenously. None of the other compounds (VIII-XIII) displayed significant inhibitory effects *in vitro* at concentrations ranging from 10^{-4} to 10^{-5} M.

EXPERIMENTAL (10)

N-(2,1,3-Benzothiadiazol-4-yl)anthranilic Acid (V).

4-Amino-2,1,3-benzothiadiazole (IV) (Aldrich) (30.0 g., 0.2 mole), diphenyliodonium-2-carboxylate (77.0 g., 0.24 mole), cupric acetate (1.5 g.), and 2-propanol (300 ml.) were heated at reflux under nitrogen for 24 hours. The reaction mixture was concentrated *in vacuo*, diluted with water, and made alkaline with sodium hydroxide. The mixture was washed with ether and the ether extracts were discarded. The alkaline mixture was filtered through Super-Cel and carefully acidified. The crude yellow-brown acid was collected by filtration (46.8 g., 87%), m.p. 184-198° dec. The product was triturated with several portions of ether and filtered. The combined ether extracts were concentrated *in vacuo*, and the residue was crystallized four times from dimethylformamide-water to give 5.8 g. of product, m.p. 232-235° dec. The residue from the ether extraction was crystallized successively from 2-propanol-water and dimethylformamide-water to give 9.4 g. m.p. 228-235° dec. Total yield, 15.2 g. (28%).

Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.56; H, 3.34; N, 15.49; S, 11.82. Found: C, 57.76; H, 3.31; N, 15.48; S, 11.79.

6-Chloro[1,2,5]thiadiazolo[3,4-c]acridine (VI).

N-(2,1,3-Benzothiadiazol-4-yl)anthranilic acid (V) (9.0 g., 0.033 mole) was added slowly with stirring to 90 g. of phosphorus oxychloride, and the mixture was gradually heated to reflux and was maintained at reflux for 4 hours. The reaction did not appear to be exothermic. The mixture was cooled and was poured into an excess of ammonium hydroxide, ice, and chloroform with vigorous stirring. When the hydrolysis of the phosphorus oxychloride was complete, additional chloroform was added, the mixture was shaken, and the layers were separated. The chloroform layer was washed with water, dried over anhydrous potassium carbonate, and the chloroform was removed *in vacuo*. The residue was crystallized from benzene to give 7.5 g. (84%) of product, m.p. 208-209°.

Anal. Calcd. for $C_{13}H_6ClN_3S$: C, 57.47; H, 2.23; S, 11.80. Found: C, 57.35; H, 2.42; S, 11.92.

6-[[3-(Dimethylamino)propyl]thio][1,2,5]thiadiazolo[3,4-c]acridine (VII).

A mixture of 3.5 g. (0.013 mole) of 6-chloro[1,2,5]thiadiazolo[3,4-c]acridine (VI), 2.5 g. (0.013 mole) of 80% 3-(dimethylamino)-1-propanethiol hydrochloride (Evans), and 15 g. of phenol was stirred and heated on a steam bath for 3 hours. The mixture was allowed to cool and was poured into 500 ml. of acetone with vigorous stirring. The crude hydrochloride salt was collected by filtration, dissolved in water, and the water solution was made strongly alkaline with 50% aqueous sodium hydroxide. The base was extracted with ether, and the combined ether extracts were washed with water and dried over anhydrous potassium carbonate. The ether was removed *in vacuo* and the residue was crystallized from acetonitrile to give 3.0 g. (65%) of fluffy yellow needles, m.p. 102-103°.

Anal. Calcd. for $C_{18}H_{18}N_4S_2$: C, 60.99; H, 5.12; N, 15.81. Found: C, 61.46; H, 5.03; N, 15.94.

7,9,10,11-Tetrahydro[1,2,5]thiadiazolo[3,4-c]acridin-6(8H)one (VIII).

4-Amino-2,1,3-benzothiadiazole (IV) (Aldrich) (15.1 g., 0.1 mole), a commercial mixture (Aldrich) containing 40% methyl 2-oxocyclohexanecarboxylate and 60% ethyl 2-oxocyclohexanecarboxylate (17.0 g., 0.104 mole), and one drop of concentrated hydrochloric acid were combined and kept in a vacuum oven at 54° for 5.5 days. The crude adduct was added to 200 ml. of refluxing Dowtherm A, and the mixture was heated under reflux for an additional 20 minutes. The crystalline mass that separated upon cooling was collected by filtration, washed thoroughly with ether, and dried. The yellow-brown crystals thus obtained (18.0 g., 70%) melted at 340-342°.

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.79; H, 4.06; N, 16.66.

6-Chloro-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-c]acridine (IX).

7,9,10,11-Tetrahydro[1,2,5]thiadiazolo[3,4-c]acridin-6(8H)one (VIII) (10.0 g., 0.039 mole) was cautiously added to 100 g. of phosphorus oxychloride and the mixture was heated under reflux for 16 hours. The mixture was worked up according to the procedure described for the preparation of 6-chloro[1,2,5]thiadiazolo[3,4-c]acridine (VI), and the product was obtained as beige crystals from acetonitrile, m.p. 147-148°. Yield, 9.0 g. (84%).

Anal. Calcd. for $C_{13}H_{10}ClN_3S$: C, 56.63; H, 3.66; N, 12.86. Found: C, 56.33; H, 3.76; N, 12.93.

6-[[3-(Dimethylamino)propyl]thio]-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-c]acridine (X).

Utilizing the procedure described for the preparation of 6-[[3-(dimethylamino)propyl]thio][1,2,5]thiadiazolo[3,4-c]acridine (VII), the reaction of 8.0 g. (0.029 mole) of 6-chloro-7,8,9,10-tetrahydro[1,2,5]thiadiazolo[3,4-c]acridine (IX) with 5.3 g. (0.029 mole) of 85% 3-(dimethylamino)-1-propanethiol hydrochloride (Evans) in 20 g. of phenol afforded 3.0 g. (27%) of product as beige crystals from *n*-heptane, m.p. 63-65°.

Anal. Calcd. for $C_{18}H_{22}N_4S_2$: C, 60.30; H, 6.19; N, 15.63. Found: C, 60.49; H, 6.05; N, 15.69.

7,8,9,10-Tetrahydro-6H-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinolin-6-one (XI).

To 30.2 g. (0.2 mole) of 4-amino-2,1,3-benzothiadiazole (IV) (Aldrich) and 31.2 g. (0.2 mole) of a commercial mixture (Aldrich) containing 50% methyl 2-oxocyclopentanecarboxylate and 50% ethyl 2-oxocyclopentanecarboxylate was added one drop of

concentrated hydrochloric acid, and the mixture was placed in a vacuum oven at 54° for 24 hours. The intermediate adduct solidified and 10.0 g. was recrystallized from cyclohexane (decolorizing charcoal) to give 7.0 g., m.p. 110-113°.

Anal. Calcd. for 50/50 CH₃/C₂H₅ mixture: C, 57.42; H, 5.00; N, 14.88. Found: C, 57.40; H, 4.89; N, 14.86.

The remainder of the crude adduct (52.0 g., 0.184 mole) was slowly added to 500 ml. of refluxing Dowtherm A, and the mixture was heated under reflux for 20 minutes and cooled. The crystals that separated were slurried with several portions of ether and dried. The olive colored product weighed 38.0 g. (85%), m.p. 247-250° dec.

Anal. Calcd. for C₁₂H₉N₃OS: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.45; H, 3.25; N, 17.45; S, 13.31.

6-Chloro-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]-quinoline (XII).

7,8,9,10-Tetrahydro-6*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinolin-6-one (XI) (20.0 g., 0.082 mole) was allowed to react with phosphorus oxychloride (200 ml.) and the reaction mixture was processed according to the procedure described for the preparation of 6-chloro[1,2,5]thiadiazolo[3,4-*c*]acridine (VI). The product was obtained (12.0 g., 56%) as pale yellow crystals from acetonitrile, m.p. 195.5-197°.

Anal. Calcd. for C₁₂H₈ClN₃S: C, 55.07; H, 3.08; Cl, 13.55; N, 16.06. Found: C, 55.20; H, 2.83; Cl, 13.41; N, 16.06.

6-[[3-(Dimethylamino)propyl]thio]-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline (XIII).

6-Chloro-8,9-dihydro-7*H*-cyclopenta[*b*][1,2,5]thiadiazolo[3,4-*h*]quinoline (XII) (7.0 g., 0.027 mole) and 85% 3-(dimethylamino)-1-propanethiol hydrochloride (Evans) (5.0 g., 0.027 mole) were condensed in 20 g. of phenol, and the product was worked up according to the procedure described for the preparation of 6-[[3-(dimethylamino)propyl]thio][1,2,5]thiadiazolo[3,4-*c*]acridine (VII). The product (2.3 g., 25%) was obtained as off-white

crystals from *n*-heptane, m.p. 65-67°.

Anal. Calcd. for C₁₇H₂₀N₄S₂: C, 59.27; H, 5.85; N, 16.26. Found: C, 59.50; H, 5.73; N, 16.27.

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