tropane methanesulfonate) in the same test was 4.3 mg./kg. (s.c.). The reported LD_{50} of benztropine is 55 mg./kg. (s.c.).[7] Compound XI, although less potent than benztropine, has a better therapeutic ratio in this test.

Experimental

2-Phenyl-1,4-benzothiazin-3(4H)-one.—A well-stirred solution of 325 g. (2.6 moles) of 2-aminobenzenethiol in 600 ml. of xylene was treated in one portion with a solution of 281 g. (1.3 moles) of α-bromophenylacetic acid[4] in 600 ml. of xylene. Cooling in a water bath was necessary to maintain the reaction temperature below 80°. After the exothermic reaction subsided, the mixture was heated to (and maintained at) 100° for 30 min. while 21 ml. of water distilled azeotropically from the reaction mixture. The latter was then heated at 137–142° for 1 hr. (during which time an additional 2 ml. of water was collected), cooled to room temperature and the precipitate filtered and washed with xylene. The air-dried solid (554 g.) was triturated with 1 l. of water to remove 2-aminobenzenethiol hydrobromide. It was suspended in 1 l. of 5% sodium bicarbonate and filtered to give 290 g. of product, m.p. 198–204°. After trituration with 1 l. of cold acetonitrile, the colorless product weighed 285 g. (91%) and melted at 202–204°. Crystallization from ethanol raised the m.p. to 205–206° (reported[3] m.p. is 204°), λ_{max}^{Nujol} 3.15, 5.95 μ.

4-(2-Diethylaminoethyl)-2-phenyl-1,4-benzothiazin-3(4H)-one Hydrochloride (I).—A slurry of 50.0 g. (1.28 moles) of sodamide in 3 l. of toluene was treated with 300 g. (1.24 moles) of the above material (m.p. 202–204°) in one portion; the mixture was stirred and refluxed for 1 hr., cooled and treated with 200 g. (1.48 moles) of 2-diethylaminoethyl chloride [b.p. 50–55° (30 mm.)]. The resulting solution was stirred at room temperature for 30 min., refluxed for 3 hr., cooled and treated with 300 ml. of water. The layers were separated and the organic phase washed with 100 ml. of water; the aqueous layer was discarded and the organic phase then extracted with 900 ml. of 2 *N* hydrochloric acid. The acidic aqueous phase was cooled and treated with 400 ml. of 20% NaOH solution to liberate the base. The mixture was extracted 5 times with 600 ml. portions of ether and the combined ether phase dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to give 374 g. of a yellow-orange liquid; b.p. 200–210° (0.5 mm.). A solution of this material in 200 ml. of ethanol was treated with the equivalent quantity of hydrogen chloride in 200 ml. of ethanol and the resulting solution diluted to 2 l. with ether to give a crystalline product weighing 394 g., m.p. 158–175°. This material was triturated with 800 ml. of acetonitrile and filtered to give 380 g. (81%) of a colorless product; m.p. 173–175°, λ_{max}^{Nujol} 3.78, 5.95 μ. Recrystallization of this material from acetonitrile did not change the melting point.

Acknowledgment.—The authors are indebted to Dr. Bernard Rubin and Mr. Jack High for the pharmacological data, to Miss Barbara Keeler for interpretation of the infrared spectra, and to Mr. Joseph Alicino and his associates for the analyses reported herein.

Antiviral Activity of 2,2-Dichloro-4′-formylacetanilide Thiosemicarbazone

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Received February 27, 1962

Hamre and her associates[2] first reported the antivaccinial activity of 4′-formylacetanilide thiosemicarbazone (I), and this activity was confirmed by Thompson and co-workers.[3] Because substitution of a dichloroacetyl group on an amino group of certain drugs leads to an enhancement of their activity, it was decided to prepare and test a sample of the title compound (II), for comparison of its properties with those of I.

By deacetylation of 4′-formylacetanilide (III), *p*-aminobenzaldehyde (IV) was obtained. This preparation is given in some detail because, although IV (which polymerizes with ease) has been described repeatedly in the literature, no satisfactory method for its preparation and preservation could be found therein. Compound IV then was acylated with dichloroacetyl chloride to give 2,2-dichloro-4′-formylacetanilide (V), which was condensed with thiosemicarbazide, affording II in quantitative yield.

In tests for antiviral activity, compound II was found to be about as active as I *versus* vaccinia (see Table I). Both compounds were inactive *versus* four other viruses in mice.

Experimental

***p*-Aminobenzaldehyde (IV).**—To a refluxing solution of 81.6 g. (0.5 mole) of III in 100 ml. of absolute ethanol and 200 ml. of water was added slowly a solution of 22 g. (0.55 mole) of sodium hydroxide in 55 ml. of water, and the solution was boiled for 20 min. Nuchar (0.5 g.) was added and the suspension was boiled in an open flask and fluted-filtered, giving a pale-orange filtrate which deposited some red-orange oil. (a) The supernatant liquor was decanted, boiled until the odor of ethanol had disappeared, fluted-filtered, cooled in ice, and nucleated, to give crop 1 (12 g.) of IV. (b) The oil was kept overnight in the refrigerator, giving a mass of orange crystals which was extracted with three 200-ml. portions of boiling water; the extracts were combined and treated as before, to give crop 2 (24 g.) of IV. Crops 1 and 2 were combined (36 g.) and recrystallized from 400 ml. of boiling water, giving 23.5 g. of IV as yellow platelets. The mother liquor was combined with those of crops 1 and 2; this solution was extracted with neutral 1,2-dichloroethane[4] and the extract was dried (anhydrous sodium sulfate) and evaporated to give crop 3 (22 g.) of yellow crystals; total yield, 45.5 g. (75%); m.p. 71°; lit. m.p.[5] 71°. Solutions of IV in neutral 1,2-dichloroethane may be kept in the refrigerator for several days without formation of the polymer[6] (which is insoluble in this solvent).

2,2-Dichloro-4′-formylacetanilide (V).—To a solution of 22 g. of IV in 100 ml. of anhydrous, neutral 1,2-dichloroethane[4] at 0° was added 17.5 ml. of dry pyridine. With exclusion of moisture, a solution of 22 ml. of dichloroacetyl chloride in 25 ml. of 1,2-dichloroethane[4] was added dropwise, with magnetic stirring, during 1.75 hr. at 0°. Water (1 + 1 + 3 ml.) now was added at 5-min. intervals, with stirring at 0°; 100 ml. of water was added and the product was isolated in the usual way, to give 26.4 g. of a yellow-orange, crystalline mass. A portion (20 g.) was recrystallized from 95% ethyl alcohol (2 vols.) and the crystals were washed with 20 ml. of this solvent, to give 12.3 g. of very pale-yellow crystals; m.p. 128–129°. Its infrared absorption spectrum showed bands that were absent from the spectrum of compound II: at 1701, 1511, 1422, 1325, 1255, 1220, 1020, 778, and 715 cm.$^{-1}$.

Anal. Calcd. for $C_9H_7Cl_2NO_2$: C, 46.58; H, 3.04; Cl, 30.56; N, 6.04. Found: C, 46.50; H, 3.16; Cl, 30.58; N, 6.26.

2,2-Dichloro-4′-formylacetanilide Thiosemicarbazone (II).—To a refluxing solution of 5.8 g. (0.025 mole) of V in 75 ml. of absolute ethanol plus 100 ml. of water was added a hot solution of

(1) Division of Physical Chemistry, National Bureau of Standards, Washington 25, D. C.

(2) D. Hamre, J. Bernstein, and R. Donovick, *Proc. Soc. Exptl. Biol. Med.*, **73**, 275 (1950); K. A. Brownlee and D. Hamre, *J. Bacteriol.*, **61**, 127 (1951); D. Hamre, K. A. Brownlee, and R. Donovick, *J. Immunol.*, **67**, 305 (1951).

(3) R. L. Thompson, M. L. Price, and S. A. Minton, Jr., *Proc. Soc. Exptl. Biol. Med.*, **78**, 11 (1951); S. A. Minton, Jr., J. E. Officer, and R. L. Thompson, *J. Immunol.*, **70**, 222 (1953); R. L. Thompson, S. A. Minton, Jr., J. E. Officer, and G. H. Hitchings, *ibid.*, **70**, 229 (1953); R. L. Thompson, J. Davis, P. B. Russell, and G. H. Hitchings, *Proc. Soc. Exptl. Biol. Med.*, **84**, 496 (1953).

(4) Commercial 1,2-dichloroethane is acidic; it was prewashed with aqueous sodium bicarbonate solution and water.

(5) L. C. Janse, *Rec. trav. chim.*, **40**, 285 (1921).

(6) Polymer may be dissolved from glassware by means of concentrated nitric acid.

2.3 g. (0.025 mole) of thiosemicarbazide in 35 ml. of water; the mixture was boiled for 5 min. and filtered hot, to give 7.7 g. of very pale yellow crystals which were recrystallized from boiling, glacial acetic acid (25 vols.); m.p. above 245° (slight browning at 190°, dark brown at 220°). Its infrared spectrum differed from those of the two parent compounds. The spectrum of compound II showed bands that were absent from the spectrum of thiosemicarbazide: at 3356, 1664, 1245, 1179, 973, 953, 877, 834, 824, and 732 cm.$^{-1}$. Compound II showed bands that were absent from the spectra of both compound V and thiosemicarbazide: at 1600, 1555, 1497, 1412, 1346, 1087, 926, 860, and 759 cm.$^{-1}$. The spectrum of thiosemicarbazide showed bands at 1311, 1156, and 995 cm.$^{-1}$ that were absent from the spectrum of compound II.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_4OS$: C, 39.35; H, 3.30; Cl, 23.24; N, 18.36; S, 10.50. Found: C, 39.44; H, 3.20; Cl, 23.21; N, 18.41; S, 10.54.

Antiviral Activity.[7]—In tests for antivaccinial activity, Swiss mice (weighing approximately 15 g. each) were inoculated intranasally with one LD_{50} of a mouse lung-adapted strain of International Health Division neutrotropic vaccinia virus.[8] Groups of treated and control mice were compared as to life span, survival rate, and infectivity score (a weighted score on lung consolidation). For each drug, half of the daily dose (one third of the single-dose intraperitoneal LD_{50}) was given intraperitoneally to each mouse (a) in the morning and (b) in the late afternoon, for 5 days, beginning 30 to 60 min. after virus inoculation; the daily dose of each drug was 167 mg./kg. The results are given in Table I.

Both compounds were inactive in mice infected intranasally with (a) feline pneumonitis virus or (b) influenza A (PR 8) virus; and in mice infected by intracerebral inoculation of (a) Type II (Lansing) poliomyelitis virus or (b) Western equine encephalomyelitis virus.

TABLE I

EFFECTS OF THIOSEMICARBAZONE TREATMENT ON VACCINIAL INFECTION IN MICE

Compound	Dead/Total	Survivors, %	Infectivity score[a]	Survival index[b]
I	2/20	90	1.6	>1.96
II	1/19	95	0.5	>2.06
—(Control)	16/20	20	4.3	

[a] Infectivity score. Averages of all mice scored as follows: death with complete lung consolidation, 5; alive at 10–14 days with 4/4, 3/4, 1/2, and 1/4 lung consolidation, 4, 3, 2, and 1, respectively. [b] Survival index = (average survival time, in days, of treated mice)/(average survival time, in days, of control mice). Treated mice were sacrificed on the 14th post-infection, 9th post-treatment day for infectivity scoring, and, for purposes of calculating the survival index, were considered to have died on the sacrifice day.

(7) These tests were kindly performed by Dr. Frank M. Schabel, Jr., Head of the Chemotherapy Division, Southern Research Institute, Birmingham, Alabama.

(8) The procedures used have been described: F. M. Schabel, Jr., W. R. Laster, Jr., R. W. Brockman, and H. E. Skipper, *Proc. Soc. Exptl. Biol. Med.*, **83**, 1 (1953); F. M. Schabel, Jr., and H. E. Skipper, *Cancer Research*, Suppl. No. **3**, 52 (1955).

Communications to the Editor

[4-(Aminoalkylamino)-1-naphthylazo]heterocyclic Compounds, a Novel Class of Schistosomicides

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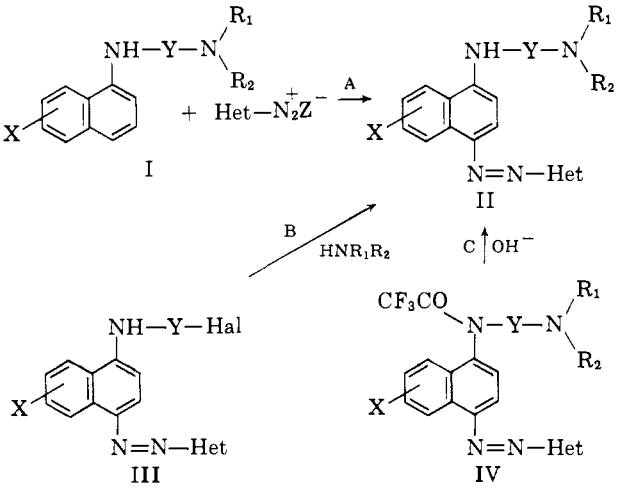
Received December 12, 1962

We wish to report the synthesis and biological evaluation of a novel class of schistosomicides, namely, [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds of structure II, where R_1 and R_2 represent alkyl groups, Y an alkylene radical, X a hydrogen or halogen atom or a lower alkoxy or alkyl group, and Het a heterocyclic radical.

A majority of the compounds was synthesized by coupling a diazotized heterocyclic amine with the appropriate 1-(aminoalkyl)naphthylamine (I) (route A). These naphthylamine intermediates were prepared by: (1) alkylation of a 1-naphthylamine[1] or an alkaline metal salt thereof with a dialkylaminoalkyl halide; (2) hydrogenation of a Schiff base resulting from the condensation of 1-naphthylamine with a dialkylamino aldehyde or ketone; (3) condensation of 1-naphthol with an alkylaminoalkylamine in the presence of sodium bisulfite or sodium hydrosulfite; (4) amination of an ω-haloalkyl-1-naphthylamine with an aliphatic amine.

Alternatively, compounds of structure II were prepared by allowing a N-(ω-haloalkyl)-4-(heterocyclicazo)-1-naphthylamine (III) to react with the appropriate amine (route B) or by alkaline hydrolysis of the corresponding N-(aminoalkyl)-2,2,2-trifluoro-N-[4-(heterocyclicazo)-1-naphthyl]acetamides IV (route C). Analyses for all intermediates and products were satisfactory.



The [4-(dialkylaminoalkylamino)-1-naphthylazo]-heterocycles (II) were evaluated in albino mice infected with a Puerto Rican strain of *Schistosoma mansoni*.[2] Antischistosome activity is widespread within this series. Compounds II a through o (Table I), which are representative of the more promising members of the series, effected a 97–100% reduction of live worms at

(1) M. A. Stahmann and A. C. Cope, *J. Am. Chem. Soc.*, **68**, 2494 (1946).

(2) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962).