96.0° (lit.[27] mp 96–97°); R_f 0.81; infrared maxima at 2.9–3.2 (NH), 6.15 μ (C=O in the thiadiazolone); nmr, $CDCl_3$ at τ −0.1 (NH bonded) and 7.38 (SCH_3) with relative weight 1:3; λ_{max}^{MeOH} 262 mμ (ϵ 6430), $\lambda_{max}^{0.1NNaOH}$ 278 mμ (ϵ 6970).

Anal. Calcd for $C_3H_9N_2OS_2$: C, 24.3; H, 2.7; N, 19.0; S, 43.3. Found: C, 24.6; H, 2.7; N, 19.1; S, 43.4.

Refluxing 1 hr with 2 moles of KOH in methanol gave the identical product in similar yield. When refluxed with 0.1 equiv of methoxide in methanol, mostly starting material was left after 12 hr by paper chromatography.

2-Amino-5-chloro-1,3,4-thiadiazole.—Heating 2-amino-5-bromo-1,3,4-thiadiazole[28] (18) on the steam bath with excess concentrated HCl for 15 hr caused disappearance of infrared absorption at 9.75 μ and appearance of strong absorption at 9.15 μ. Differential halogen analysis of the isolated material demonstrated conversion to 2-amino-5-chloro-1,3,4-thiadiazole:[14] 0.80 g-atom of chlorine and 0.21 g-atom of bromine. The bromo compound was unchanged after 0.5 hr, at 20° or by refluxing 2 *N* ethanolic HCl for 1 hr.

Reaction of 2-Amino-5-bromo-1,3,4-thiadiazole with *p*-Nitrobenzenesulfonyl Chloride.—A solution of 0.222 g (0.001 mole) of *p*-nitrobenzenesulfonyl chloride in 1 ml of dry pyridine added rapidly to a slurry of 0.180 g (0.001 mole) of 2-amino-5-bromo-1,3,4-thiadiazole[23] (18) in 1 ml of pyridine gave a slight exotherm and heavy precipitation. An additional 3 ml of dry pyridine was added and the mixture was stirred for 2 hr. The yellow product (0.25 g, mp 222–226.5° dec) was very soluble in water, insoluble in ether, and gave a positive silver nitrate test. Elemental analyses (C, 35.2; H, 3.2; N, 20.3; S, 12.4; ionic Br, 28.7) and the infrared spectrum (NH_2, 3.05, 3.20 μ; NO_2, 6.5, 7.4 μ) suggested that this product was 1-(2-aminothiadiazol-5-yl)pyridinium bromide containing about 25% of the corresponding sulfonylated product. 2-Amino-5-bromo-1,3,4-thiadiazole was recovered unchanged from pyridine after 24 hr at 25° in the absence of the sulfonyl chloride.

Complete sulfonylation was achieved by running the reaction[29] at 80° for 20 min (negative Bratton–Marshall test for starting amine). The yellow product (67%, mp 250–253° dec) was isolated as the chloride by pouring the reaction mixture into 3 *N* HCl. A pyridinium moiety was indicated by the analyses below and by the formation of a red precipitate (mp 165°) of a glutacondialdehyde anil[30] from acidification of its solution in alkali. Recrystallization from glacial acetic acid gave a halogen-free light yellow solid (mp 290°) whose analysis agreed with the 1-[2-(*p*-nitrobenzenesulfonamido)-1,3,4-thiadiazol-5-yl]pyridinium zwitterion (sulfonamide anion). Characteristic infrared bonds were present at 6.15, 6.25, 6.65, 7.0, 7.4, 9.25, 10.6, 12.8, 14.45 (pyridine, N-pyridinium), 6.52, 7.43 (NO_2), 7.72, 8.66 (sulfonamide SO_2), 11.63, 13.55 μ (*para*-substituted phenyl).

Anal. Calcd for $C_{13}H_9N_5O_4S_2$: C, 43.0; H, 2.5; N, 19.3. Found: C, 42.4; H, 2.6; N, 19.3.

Acknowledgments.—We thank Mr. W. Fulmor and staff for nmr spectra, Mr. L. Brancone and staff for microanalyses, and Mr. C. Pidacks and staff for partition chromatographic separations.

(27) P. C. Guha and S. C. Guha, *Quart. J. Indian Chem. Soc.*, **4**, 239 (1927).

(28) Prepared by R. B. Angier, J. Semb, and K. Cyr (132nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1957, p 31-O) from 2-amino-1,3,4-thiadiazole and bromine in acetic acid, mp 180–181°.

(29) Carried out by Dr. J. L. Fedrick, of these laboratories.

(30) T. Zincke, *Ann. Chem.*, **330**, 367 (1904).

Novel Broad-Spectrum Anthelmintics. Tetramisole[1] and Related Derivatives of 6-Arylimidazo[2,1-*b*]thiazole

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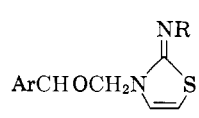
Received August 10, 1965

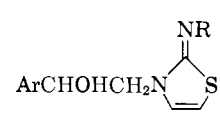
In a critical screening test in chickens, 2-acetylimino-3-[2-hydroxy-2-(2-thienyl)ethyl]thiazoline (IV, thiazothienol) was found to be active against heterakids, ascarids, and capillarids. IV was also active against various nematodes in sheep, but not in rats or in mice. In chickens and in sheep, but not in mice or in rats, IV undergoes metabolic ring closure to 5,6-dihydro-6-(2-thienyl)imidazo[2,1-*b*]thiazole (VII, thiazothielite), which is active as an anthelmintic in all four species. A large series of imidazothiazole derivatives related to VII were prepared and screened. From these studies emerged tetramisole (XII), the stable, water-soluble hydrochloride of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole, as the most promising novel broad-spectrum anthelmintic of the series. Tetramisole is active at low, atoxic oral and parenteral dose levels against all adult and immature gastrointestinal and pulmonary nematodes tested in 14 different hosts.

The purpose of this paper is to describe briefly the experiments which led to the discovery of tetramisole, a novel broad-spectrum anthelmintic.[1]

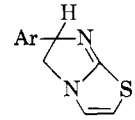
The first relevant experiments involved the synthesis of new derivatives of 2-aminothiazole as potential anthelmintics. The condensation of a bromomethyl aryl ketone with 2-aminothiazole proceeded easily to give the hydrobromide of a 3-aroylmethyl-2-iminothiazoline (Ia)[2–4] (Table I). Acylation of Ia with acetic anhydride in the presence of pyridine gave the corresponding 3-aroylmethyl-2-acetyliminothiazoline (Ib)



Ia, R = H
b, R = $COCH_3$



IIa, R = H
b, R = $COCH_3$



III

(Table I), which was reduced to the racemic 2-acetylimino-3-(2-hydroxyarylethyl)thiazoline (IIb) with sodium borohydride at reflux temperature (Table II). The imino ketones Ia were similarly reduced, preferably at lower temperature, to the imino alcohols IIa (Table II). These four reactions proceeded in high yield and without unexpected preparative difficulties.

In a routine critical screening test for anthelmintic activity in naturally infected chickens, one of these

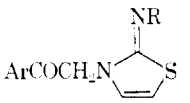
(1) D. C. I. Thienpont, O. F. J. Vanparijs, A. H. M. Raeymaekers, J. Vandenberk, P. J. A. Demoen, F. T. N. Allewijn, R. P. H. Marsboom, C. J. E. Niemegeers, K. H. L. Schellekens, P. A. J. Janssen, *Nature*, **209**, 1084 (1966).

(2) B. Kickhöfen, and F. Kröhnke, *Ber.*, **88**, 1109 (1955).

(3) Th. Pyl, R. Giebelmann, and H. Beyer, *Ann. Chem.*, **643**, 145 (1961).

(4) Th. Pyl, L. Bulling, K. Wunsch, and H. Beyer, *ibid.*, **643**, 153 (1961).

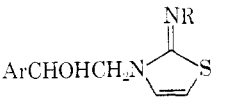
TABLE I



Ar	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	H	128–129.5[a]	$C_{11}H_{10}N_2OS$	60.53	4.62	12.84	60.66	4.62	12.89
2-HOC_6H_4	H	183–184	$C_{11}H_{10}N_2O_2S \cdot HBr$	41.91	3.52	8.89	41.48	3.54	8.83
3-ClC_6H_4	H	215–216	$C_{11}H_9ClN_2OS \cdot HBr$	39.60	3.02	8.40	39.48	3.08	8.21
3-$NO_2C_6H_4$	H	230 dec	$C_{11}H_9N_3O_3S \cdot HBr$	38.38	2.93	12.21	38.50	2.76	12.41
3-BrC_6H_4	H	203–205	$C_{11}H_9BrN_2OS \cdot HBr$	34.94	2.40	7.41	34.91	2.70	7.43
3,4-$(CH_3)_2C_6H_3$	H	257–260	$C_{13}H_{14}N_2OS \cdot HBr$	47.71	4.62	8.56	47.60	4.66	8.76
4-FC_6H_4	H	235–237.5	$C_{11}H_9FN_2OS \cdot HBr$	41.65	3.18	8.83	41.79	3.14	8.77
C_4H_3S[b]	H	119.5–120	$C_9H_8N_2OS_2$	48.19	3.60	12.49	48.30	3.73	12.45
C_4H_2BrS[c]	H	223.5–227	$C_9H_7BrN_2OS_2 \cdot HBr$	28.14	2.10	7.29	28.30	2.09	7.32
C_4H_3O[d]	H	198–198.5	$C_9H_8N_2O_2S \cdot HBr$	37.38	3.14	9.69	37.63	3.12	9.78
3-ClC_6H_4	$COCH_3$	145–147	$C_{13}H_{11}ClN_2O_2S$	52.97	3.76	9.50	53.08	3.88	9.55
3-$NO_2C_6H_4$	$COCH_3$	151–152	$C_{13}H_{11}N_3O_4S$	51.14	3.63	13.76	51.04	3.71	13.66
C_4H_3S[b]	$COCH_3$	146–147.5	$C_{11}H_{10}N_2O_2S_2$	49.63	3.79	10.52	49.87	3.50	10.32
C_4H_2BrS[c]	$COCH_3$	160–161.5	$C_{11}H_9BrN_2O_2S_2$	38.27	2.63	8.11	38.51	2.65	8.10
C_4H_3O[d]	$COCH_3$	142.5–143.5	$C_{11}H_{10}N_2O_3S$	52.78	4.03	11.19	52.91	3.96	11.34

[a] See ref 2. [b] 2-Thienyl. [c] 5-Bromo-2-thienyl. [d] 2-Furyl.

TABLE II



Ar	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2-HOC_6H_4	H	195–196	$C_{11}H_{12}N_2O_2S \cdot HBr$	41.65	4.13	8.83	41.26	4.25	8.63
3-$NO_2C_6H_4$	H	138.5–154 dec	$C_{13}H_{13}N_3O_4S$	50.81	4.26	13.68	53.04	4.31	14.15
3-BrC_6H_4	H	245.5–246	$C_{11}H_{11}BrN_2OS \cdot HBr$	34.75	3.18	7.37	34.41	3.23	7.18
3,4-$(CH_3)_2C_6H_3$	H	223–224.5	$C_{13}H_{16}N_2OS \cdot HBr$	47.42	5.20	8.51	47.14	5.24	8.38
4-FC_6H_4	H	196–203	$C_{11}H_{11}FN_2OS \cdot HBr$	41.39	3.79	8.78	41.55	3.88	8.80
4-$CH_3OC_6H_4$[a]	H	187–189	$C_{12}H_{14}N_2O_2S \cdot HBr$	43.51	4.56	8.46	43.29	4.59	8.20
4-ClC_6H_4	H	198.5–215	$C_{11}H_{11}ClN_2OS \cdot HBr$	39.36	3.60	8.35	39.36	3.62	8.05
4-$CH_3C_6H_4$[a]	H	222–223.5	$C_{12}H_{14}N_2OS \cdot HBr$	45.72	4.80	8.89	45.78	4.89	8.60
C_4H_3S[b]	H	100–101	$C_9H_{10}N_2OS_2$	47.79	4.46	12.42	48.07	4.41	12.42
C_6H_5	$COCH_3$	157–159	$C_{13}H_{14}N_2O_2S$	59.52	5.38	10.67	59.65	5.40	10.59
3-ClC_6H_4	$COCH_3$	140–141	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.15	4.39	9.62
C_4H_3S[b]	$COCH_3$	132.5–133	$C_{11}H_{12}N_2O_2S_2$	49.25	4.51	10.45	49.15	4.23	10.42
C_4H_2BrS[c]	$COCH_3$	120–121	$C_{11}H_{11}BrN_2O_2S_2$	38.04	3.19	8.07	38.08	3.29	8.07
C_4H_3O[d]	$COCH_3$	115–116.5	$C_{11}H_{12}N_2O_3S$	52.36	4.79	11.10	52.31	4.86	11.14

[a] The starting ketone is prepared according to Pyl, *et al.*[4] [b] 2-Thienyl. [c] 5-Bromo-2-thienyl. [d] 2-Furyl.

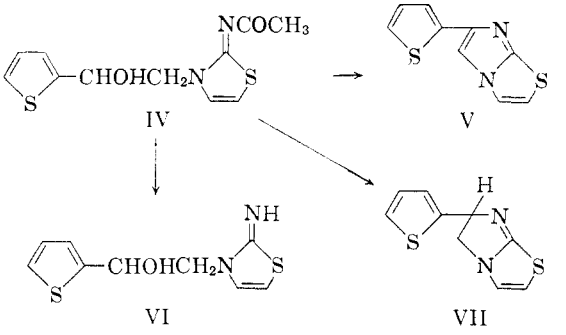
compounds, 2-(acetylimino)-3-[2-hydroxy-2-(2-thienyl)-ethyl]thiazoline (IV, thiazothienol), was found to be active at atoxic dose levels against heterakids, ascarids, and capillarids.[1] Most of the other compounds, including the isosteric phenyl analog IIb (Ar = phenyl), were surprisingly inactive against these nematodes. Thiazothienol (IV) was subsequently found to be highly active against a variety of gastrointestinal nematodes in critical tests in sheep, but in mice and in rats subtoxic doses of IV failed to expel roundworms.

In order to find out whether these marked species differences could be explained by the metabolic conversion of IV to an anthelmintically active metabolite in chickens and in sheep, but not in rats or in mice, an effort was made to isolate, identify, synthesize, and test the major metabolites of IV in these species.

Chickens were given IV by the oral route and the feces were extracted with acid. From the ethereal extract of the alkalized filtrate thiazothienol (IV) itself as well as three of its metabolites were detected and isolated chromatographically. Two of the metabolites were readily identified as V and VI. Both had been synthetized before and were known to be inactive against nematodes in chickens (see Scheme I).

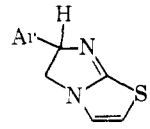
SCHEME I

METABOLIC FATE OF IV IN THE CHICKEN



The third metabolite was an unknown compound. Its structure, 5,6-dihydro-6-(2-thienyl)imidazo[2,1-*b*]-thiazole (VII, thiazothielite), originally postulated on

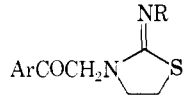
TABLE III



Ar	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	175–177	$C_{11}H_{10}N_2S \cdot HCl$	55.34	4.64	11.74	55.31	4.70	11.59
3-ClC_6H_4	155–157	$C_{11}H_9ClN_2S \cdot C_2H_2O_4$	47.78	3.39	8.57	47.66	3.57	8.78
3-$NO_2C_6H_4$	192–195	$C_{11}H_9N_3O_2S \cdot C_2H_2O_4$	46.29	3.29	12.46	46.54	3.38	12.72
3-BrC_6H_4	153–155	$C_{11}H_9BrN_2S \cdot C_2H_2O_4$	42.06	2.99	7.55	42.10	3.00	7.86
4-FC_6H_4	168–173	$C_{11}H_9FN_6S \cdot C_2H_2O_4$	50.32	3.57	9.03	50.29	3.68	8.80
4-$CH_3OC_6H_4$	189.5–190	$C_{12}H_{12}N_2OS \cdot C_2H_2O_4$	52.16	4.38	8.69	52.09	4.45	8.55
4-ClC_6H_4	194–195	$C_{11}H_9ClN_2S \cdot C_2H_2O_4$	47.78	3.39	8.57	47.79	3.49	8.47
4-$CH_3C_6H_4$	212.5–213.5	$C_{12}H_{12}N_2S \cdot C_2H_2O_4$	54.89	4.61	9.15	54.88	4.68	9.06
4-$NO_2C_6H_4$	156–157.5	$C_{11}H_9N_3O_2S \cdot C_2H_2O_4$	46.29	3.29	12.46	46.65	3.27	12.50
C_4H_3S[a]	192–193	$C_9H_8N_2S_2 \cdot C_2H_2O_4$	44.28	3.38	9.39	44.44	3.36	9.30
C_4H_3O[b]	158.5–161	$C_9H_8N_2OS \cdot HCl$	47.26	3.97	12.25	47.23	4.09	12.14

[a] 2-Thienyl. [b] 2-Furyl.

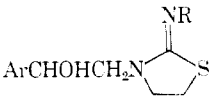
TABLE IV



Ar	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	H	200	$C_{11}H_{12}N_2OS \cdot HBr$	43.86	4.35	9.30	43.88	4.49	9.43
2-ClC_6H_4	H	197–198	$C_{11}H_{11}ClN_2OS \cdot HBr$	39.36	3.60	8.35	39.28	3.64	8.27
3-ClC_6H_4	H	276–277	$C_{11}H_{11}ClN_2OS \cdot HBr$	39.36	3.60	8.35	39.26	3.67	8.37
4-ClC_6H_4	H	204	$C_{11}H_{11}ClN_2OS \cdot HBr$	39.36	3.60	8.35	39.37	3.73	8.67
3,4-$Cl_2C_6H_3$	H	212–232.5	$C_{11}H_{10}Cl_2N_2OS \cdot HCl$	40.57	3.40	8.60	40.33	3.20	8.95
2,3,4-$Cl_3C_6H_2$	H	282–283	$C_{11}H_9Cl_3N_2OS \cdot HBr$	32.66	2.49	6.93	32.61	2.54	6.92
3-BrC_6H_4	H	252–253.5	$C_{11}H_{11}BrN_2OS \cdot HBr$	34.75	3.18	7.37	34.74	3.27	7.50
4-BrC_6H_4	H	199–200	$C_{11}H_{11}BrN_2OS \cdot HBr$	34.75	3.18	7.37	34.78	3.17	7.23
4-FC_6H_4	H	209–210	$C_{11}H_{11}FN_2OS \cdot HBr$	41.39	3.79	8.78	41.34	3.66	8.70
2-OCH_3-5-FC_6H_3	H	259–260	$C_{12}H_{13}FN_2O_2S \cdot HBr$	41.27	4.04	8.02	41.10	4.12	8.30
3-F-4-$CH_3OC_6H_3$	H	257	$C_{12}H_{13}FN_2O_2S \cdot HBr$	41.27	4.04	8.02	41.34	4.01	7.76
3-$CF_3C_6H_4$	H	259–263.5	$C_{12}H_{11}F_3N_2OS \cdot HBr$	39.03	3.28	7.59	38.66	3.25	7.54
4-$CH_3OC_6H_4$	H	190–191	$C_{12}H_{14}N_2O_2S \cdot HBr$	43.51	4.56	8.46	43.57	4.71	8.58
4-$CH_3C_6H_4$	H	201–202	$C_{12}H_{14}N_2OS \cdot HBr$	45.72	4.80	8.89	45.85	4.87	8.96
2,4-$(CH_3)_2C_6H_3$	H	204	$C_{13}H_{16}N_2OS \cdot HBr$	47.42	5.20	8.51	47.23	5.06	8.47
2-$NO_2C_6H_4$	H	188.5–191.5	$C_{11}H_{11}N_3O_3S \cdot HBr$	38.16	3.49	12.14	38.08	3.26	12.01
3-$NO_2C_6H_4$	H	>300	$C_{11}H_{11}N_3O_3S \cdot HBr$	38.16	3.49	12.14	38.11	3.59	12.11
C_4H_3S[a]	H	213–213.5	$C_9H_{10}N_2OS_2 \cdot HBr$	35.18	3.61	9.12	34.96	3.66	9.36
C_4H_3O[b]	H	202–203	$C_9H_{10}N_2O_2S \cdot HBr$	37.12	3.81	9.62	36.95	3.91	10.06
C_6H_5	$COCH_3$	140–141	$C_{13}H_{14}N_2O_2S$	59.53	5.38	10.68	59.66	5.45	10.64
2-ClC_6H_4	$COCH_3$	116–116.5	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.86	4.50	9.39
3-ClC_6H_4	$COCH_3$	90.5–91.5	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	53.03	4.56	9.58
4-ClC_6H_4	$COCH_3$	126.5–129	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.87	4.50	9.53
3,4-$Cl_2C_6H_3$	$COCH_3$	119.5–121.5	$C_{13}H_{12}Cl_2N_2O_2S$	47.14	3.65	8.46	47.17	3.68	8.59
2,3,4-$Cl_3C_6H_2$	$COCH_3$	122.5–126	$C_{13}H_{11}Cl_3N_2O_2S$	42.70	3.03	7.66	42.50	2.94	7.36
3-BrC_6H_4	$COCH_3$	162–165	$C_{13}H_{13}BrN_2O_2S \cdot HCl$	41.34	3.74	7.42	41.32	3.86	7.31
4-BrC_6H_4	$COCH_3$	147.5–149	$C_{13}H_{13}BrN_2O_2S$	45.76	3.84	8.21	46.01	3.89	8.15
4-FC_6H_4	$COCH_3$	126–127	$C_{13}H_{13}FN_2O_2S$	55.70	4.67	9.99	55.84	4.75	10.25
2-$CH_3OC_6H_4$	$COCH_3$	157–159.5	$C_{14}H_{15}FN_2O_3S$	54.18	4.87	9.03	54.50	4.86	9.08
3-F, 4-$CH_3OC_6H_3$	$COCH_3$	121.5–123	$C_{14}H_{15}FN_2O_3S$	54.18	4.87	9.03	54.34	4.91	9.07
3-$CF_3C_6H_4$	$COCH_3$	108–109	$C_{14}H_{13}F_3N_2O_2S$	50.90	3.97	8.48	51.05	3.92	8.74
4-$CH_3OC_6H_4$	$COCH_3$	117–119	$C_{14}H_{16}N_2O_3S$	57.51	5.52	9.58	57.78	5.63	9.72
4-$CH_3C_6H_4$	$COCH_3$	133–135	$C_{14}H_{16}N_2O_2S$	60.84	5.84	10.14	60.63	5.96	10.02
2,4-$(CH_3)_2C_6H_3$	$COCH_3$	102–104	$C_{15}H_{18}N_2O_2S$	62.05	6.25	9.65	62.33	6.23	9.53
2-$NO_2C_6H_4$	$COCH_3$	120–123.5	$C_{13}H_{13}N_3O_4S$	50.80	4.26	13.67	50.63	4.03	13.97
3-$NO_2C_6H_4$	$COCH_3$	116–145	$C_{13}H_{13}N_3O_4S$	50.80	4.26	13.67	50.96	4.36	13.40
C_4H_3S[a]	$COCH_3$	145.5–147	$C_{11}H_{12}N_2O_2S_2$	49.29	4.51	10.44	49.27	4.65	10.50
C_4H_3O[b]	$COCH_3$	132–135	$C_{11}H_{12}N_2O_3S$	52.38	4.80	11.11	52.65	4.91	11.22

[a] 2-Thienyl. [b] 2-Furyl.

TABLE V



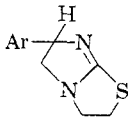
Ar	R	Mp, °C	Formula	Calcd, % C	H	N	Found, % C	H	N
C_6H_5	H	183–184.5	$C_{11}H_{14}N_2OS \cdot HBr$	43.57	4.99	9.24	43.36	5.07	9.14
C_6H_5	$COCH_3$	100–103.5	$C_{13}H_{16}N_2O_2S$	59.08	6.10	10.60	59.37	6.17	10.49
2-ClC_6H_4	$COCH_3$	163–164	$C_{13}H_{15}ClN_2O_2S$	52.25	5.06	9.38	52.15	5.12	9.26
3-ClC_6H_4	$COCH_3$	138–139	$C_{13}H_{15}ClN_2O_2S$	52.25	5.06	9.38	52.45	5.20	9.02
4-ClC_6H_4	$COCH_3$	120–121	$C_{13}H_{15}ClN_2O_2S$	52.25	5.06	9.38	52.20	5.13	9.33
3,4-$Cl_2C_6H_3$	$COCH_3$	104–106	$C_{13}H_{14}Cl_2N_2O_2S$	46.57	4.21	8.36	46.72	4.28	8.61
2,3,4-$Cl_3C_6H_2$	$COCH_3$	156–156.5	$C_{13}H_{13}Cl_3N_2O_2S$	42.46	3.56	7.62	42.50	3.56	7.74
3-BrC_6H_4	$COCH_3$	141.5–142.5	$C_{13}H_{15}BrN_2O_2S$	45.49	4.40	8.16	45.36	4.52	8.14
4-BrC_6H_4	$COCH_3$	126–127	$C_{13}H_{15}BrN_2O_2S$	45.49	4.40	8.16	45.54	4.43	7.90
4-FC_6H_4	$COCH_3$	118–121	$C_{13}H_{15}FN_2O_2S$	55.30	5.36	9.92	55.30	5.58	9.93
2-OCH_3-5-FC_6H_3	$COCH_3$	138–139	$C_{14}H_{17}FN_2O_3S$	53.83	5.49	8.97	54.10	5.53	9.03
3-F-4-$CH_3OC_6H_3$	$COCH_3$	92–93	$C_{14}H_{17}FN_2O_3S$	53.83	5.49	8.97	53.90	5.52	9.02
3-$CF_3C_6H_4$	$COCH_3$	142–143	$C_{14}H_{15}F_3N_2O_2S$	50.59	4.55	8.43	50.54	4.51	8.60
4-$CH_3OC_6H_4$	$COCH_3$	132–133.5	$C_{14}H_{18}N_2O_3S$	57.13	6.17	9.52	57.21	6.28	9.22
4-$CH_3C_6H_4$	$COCH_3$	102–103	$C_{14}H_{18}N_2O_2S$	60.42	6.52	10.07	60.32	6.55	9.91
2,4-$(CH_3)_2C_6H_3$	$COCH_3$	160–162	$C_{15}H_{20}N_2O_2S$	61.61	6.89	9.58	61.82	6.98	9.71
2-$NO_2C_6H_4$	$COCH_3$	119–120	$C_{13}H_{15}N_3O_4S$	50.47	4.89	13.59	50.42	4.92	13.70
3-$NO_2C_6H_4$	$COCH_3$	122–140	$C_{13}H_{15}N_3O_4S$	50.47	4.89	13.59	50.20	4.55	13.91
C_4H_3S[a]	$COCH_3$	85.5–88	$C_{11}H_{14}N_2O_2S_2$	48.89	5.22	10.36	49.23	5.30	10.28
C_4H_3O[b]	$COCH_3$	110.5–112	$C_{11}H_{14}N_2O_3S$	51.96	5.55	11.02	52.30	5.80	11.06

[a] 2-Thienyl. [b] 2-Furyl.

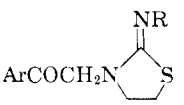
the basis of spectrophotometric and elemental analysis of a metabolically formed sample, was confirmed by unambiguous synthesis. The details of this metabolic experiment are given in the Experimental Section.

Metabolically formed and synthetic thiazothielite (VII) was tested in chickens and found to be fully effective in expelling heterakids, ascarids, and capillarids at significantly lower oral dose levels than the parent compound, thiazothienol (IV). Synthetic metabolite VII was also found to be a potent anthelmintic against nematodes, not only in chickens and in sheep, but also in mice and in rats. Subsequent metabolic studies showed that VII is also a major metabolite of IV in sheep, but not in rats and in mice, which explains the species differences described above. It was further found that in the chicken the anthelmintically inactive phenyl analog of thiazothienol, *i.e.*, IIb (Ar = phenyl), is not metabolically converted to the phenyl analog of thiazothielite, *i.e.*, III (Ar = phenyl), which is a highly potent anthelmintic against nematodes in chickens, sheep, rats, and mice.

A large series of derivatives of imidazothiazole and related heterocycles were then synthesized and screened. Highest anthelmintic activity was found among 5,6-dihydro-6-arylimidazo[2,1-*b*]thiazoles (III, Table III) and 2,3,5,6-tetrahydro-6-arylimidazo[2,1-*b*]thiazoles (VIII, Table VI). Compounds VIII, listed in Table



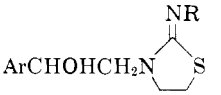
VIII



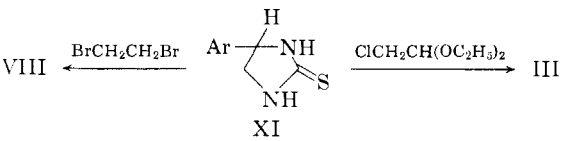
IXa, R = H
b, R = $COCH_3$

VI, were generally prepared as described above from the condensation product of a bromomethyl aryl ketone and 2-aminothiazoline (IXa, Table IV) followed by acetylation (IXb, Table IV), sodium borohydride reduction (Xb, Table V), and ring closure to VIII with thionyl chloride, phosphorus oxychloride, or phosphorus pentachloride.

One of the alternative routes of synthesis of III and of VIII consisted in treating an imino alcohol IIa or Xa with concentrated sulfuric acid or with thionyl chloride in the presence of acetic anhydride. Another



Xa, R = H
b, R = $COCH_3$



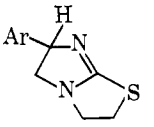
XI

alternative route to III or VIII consisted in ring closing a suitable 4(5)-aryl-2-mercaptoimidazolidine (XI) with either 1,2-dibromoethane to give VIII or with the diethyl acetal of chloroacetaldehyde to give III.[5] The 4-nitro-, 4-amino-, and 4-hydroxyphenyl derivatives III or VIII (Ar = phenyl), listed in Tables III and IV, were obtained by nitration, reduction, and diazotation of the unsubstituted phenyl derivative III or VIII, respectively.

All compounds listed in Tables I–VI were screened in several parasitological and pharmacological tests and as a result tetramisole (2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride) emerged as the most promising broad-spectrum anthelmintic of the series.[1] This compound was extensively studied and found highly active at low, atoxic, oral, or parenteral doses (2.5–40 mg/kg) against all adult and immature gastrointestinal and pulmonary nematodes tested in sheep, cattle, pigs, horses, chickens, pigeons,

(5) W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955).

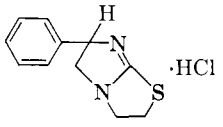
TABLE VI



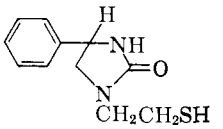
Ar	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	261.5–264.5	$C_{11}H_{12}N_2S \cdot HCl$	54.87	5.44	11.64	54.80	5.44	11.72
2-ClC_6H_4	157–170	$C_{11}H_{11}ClN_2S \cdot C_2H_2O_4$	47.49	3.99	8.52	47.42	4.07	8.54
3-ClC_6H_4	168–172	$C_{11}H_{11}ClN_2S \cdot C_2H_2O_4$	47.49	3.99	8.52	47.45	4.10	8.55
4-ClC_6H_4	192–193	$C_{11}H_{11}ClN_2S \cdot C_2H_2O_4$	47.49	3.99	8.52	47.31	4.02	8.38
3,4-$Cl_2C_6H_3$	209–214	$C_{11}H_{10}Cl_2N_2S \cdot HCl$	42.66	3.58	9.05	42.88	3.65	8.83
2,3,4-$Cl_3C_6H_2$	255–256.5	$C_{11}H_9Cl_3N_2S \cdot HCl$	38.39	2.93	8.14	38.48	2.97	8.22
3-BrC_6H_4	194–195.5	$C_{11}H_{11}BrN_2S \cdot HCl$	41.33	3.78	8.76	41.34	3.86	8.67
4-BrC_6H_4	183.5–184	$C_{11}H_{11}BrN_2S \cdot C_2H_2O_4$	41.33	3.78	8.76	42.02	3.51	7.65
4-FC_6H_4	249–252	$C_{11}H_{11}FN_2S \cdot HCl$	51.06	4.67	10.83	51.20	4.55	11.05
2-OCH_3-5-FC_6H_3	187–190	$C_{12}H_{13}FN_2OS \cdot HCl$	49.91	4.89	9.70	50.03	4.91	9.63
3-F-4-$CH_3OC_6H_3$	208–214	$C_{12}H_{13}FN_2OS \cdot HCl$	49.91	4.89	9.70	50.09	4.85	9.38
3-$CF_3C_6H_4$	173–179	$C_{12}H_{11}F_3N_2S \cdot HCl$	46.68	3.92	9.07	46.57	4.05	8.93
4-$CH_3OC_6H_4$	168–169.5	$C_{12}H_{14}N_2OS \cdot C_2H_2O_4$	51.84	4.97	8.64	51.82	4.97	8.80
4-$CH_3C_6H_4$	240–242	$C_{12}H_{14}N_2S \cdot HCl$	56.57	5.93	11.00	56.53	6.02	10.83
2,4-$(CH_3)_2C_6H_3$	192–196	$C_{13}H_{16}N_2S \cdot HCl$	58.09	6.38	10.42	58.06	6.36	10.50
2-$NO_2C_6H_4$	173.5–175.5	$C_{11}H_{11}N_3O_2S \cdot C_2H_2O_4$	46.01	3.86	12.38	46.01	3.99	12.87
3-$NO_2C_6H_4$	183–184	$C_{11}H_{11}N_3O_2S \cdot C_2H_2O_4$	46.01	3.86	12.38	45.51	3.96	12.40
4-$NO_2C_6H_4$	203.5–206	$C_{11}H_{11}N_3O_2S \cdot HCl$	46.23	4.23	14.71	46.45	4.37	14.65
4-$NH_2C_6H_4$	245–250	$C_{11}H_{13}N_3S \cdot 2HCl$	45.21	5.17	14.38	45.05	5.24	14.36
4-HOC_6H_4	215–216.5	$C_{11}H_{12}N_2OS$	59.97	5.49	12.72	59.74	5.78	12.41
C_4H_3S[a]	216–220	$C_9H_{10}N_2S_2 \cdot HCl$	43.80	4.49	11.35	43.96	4.53	11.39
C_4H_3O[b]	206.5–209	$C_9H_{10}N_2OS \cdot HCl$	46.85	4.85	12.14	47.05	4.91	11.98

[a] 2-Thienyl. [b] 2-Furyl.

pheasants, ducks, cats, tigers, rats, mice, monkeys, and man.[1] In alkaline solution and/or at high temperature XII hydrolyzes to the water-insoluble 1-(2-mercaptoethyl)-2-oxo-4-phenylimidazolidine (XIII), which is inactive against nematodes and almost atoxic. The mercaptoimidazolidine XIII is also a major metabolite of tetramisole (XII) in sheep, chickens, and rats.



XII



XIII

Experimental Section[6]

The examples given are illustrative of the preparative procedures used for all the members of a series. Details of the biological testing procedures are being described elsewhere.[1]

2-Imino-3-(2-thenoylmethyl)thiazoline Hydrobromide (Ia, Ar = 2-Thienyl).—A solution of 4.0 g (0.04 mole) of 2-aminothiazole, 8.0 g (0.04 mole) of bromoethyl 2-thienyl ketone in 60 ml of 2-propanol was stirred and refluxed for 1.5 hr. The precipitated **hydrobromide salt** was filtered off and dried *in vacuo;* yield 8.8 g (72%), mp 206–206.3°.

2-Acetylimino-3-(2-thenoylmethyl)thiazoline (Ib, Ar = 2-Thienyl).—To a mixture of 15.3 g (0.05 mole) of the hydrobromide salt of Ia (Ar = 2-thienyl) and 7.9 g (0.1 mole) of pyridine in 100 ml of chloroform was added 10.2 g (0.1 mole) of acetic anhydride. The mixture was stirred and refluxed for 1.5 hr. After cooling, the mixture was made alkaline (NH_4OH). The organic layer was separated and dried ($MgSO_4$). The solvent was removed and the crude residue recrystallized from toluene, giving 11.6 g (88%) of the product, mp 146–147°.

2-Acetylimino-3-[2-hydroxy-2-(2-thienyl)ethyl]thiazoline (IV).—To a stirred solution of 13 g (0.05 mole) of Ib (Ar = 2-thienyl) in 125 ml of 2-propanol was added portionwise 0.76 g (0.02 mole) of $NaBH_4$. After the addition was complete, the mixture was stirred and refluxed for 1 hr. The solvent was removed and the solid residue dissolved in 4 *N* HCl. The solution was made alkaline and the free base was extracted with chloroform. The $CHCl_3$ layer was dried and evaporated. The solid residue was crystallized from 2-propanol, yielding 10.5 g (80%) of product, mp 132.5–133°.

6-(2-Thienyl)imidazo[2,1-*b*]thiazole (V).—A mixture of 9.1 g (0.03 mole) of the hydrobromide salt of Ia (Ar = 2-thienyl) in 200 ml of 0.1 *N* HBr was refluxed for 5 min. The solution was made alkaline and the product was extracted with chloroform. The extract was dried and the solvent was removed. Recrystallization of the crude product from 2-propanol–water (2:1) gave 4.1 g (67%) of free base, mp 143.5–144°.

5,6-Dihydro-6-(2-thienyl)imidazo[2,1-*b*]thiazole (VII).—$SOCl_2$ (30 ml) was cooled to 5°, and 20.1 g (0.075 mole) of IV was added under cooling over a period of 1 hr. The mixture was stirred for 1 hr at room temperature. Acetic anhydride (150 ml) was added and the formed acetyl chloride was distilled during a 1-hr period. The mixture was refluxed for an additional hour. The solvents were then removed. The residual oil was dissolved in dilute HCl and impurities were filtered off. The filtrate was rendered alkaline and the product was extracted with toluene. Drying of the organic phase and removal of the solvent left an oil, which was dissolved in 2-propanol. The **oxalate salt** was formed by adding a solution of oxalic acid in 2-propanol. After cooling, the product was collected and washed with 2-propanol, yielding 12.3 g (56%) of crystals melting at 192–193°.

2-Acetylimino-3-(β-hydroxyphenethyl)thiazoline (IIb, Ar = phenyl).—A solution of 6.5 g (0.025 mole) of Ib (Ar = phenyl)[2] in 50 ml of 2-propanol was treated portionwise with 0.27 g (0.007 mole) of $NaBH_4$. After addition, the mixture was stirred and refluxed for 2 hr. The solvent was evaporated. The solid residue was dissolved in dilute HCl and filtered. The filtrate was made alkaline whereupon the precipitate was collected and recrystallized from 2-propanol; 5.3 g (81%) of material, mp 157–159°, was obtained.

5,6-Dihydro-6-phenylimidazo[2,1-*b*]thiazole (III, Ar = phenyl). Method A.—Treatment of 19.7 g (0.075 mole) of IIb (Ar = phenyl) with 30 ml of $SOCl_2$ as described above for VII, gave 10.1 g (74%) of the **oxalate salt,** mp 186.8–187.5° (ethanol).

(6) Melting points were taken in a Tottoli apparatus and are reported as corrected values. Analytical data are given in Tables I–VI.

Method B.—To a mixture of 7.5 g (0.025 mole) of the hydrobromide salt of IIa (Ar = phenyl)[7] and 11.5 ml of $SOCl_2$ was added cautiously and with cooling 60 ml of acetic anhydride. When a solution was obtained the cooling bath was removed and the mixture refluxed for 10 min. An additional 6 ml of $SOCl_2$ was added and refluxing was continued for 30 min. The formed acetyl chloride was removed. The acetic anhydride was removed *in vacuo* and the resulting oil dissolved in dilute HCl. The base, liberated with NH_4OH, was extracted with toluene. The extract was dried and the solvent was removed. The oily residue was dissolved in 2-propanol and the **oxalate salt** formed in the usual manner to yield 4.9 g (67%) of salt, mp 186–187°.

Method C.—To a solution of 0.02 mole of freshly prepared sodium ethoxide in 80 ml of ethanol, was added 3.6 g (0.02 mole) of 2-thio-4(5)-phenylimidazolidine (XI).[8] The reaction mixture was stirred and refluxed for 15 min; 3.1 g (0.02 mole) of chloroacetaldehyde diethyl acetal was added. Stirring and refluxing was continued for 1 hr. The ethanol was evaporated and to the residue was added 28 ml of concentrated HCl and it was filtered. After refluxing the filtrate for 1 hr, the solution was made alkaline and extracted with chloroform. The extract was dried and evaporated to leave a basic residue. The **oxalate salt** (2.4 g, 41%), mp 184–185°, was prepared in the usual way.

2-Imino-3-(phenacyl)thiazoline Hydrobromide (IXa, Ar = Phenyl).—To a solution of 4.9 g (0.05 mole) of 2-amino-4,5-dihydrothiazole in 40 ml of acetonitrile was added portionwise 10 g (0.05 mole) of phenacyl bromide. The reaction was exothermic. The mixture was stirred and refluxed for 30 min. After cooling, the precipitate was collected and dried, yielding 13.5 g (90%) of the hydrobromide salt, mp 200°.

2-(Acetylimino)-3-(phenacyl)thiazoline (IXb, Ar = phenyl) was obtained in 80% yield from 15.1 g (0.05 mole) of the hydrobromide salt of IXa (Ar = phenyl) and 10.2 g (0.1 mole) of acetic anhydride as described for IIb (Ar = 2-thienyl); mp 140–141°.

2-Imino-3-(β-hydroxyphenethyl)thiazolidine Hydrobromide (Xa, Ar = Phenyl).—To a stirred suspension of 12.1 g (0.04 mole) of the hydrobromide salt of IXa in 125 ml of ethanol was added portionwise 1.9 g (0.05 mole) of $NaBH_4$. The temperature was kept between 5 and 10°. Stirring was continued for an additional hour. Upon evaporation of the solvent, the resulting solid was crystallized from dilute HBr yielding 10 g (83%) of the salt melting at 183–184.5°.

2-Acetylimino-3-(β-hydroxyphenethyl)thiazolidine (Xb, Ar = Phenyl).—To a solution of 10.5 g (0.04 mole) of IXb (Ar = phenyl) in 50 ml of methanol was introduced portionwise 0.76 g (0.02 mole) of $NaBH_4$ at 5–10°. After stirring at room temperature for 1 hr the solvent was removed and the residual solid was suspended in water. The product was extracted with chloroform and dried, and the solvent was removed. Recrystallization of the solid residue from toluene yields 8.3 g (81%) of crystals, mp 100–103°.

2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (XII). Method A.—Starting from 10.8 g (0.075 mole) of Xb (Ar = phenyl) and 30 ml of $SOCl_2$, according to the method employed for VII, one obtained 7.8 g (36%) of the **oxalate salt**, mp 195.5–196°; the free base melts at 90.5–92°.

Method B.—A solution of 5.3 g (0.02 mole) of Xb (Ar = phenyl) in 150 ml of chloroform was treated with 2.4 g (0.02 mole) of $SOCl_2$ at 20°. A 10% solution of Na_2CO_3 (83 ml) was added and the mixture refluxed for 1 hr. The organic layer was separated, dried, and evaporated. The oily residue was dissolved in 2-propanol and the hydrochloride salt precipitated by adding 2-propanolic HCl. Recrystallization from ethanol gave 3.6 g (75%) of the **hydrochloride salt**, mp 261–264.5°.

Method C.—To a suspension of 17 g (0.09 mole) of 1,2-dibromoethane, 7.8 g (0.093 mole) of Na_2CO_3 in 60 ml of 2-propanol was added over a period of 1 hr a suspension of 3.6 g (0.02 mole) of 4(5)-phenylimidazoline-2-thione (XI)[8] in 120 ml of 1.5% NaOH. The mixture was stirred and refluxed for 3 hr and the solvent was removed. Then 18 ml of 15% KOH was added and the product was extracted with toluene. The organic phase was dried and the solvent was removed. The crude oil was dissolved in acetone and the **hydrochloride salt** was formed by adding a solution of HCl in 2-propanol. Recrystallization from ethanol yielded 3.0 g (63%) of the salt, mp 263–265°.

Method D.—A solution of 3.0 g (0.01 mole) of the hydrobromide salt of Xa (Ar = phenyl) in 5 ml of concentrated H_2SO_4 (*d* 1.83) was stirred at room temperature for 1 hr, poured on crushed ice, and made alkaline with ammonia, and the product was extracted with toluene. The extract was dried ($MgSO_4$) and evaporated. The solid residue was dissolved in acetone. Upon addition of HCl in 2-propanol 1.9 g of the **hydrochloric salt** of XII (80%) precipitated, mp 263–265°.

Tetramisole (XII) is a white, stable, crystalline hydrochloride ($C_9H_{12}N_2S \cdot HCl$, mp 260–270°) freely soluble in water (21% at 20°), in methanol (11%), and propylene glycol (7%). It is sparingly soluble in ethanol (1.6%) and very slightly soluble (less than 0.1%) in chloroform, hexane, and acetone. The free base of XII is freely soluble in chloroform, methanol, and ethanol (more than 40%) as well as in a variety of aqueous solutions of organic acids, *e.g.*, 58% in 40% tartaric acid, 52% in 40% citric acid, and 56% in 40% acetic acid. Aqueous solutions of XII are acidic and very stable at room temperature.

2,3,5,6-Tetrahydro-6-(4-nitrophenyl)imidazo[2,1-*b*]thiazole Hydrochloride (VIII, Ar = 4-Nitrophenyl).—A mixture of 6.0 g (0.022 mole) of the nitrate salt of XII (prepared from the free base with nitric acid in tetrahydrofuran, mp 168–168.5°) in 100 ml of H_2SO_4 (*d* 1.83) was stirred at room temperature for 5 days. The solution was poured onto crushed ice and made alkaline, and the product was extracted with chloroform. The extract was dried and evaporated. The oily residue was dissolved in 2-propanol and the **hydrochloride salt** was formed by adding 2-propanolic HCl. Recrystallization from ethanol yielded 5 g (60%) of material, mp 203.5–206° dec.

2,3,5,6-Tetrahydro-6-(4-aminophenyl)imidazo[2,1-*b*]thiazole Dihydrochloride (VIII, Ar = 4-Aminophenyl).—A solution of 14.9 g (0.052 mole) of the hydrochloride salt of VIII (Ar = 4-nitrophenyl) in 200 ml of methanol was filtered over Norit FNx. The filtrate was strongly acidified with a saturated solution of HCl in 2-propanol and hydrogenated at normal pressure and at room temperature, in the presence of 3.0 g of 10% Pd–C. After theoretical hydrogen uptake, the catalyst was filtered off and the solvent was concentrated to 100 ml; a crystalline product separated out and filtration gave 6.4 g (42%) of the salt, mp 245–250° dec.

2,3,5,6-Tetrahydro-6-(4-hydroxyphenyl)imidazo[2,1-*b*]thiazole (VIII, Ar = 4-Hydroxyphenyl).—A stirred solution of 2.9 g (0.01 mole) of the dihydrochloride salt of VIII (Ar = 4-aminophenyl) in 20 ml of 5% HCl was cooled to 0°. At this temperature a solution of 0.76 g (0.011 mole) of $NaNO_2$ in 10 ml of water was added dropwise. After addition, the mixture was stirred for 30 min at room temperature, then slowly heated and kept at 60° for another 30 min. The solution was filtered over charcoal and the filtrate was made alkaline with ammonia. The precipitate was filtered off, washed with water, and recrystallized from ethanol yielding 1.5 g (65%) of product, mp 215–216.5°.

Metabolite Experiment.—A single oral dose of 750 mg of IV was given to each of 8 Leghorn chickens, the feces were collected for 3 days (2549 g), dried (532 g), homogenized in a ball mill, suspended in 3 l. of 5 *N* HCl, shaken for 1 hr, and filtered with addition of 2 l. of water. The brown, clear filtrate was alkalized to pH 10 with NaOH and extracted with 10 l. of ether. The concentrated ethereal extract (1 l.) was shaken with 350 ml of 0.1 *N* HCl, and the water layer was made alkaline with NaOH and extracted with 50 ml of chloroform. The concentrated extract (15 ml) was separated by column chromatography (35 × 3 cm, silica gel in methanol, flow rate: 5 ml of methanol/hr). Each 10-ml fraction was analyzed by thin layer chromatography [silica gel G, 250 μ, solvent system: $CHCl_3$–methanol (95:5 v/v) spraying with a mixture of ethanol–acetic anhydride–H_2SO_4 (*d* 1.84) (80:10:10 v/v/v) followed by heating at 110° for 20 min]. Two spots were present in fractions 16–24, one spot in fractions 23–64 and one in fractions 106–124. The major blue-violet spot in the first group of fractions (R_f 0.5) was identified as thiazothienol (IV) itself, the minor spot (R_f 0.9) as the previously synthesized 6-(2-thienyl)imidazo[2,1-b]thiazole (V), which is inactive as an anthelmintic. The blue-violet spot (R_f 0.05) in the last group of fractions was identified as deacetylated thiazothienol (VI) which is equally inactive against nematodes. The blue-violet spot (R_f 0.27 ± 0.03) in fractions 13–64 was an unknown compound. After evaporation *in vacuo*, spectrophotometric analysis of the oily residue led to the following conclusions: (1) absence of OH, =NH, and C=O in infrared; (2) presence of a nonconjugated thiophene ring (infrared band at 690 cm^{-1}

(7) J. H. Biel [U. S. Patent 3,040,050 (1962); *Chem. Abstr.*, **57**, 13671*g* (1962)] reports mp 167–168° for the base.

(8) F. Feist and H. Arnstein, *Ber.*, **28**, 3173 (1895).

and ultraviolet maximum at 235 mμ); (3) probable presence of a C=N- moiety in a five-membered ring (infrared band at 1570 cm^{-1} and ultraviolet maximum at 271 mμ); (4) probably structure 5,6-dihydro-6-(2-thienyl)imidazo[2,1-*b*]thiazole (VII).

The oily residue was crystallized with oxalic acid from 2-propanol to furnish 190 mg of an oxalate salt, after drying, mp 191–192°. Elemental analysis was in agreement with the proposed structure VII oxalate.

Anal. Calcd for $C_9H_8N_2S_2 \cdot C_2H_2O_4$: C, 44.28; H, 3.38; N, 9.39; S, 21.50. Found: C, 44.05; H, 3.36; N, 9.55; S, 21.51.

Compound VII (thiazothielite) was then synthesized by ring closure of thiazothienol (IV) with $SOCl_2$ in the presence of acetic anhydride. Synthetic VII and the metabolite isolated from fractions 23–64 were found to be the same compound (mmp 192–193°, ultraviolet and infrared spectra).

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Semisynthetic Penicillins. III. Heterocyclic Penicillins

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This report describes a group of penicillins related to 2-biphenylylpenicillin,[1] in which one of the two phenyl rings is replaced by a heterocyclic ring. The structure–activity relationship of these penicillins is discussed. The preparation of some new side-chain acids used in the synthesis of these penicillins is reported.

In part I of this series[2] the preparation of a group of 2-biphenylylpenicillins which are highly active against a resistant[3] strain of staphylococcus was reported. In a subsequent paper[4] a variety of further structural modifications of the 2-biphenylyl side chain was reported. These studies indicated that replacing either benzene ring with α- and β-naphthyl resulted in compounds having activity similar to that of the parent compound, while replacing either benzene ring with a cyclohexyl moiety, gave compounds having only modest activity against resistant staphylococci. These studies also demonstrated that in the modification of the biphenylyl group the proximal[5] ring must be sufficiently aromatic and that the distal ring must conform to very exacting structural requirements for the compound to be highly active against resistant staphylococci.

This paper describes the preparation of a group of heterocyclic analogs of 2-biphenylylpenicillin and a study of the effect on biological activity of replacing either ring with certain heterocyclic systems. These penicillins are tabulated in Table I.

Earlier conjecture as to the requirements of the size and substitution of the proximal ring in determining the degree of penicillinase resistance of the penicillin is supported by the activities of compounds **1–6**. Our previous studies, and the work of Doyle, *et al.*,[6] suggest that while the six-membered ring with only one *o*-phenyl substituent can confer penicillinase resistance on the penicillin, the phenyl-substituted unfused five-membered ring must be reinforced by *o,o'* disubstitution with respect to the carboxamido grouping to achieve the same effect. In this case **1–5**, without the *o,o'* disubstitution, are essentially inactive against the resistant strain, while oxacillin, 5-methyl-3-phenyl-4-isoxazolylpenicillin, having an *o,o'*-disubstituted five-membered heterocyclic ring, and **6**, having a phenyl-substituted, unfused six-membered ring, have activity against the resistant strain similar to their activity against the susceptible strain.

For the fused heterocyclic compounds **7–20** the same relationships hold as were found for the phenylpenicillins described in the preceding studies. Apparently the proximal phenyl ring can be replaced by a heterocyclic ring of sufficient size and aromaticity (*e.g.*, six-membered ring or fused-heterocyclic but not unfused five-membered ring) with the retention of activity against the resistant staphylococcus, provided that there is adjacent to the carboxamido group a phenyl or an equivalent substituent. As reflected in the preceding studies, when the adjacent carbon carries hydrogen or alkyl (**10**, **13**, **15**, and **16**) the activity against the resistant strain is lost, although the cyclohexyl ring can be a fairly efficient substitute for the distal phenyl substituent (see **14**, Table I, in ref 4: MIC of *o*-cyclohexylphenylpenicillin, susceptible 0.09 μg/ml, resistant 7.5 μg/ml). The *o*-phenyl substituent is less efficient in confering penicillinase resistance on the molecule when the carboxamido group is attached adjacent to the hetero atom rather than adjacent only to carbons (compare **7** and **11**, **14** and **17**).

The minimum inhibitory concentration values for **21** and **22** indicate that the distal phenyl group can be replaced by an aromatic heterocyclic system with the retention of activity against the resistant staphylococcus.

(1) 2-Biphenylylpenicillin has also been referred to as Ancillin in various publications.

(2) J. R. E. Hoover, A. W. Chow, R. J. Stedman, N. M. Hall, H. S. Greenberg, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.*, **7**, 245 (1964).

(3) The term "susceptible" is used for those staphylococci that are sensitive to penicillins G and V while the term "resistant" is used for those penicillinase-producing staphylococci unaffected by high levels (*e.g.*, 500–1000 μg/ml) of these antibiotics.

(4) R. J. Stedman, J. R. E. Hoover, A. W. Chow, M. M. Dolan, N. M. Hall, and R. J. Ferlauto, *J. Med. Chem.*, **7**, 251 (1964).

(5) See ref 4, p 252, for a definition of the proximal and distal rings.

(6) F. P. Doyle, J. C. Hanson, A. A. W. Long, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.*, 5838 (1963).