Certain Thiazolo-Benzimidazoles and Thiazino-Benzimidazoles

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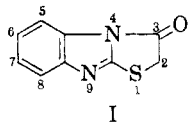
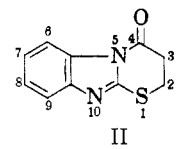
Since anthelmintic activity *in vitro* against *Fasciola hepatica* had earlier been recorded by Mackie and co-workers[1-3] in certain aralkylidene derivatives of 2-thioketo-4-oxothiazolidine and some derivatives of 2*H*-1,4-benzothiazin-3(4H)one, it appeared of interest to prepare the derivatives of the thiazolo[3,2-*a*]benziimidazol-3(2H)one (I) and the tetrahydro thiazinobenzimidazolones (II,III) of similar structures, with a view to testing of their anthelmintic activity against liver flukes, hookworms, and the ascaris infection in poultry and dogs.



I



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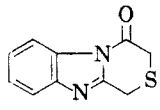

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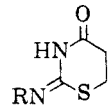
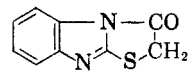
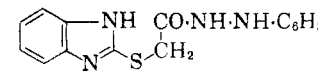


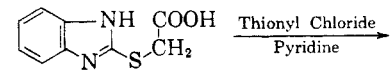
IVa R = ·$COCH_3$
b R = ·C_6H_5

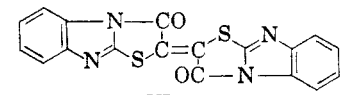
The compound (I) was prepared by the method of Duffin and Kendall[4] by the cyclization of 2-benzimidazolyl thioglycollic acid with a mixture of pyridine and acetic anydride. The 5-substituted aralkylidenes of I were prepared by refluxing the thiazolidone with a slight excess of an appropriate aldehyde in the presence of glacial acetic acid and fused sodium acetate. On gentle warming with phenylhydrazine in glacial acetic acid, the thiazolo[3,2-*a*]benzimidazol-3(2H)one (I) was decomposed to the phenyl hydrazide of 2-benzimidazolylthioglycollic acid (V). Thionyl chloride in the presence of dry pyridine as catalyst, vigorously reacted with the 2-benzimidazolylthioglycollic acid to give a bronze colored product, to which a *trans*-thioindigoid type of structure VI has been assigned on the basis of the analysis and infrared spectra. This compound was insoluble in the usual organic solvents but could be crystallized from the boiling nitrobenzene. It had marked stability towards the boiling concentrated hydrochloric acid and the strong alkalies.





V

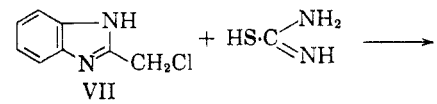




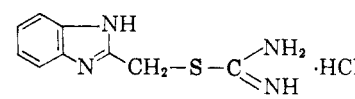
VI

The compounds II and III were prepared by the cyclization of the corresponding thioacids using a mixture of pyridine and acetic anhydride. The infrared spectra of these were identical in the 3–9 μ region, but showed dissimilarities in the region 9–14 μ. For the comparison of the anthelmintic activity, β-isothioureidopropionic and β-phenylisothioureidopropionic acids were also converted into their cyclized products (IVa,b) by a procedure similar to that used for the thiazolidone(I).

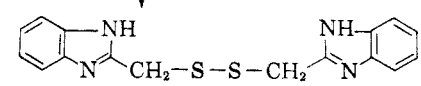
The reaction of 2-chloromethylbenzimidazole-(VII) with thiourea, led to the formation of the bis-(2-benzimidazolylmethyl) disulfide (VIII), presumably through the intermediate formation and the decomposition of the 2-benzimidazolylmethylisothiourea hydrochloride(IX)



VII



IX



VIII

The results of the biological testing of these compounds will be reported elsewhere.

EXPERIMENTAL

The following 5-aralkylidene derivatives of the thiazolidone(I) were prepared by refluxing I with a slight excess of the aldehyde in glacial acetic acid in the presence of fused sodium acetate. The derivatives were filtered, washed with a little hot water and dilute ethanol, and recrystallized from an appropriate solvent.

Reaction of phenylhydrazine with thiazolo[3,2-a]-benzimidazol-3(2H)one. A mixture of the thiazolidone (475 mg.) and phenylhydrazine (0.4 cc.) in glacial acetic acid (5 cc.) was heated for half an hour at 100° and then gently boiled for 5 min., cooled, and diluted with water. The precipitate recrystallized in needles from aqueous ethanol. Yield of the phenylhydrazide of 2-benzimidazolylthioglycollic acid was 380 mg., m.p. 191–192° (dec.).

Anal. Calcd. for $C_{15}H_{14}N_4OS$: C, 60.40; H, 4.69; N, 18.79. Found: C, 60.00; H, 4.69; N, 18.90.

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(1) A. Mackie and A. L. Misra, *J. Chem. Soc.*, 3919 (1954).

(2) A. Mackie and J. Raeburn, *Brit. J. Pharmacol.*, **7**, 219 (1952a).

(3) A. Mackie, G. M. Stewart, A. A. Cutler, and A. L. Misra, *Brit. J. Pharmacol.*, **10**, 7 (1955).

(4) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 361 (1956).

TABLE I

Compound	M.P., °C.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Benzylidene[a]	216–217	$C_{16}H_{10}N_2OS$	69.05	68.95	3.59	4.31
Salicylidene[b]	214–215	$C_{16}H_{10}N_2O_2S$	65.30	65.38	3.40	3.54
Cinnamylidene[c]	234–235	$C_{18}H_{12}N_2OS$	71.05	71.03	3.94	3.94
Furfurylidene[d]	231–232	$C_{14}H_8N_2O_2S$	62.68	63.03	2.98	3.44
Vanillidene[d]	256–257 (dec.)	$C_{17}H_{12}N_2O_3S$	62.96	63.02	3.70	4.07
Anisalidene[e]	232–233	$C_{17}H_{12}N_2O_2S$	66.23	65.77	3.89	4.25
p-Nitrobenzylidene[d]	Above 300	$C_{16}H_9N_3O_3S$	59.44	59.85	2.78	2.67
p-Dimethylaminobenzylidene[f]	267–268 (dec.)	$C_{18}H_{15}N_3OS$	67.29	67.36	4.67	5.14

[a] Yellow plates from glacial acetic acid (Ref. 4 gives m.p. 219°). [b] Light grey plates from ethanol. [c] Yellow plates from glacial acetic acid. [d] Yellow needles. [e] Yellow prisms from the same solvent. [f] Orange prisms from ethanol (Ref. 4 gives m.p. 269°).

2-Carbamylmethylmercaptobenzimidazole. To 4.5 g. of 2-mercapto benzimidazole[5] in boiling 50 cc. of absolute ethanol, was added a solution of sodium ethoxide prepared by dissolving 0.8 g. of sodium in 15 cc. of absolute ethanol. After boiling the solution for 10 min., 2.82 g. of chloroacetamide was added and the contents refluxed for 0.5 hr. The alcohol was removed under reduced pressure and the residue recrystallized as prismatic rods from aqueous ethanol. The yield was 4.5 g., m.p. 206–207°.

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.17; H, 4.34; N, 20.29. Found: C, 52.30; H, 4.55; N, 19.97.

Ethyl N¹-acetyl-2-benzimidazolylthioglycollate was prepared by refluxing ethyl 2-benzimidazolylthioglycollate with a 1:1 mixture of pyridine and acetic anhydride and crystallized in prismatic needles from ethanol, m.p. 118–119°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.03; N, 10.07. Found: C, 56.31; H, 5.21; N, 10.30.

[$\Delta^{2,2'(3H,3'H)}$-Bithiazolo[3,2-a]benzimidazol]-3,3'-dione (VI). To 1 g. of anhydrous 2-benzimidazolyl thioglycollic acid[6] suspended in 4 cc. of dry benzene, 3.5 cc. of thionyl chloride was added drop by drop with stirring. On the addition of 1 cc. of dry pyridine, a vigorous reaction took place and the contents became dark red in color. After the initial reaction subsided, the contents were warmed on a water bath for about 10 min. and cooled, and the excess of thionyl chloride and benzene was pumped off. The residue was washed with a dilute solution of sodium carbonate and finally with water and dried. Recrystallization afforded 0.75 g. of bronze plates from boiling nitrobenzene, m.p. above 300°.

Anal. Calcd. for $C_{18}H_8N_4O_2S_2$: C, 57.44; H, 2.12; N, 14.89. Found: C, 57.48; H, 2.00; N, 15.13.

The compound was insoluble in the usual organic solvents and markedly stable toward the strong alkalies and concentrated hydrochloric acid. The infrared spectrum in a Nujol mull showed the characteristic maxima at 6.03 μ (C=O); 6.29 μ and 6.71 μ (C=C aromatic; 6.71 μ may be the C=N encountered in thiazoles) 10.25 μ and 10.38 μ (C=C trans). The absence of a band in the 3.70-4.00 μ region showed that the carboxyl group was not present.

Preparation of β-2-benzimidazolylthiopropionic acid. A mixture of 4.5 g. of 2-mercaptobenzimidazole, 3.27 g. of β-chloropropionic acid, 35 cc. of 2*N* sodium hydroxide and 10 cc. water was gently refluxed for 2 hr., filtered, cooled in an ice bath, and acidified with 2*N* hydrochloric acid to *p*H 4. The precipitated solid was filtered, washed with water, and dried. It was recrystallized as prismatic thick rods from aqueous ethanol (charcoal). The yield of the β-2-benzimidazolylthiopropionic acid was 3.7 g., m.p. 175–176° (with effervescence).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.28; H, 4.45; N, 12.98.

Preparation of 2H-m- thiazino[3,2-a]benzimidazol-4(3H)-one (II). A mixture of 1 g. of the above acid and a 10:1.5 mixture of pyridine and acetic anhydride was gently heated under reflux for 0.5 hr., cooled, diluted with ice cold water, the unreacted acid and acetic acid were neutralized with a dilute solution of sodium bicarbonate, and the residue filtered. It was recrystallized as colorless prismatic needles from aqueous ethanol. The yield of II was 690 mg., sintering at 143° and melting at 151–152°.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.72. Found: C, 58.60; H, 4.05; N, 13.67.

The infrared spectrum of the compound was determined in chloroform for the 2–7 μ region and in carbon disulfide for the 7–14 μ region. The characteristic maxima were 3.42 μ and 3.51 μ (CH_2), 5.97 μ (tertiary N, may also be C=N). There was no absorption in the 3.70–4.00 μ region (no carboxyl group).

Preparation of 2-benzimidazolyl methylthio acetic acid. 2-Sulfhydrylmethylbenzimidazole was prepared by the method of Hughes and Lions.[7] A mixture of 4.9 g. of the above mercaptan, 2.9 g. of monochloracetic acid, and 35 cc. of 2*N* sodium hydroxide was heated under reflux for 1 hr. on the water bath. The color of the liquid turned crimson red and then greenish brown. The solution was filtered, cooled, and neutralized with 2*N* hydrochloric acid to *p*H 4. A flocculent precipitate that separated became gummy. The yellow mother liquor was clarified with charcoal and on concentration *in vacuo* gave pale yellow crystals, which were recrystallized in plates from boiling water, yield, 1.9 g., m.p. 188–189°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.10; H, 4.92; N, 12.30.

Preparation of 1H-p-thiazino[4,3-a]benzimidazol-4(3H)-one (III). A mixture of the above acid 1.1 g. and a 10:1.5 cc. mixture of pyridine and acetic anhydride was allowed to reflux gently for 15 min., cooled, and worked up as before. The crude product was recrystallized first from aqueous ethanol and then in light yellow prismatic rods from benzene–light petroleum (40–60°). Yield of (III), 0.5 g., m.p. 104–105°.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.72. Found: C, 59.05; H, 4.17; N, 13.40.

The infrared spectrum of this compound was identical with that of II in the 3–9 μ region, and showed no bands in the 3.70–4.00 μ region but was dissimilar in the 9–14 μ region. The characteristic band at 13.15 μ may be due to the $-CH_2-S-CH_2-$ group.

(5) J. A. Van Allen and B. D. Deacon, *Org. Synthesis*, **30**, 56 (1950).

(6) J. G. Everett, *J. Chem. Soc.*, 3042 (1931).

(7) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 209 (1938).

Cyclodehydration of β-isothioureido propionic acid. The acid was prepared using thiourea and β-propiolactone by the method of Gresham, Jansen, and Shaver.[8] Five grams of the above acid and 15 cc. of a mixture of acetic anhydride and pyridine (10:5) was gently refluxed for about 15 min. Most of the acid dissolved and the color of the liquid turned golden yellow. On cooling and leaving overnight, the crystals separated out, which were collected, washed with a small amount of ethanol (95%), and then finally recrystallized in colorless prismatic rods from boiling water. The yield of 2-acetylimino-1,3-thiazan-4-one (IVa), was 2.6 g., m.p. 198° (gradual decomposition).

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.86; H, 4.65; N, 16.27. Found: C, 42.15; H, 4.27; N, 15.72.

Cyclodehydration of β-phenylisothioureidopropionic acid. The acid was prepared from phenylthiourea and β-propiolactone by the method of Gresham and Shaver.[9] On the addition of 20 cc. of the acetic anhydride–pyridine mixture (11:5) to 7.9 g. of the above acid, dissolution took place with the evolution of heat. the deep yellow solution was warmed under reflux on a water bath for 30 min. and cooled, and the solid was filtered, washed with a dilute solution of sodium carbonate, and repeatedly crystallized from ethanol and finally in rectangular slender rods from benzene. The yield of 2-phenylimino-1:3-thiazan-4-one (IVb) was 4.8 g., m.p. 169–170°.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.85; N, 13.58. Found: C, 58.21; H, 5.29; N, 13.86.

The mother liquor from the ethanol crystallization on concentration deposited a solid, which crystallized in colorless needles from benzene, m.p. 139–140°. It was probably a mixture of the unreacted acid and the cyclized product.

Anal. Found: C, 56.90; H, 4.91; N, 13.00.

Reaction of 2-chloromethylbenzimidazole with thiourea. To a boiling solution of 1.5 g. of thiourea in 15 cc. of absolute ethanol, 3.3 g. of 2-chloromethylbenzimidazole[10] was added. After a few minutes a thick crystalline mass of needles separated. The contents were refluxed for 5 hr., the needles gradually went into solution and the yellow prisms that separated, were filtered, recrystallized in pale yellow plates from aqueous ethanol. The yield of 2-benzimidazolylmethylisothiourea hydrochloride, (IX) was 0.58 g., m.p. 258–259°.

Anal. Calcd. for $C_9H_{11}N_4SCl,H_2O$: C, 41.45; H, 4.99. Found: C, 41.35; H, 4.62.

After removal of the yellow prisms, the ethanol mother liquor from the reaction was diluted with water and the precipitate crystallized in feathery pale yellow needles from aqueous ethanol and charcoal. Yield of the bis[2-(benzimidazolyl methyl)]disulfide (VIII), 0.5 g., m.p. 110–115°.

Anal. Calcd. for $C_{16}H_{14}N_4S_2.{}^1/_2H_2O$: C, 57.31; H, 4.47; N, 16.71. Found: C, 57.68; H, 4.23; N, 17.24.

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(8) T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948).

(9) T. L. Gresham and F. W. Shaver, U. S. Patent **2,563,034**; *Chem. Abstr.*, **46**, 1594 (1952).

(10) A. Bloom and A. R. Day, *J. Org. Chem.*, **4**, 14 (1939).

A New Method for the Activation of Copper Chromium Oxide as a Reducing Catalyst

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Copper chromium oxide, when prepared by the method of Adkins, Burgoyne, and Schneider,[1] will catalyze the reduction of carbonyl groups at room temperature but only after activation. This was originally accomplished through exposure of the catalyst to a high pressure (226 atm.) of hydrogen at 100°.[1] It has now been found that the same activation can be achieved simply by refluxing the copper chromium oxide in cyclohexanol for four hours. This is illustrated in Fig. 1. Hydrogenation of acetone to 2-propanol began at room temperature when copper chromium oxide was used which had been activated either essentially according to the previous procedure[1] (Curve C) or by the present method (Curve B), but, when the catalyst had not been activated by any means, a "critical temperature" of *ca.* 100° was required before hydrogenation would proceed (Curve A).

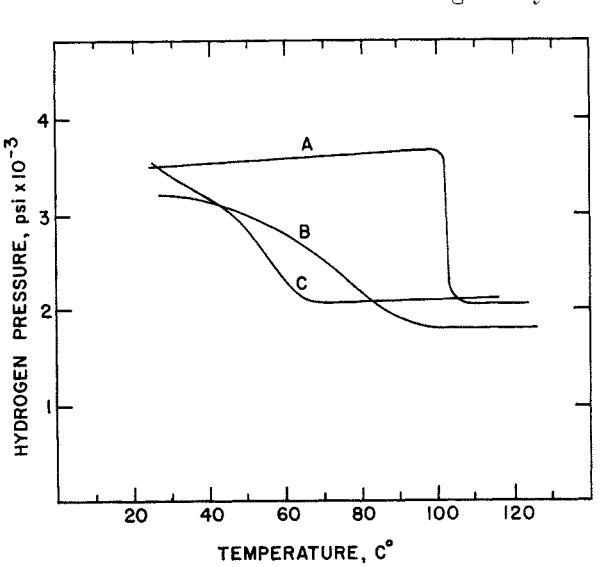

Fig. 1. The influence of temperature on the rate of hydrogenation of 20 ml. of acetone catalyzed by 6 g. of copper chromium oxide which had not been activated (Curve A), which had been activated by refluxing it in cyclohexanol (Curve B), and which had been activated by exposing it to 200 atm. pressure of hydrogen at 110° (Curve C)

The cyclohexanol which was used in the activation was simultaneously oxidized to cyclohexanone. The yield was 11% based on the isolation of cyclohexanone semicarbazone. No attempt was made to increase the percentage conversion of cyclohexanol to cyclohexanone, but it was found that under modified conditions certain steroidal alcohols could be oxidized to the corresponding ketones in a good

(1) H. Adkins, E. E. Burgoyne, and H. J. Schneider, *J. Am. Chem. Soc.*, **72**, 2626 (1950).