of 0.5 *N* aqueous hydrochloric acid. The aqueous layer was basified immediately with aqueous sodium carbonate, and the solution was extracted three times with ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a yellow oil, which was distilled to yield 1 g. (24%) of a colorless oil, b.p. 134–137° at 0.2 mm. This material was dissolved in 5 ml. of anhydrous ether; to it was added maleic acid (0.38 g., 0.0032 mole) dissolved in 2 ml. of ethanol. The white crystals which formed were recrystallized from ethanol–ether; yield: 1.0 g. (74%); m.p. 116–119°.

Anal.—Calc. for $C_{22}H_{29}NO_8$: C, 60.88; H, 6.71. Found: C, 61.05; H, 7.05.

***N*-(2-Methylene-1,3-dioxano)normeperidine Maleate**—Normeperidine (1.0 g., 0.004 mole) in 20 ml. of dimethylformamide was treated with 2-bromomethyl-1,3-dioxane (0.8 g., 0.004 mole) and anhydrous sodium carbonate (0.6 g., 0.006 mole). The mixture was stirred at 100° for 18 hr. After cooling, it was added to 20 ml. of water and extracted three times with 20-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to 10 ml. Maleic acid (0.5 g., 0.004 mole) was dissolved in 5 ml. of ethanol, and to this was added the concentrated ether extracts. The resulting crystals were recrystallized from chloroform–ether; yield: 1.6 g. (85%); m.p. 145–148°.

Anal.—Calc. for $C_{23}H_{31}NO_8$: C, 61.45; H, 6.95; N, 3.12. Found: C, 61.66; H, 6.81; N, 2.94.

***N*-(2-Ethylene-1,3-dioxolano)normeperidine Maleate**—The procedure used was the same as described for *N*-(2-methylene-1,3-dioxano)normeperidine maleate, except 2-(2-bromoethyl)-1,3-dioxolane (0.85 g., 0.0047 mole) was used instead of 2-bromomethyl-1,3-dioxane; yield: 1.35 g. (70%); m.p. 162–164°.

Anal.—Calc. for $C_{23}H_{31}NO_8$: C, 61.45; H, 6.95. Found: C, 61.32; H, 7.16.

***N*-(2-Ethylene-1,3-dioxano)normeperidine Maleate**—The procedure used was the same as described for *N*-(2-methylene-1,3-dioxano)normeperidine maleate, except 2-(2-bromoethyl)-1,3-dioxane (0.8 g., 0.004 mole) was used instead of 2-bromomethyl-1,3-dioxane; yield: 0.8 g. (40%); m.p. 135–137°.

Anal.—Calc. for $C_{24}H_{33}NO_8$: C, 62.17; H, 7.18. Found: C, 62.20; H, 7.27.

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Aromatic Amines Condensed with Aminothiazoles, Directly and with Isatoic Anhydride, for Schistosomiasis Treatment I

I. NABIH and M. ABBASI

Abstract □ Structural combination between the two moieties necessary for the biological effectiveness in both oral schistosomicidal agents, 1-(2-diethylaminoethylamino)-4-methylthiaxanthone and 1-(5-nitro-2-thiazolyl)-2-imidazolidinone, namely, the substituted aromatic amine and aminothiazole, respectively, were tried. The combination between both systems was suggested to be through amide linkage.

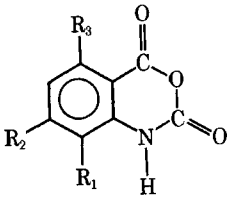
Keyphrases □ Aminothiazoles, condensation with aromatic amines—synthesis of oral schistosomiasis agents □ Aromatic amines, condensation with aminothiazoles—synthesis of oral schistosomiasis agents □ Schistosomiasis agents, oral—aromatic amines condensed with aminothiazoles, isatoic anhydride

The search for an oral chemotherapeutic agent for treatment of schistosomiasis led to the synthesis of 1-(2-diethylaminoethylamino)-4-methylthiaxanthone[1] (1), which was found also to be of carcinostatic value (2). Evidence has been accumulated that the structural feature necessary for the biological activity of this agent is a dialkylaminoalkylamine side chain *para* to a methyl on an aromatic ring (3–5). The drug was not ideal because of its undesirable side effects.

Recently, attention was attracted to the use of 5-nitrothiazole derivatives in the oral chemotherapy of schistosomiasis. The compound 1-(5-nitro-2-thiazolyl)-2-imidazolindinone[2] was found to exert good schistosomi-

[1] Lucanthone or Miracil D.

[2] Coded as Ciba-32644 or Ambilhar.



V

V*a*: $R_1 = R_2 = R_3 = H$

V*b*: $R_1 = CH_3$; $R_2 = R_3 = H$

V*c*: $R_1 = R_3 = H$; $R_2 = CH_3$

V*d*: $R_1 = Cl$; $R_2 = R_3 = H$

V*e*: $R_1 = R_3 = H$; $R_2 = Cl$

V*f*: $R_1 = CH_3$; $R_2 = H$; $R_3 = Cl$

V*g*: $R_1 = R_3 = H$; $R_2 = NO_2$

V*h*: $R_1 = R_2 = H$; $R_3 = NO_2$

cidal activity (6). But this agent is insoluble in water and it produces toxic effects during treatment.

The purpose of the present work was to synthesize compounds containing both essential systems required for the biological activity, namely the substituted aromatic amine and 2-amino-5-nitrothiazole or 2-aminothiazole. An amide linkage between the groups was sought, because it could be hydrolyzed in the body to free both entities, which could then act either independently or additively upon the parasite within the host.

Condensation of 2-amino-5-nitrothiazole with 4,6-dichloro-*m*-tolylchloride (I) gave *N*-(5-nitro-2-thiazolyl)-4,6-dichloro-3-methylbenzamide (II). Trials to replace the chlorine atom in position 6 in the amide (II) with the 2-diethylaminoethylamine side chain failed.

In an attempt to activate the 6-chlorine atom in the 4,6-dichloro-*m*-toluic acid system for replacement with the amino side chain, the corresponding 4,6-dichloro-*m*-toluamide (III) and 4,6-dichloro-*m*-tolunitrile (IV), through dehydration of the former, were prepared. But replacement of the 6-chlorine atom with the amino side chain in either the amide or the nitrile also failed to occur.

Due to the resistance of the chlorine atom in these structures for replacement by the amines, the condensation of 2-aminothiazole was attempted with systems that would furnish an amino group on the aromatic part along with the desired amide linkage. Thus, the tendency of isatoic anhydride and its derivatives to react with amines of different types to form amide linkage was investigated.

The condensation of isatoic anhydride with primary amines was found to yield the corresponding substituted anthranilamides and, concurrently, the corresponding ω-substituted *o*-ureidobenzoic acid (7–11).

In this work, 2-aminothiazole and 2-amino-5-nitrothiazole were used as the primary amine components in the condensation reaction with isatoic anhydride and derivatives.

The isatoic anhydrides, V*a–h*, were prepared through oxidation of the isatins using chromic trioxide (11). For comparison, the oxidation was also attempted using monoperphthalic acid. This was more fruitful because the yields of the anhydrides were higher (about 85%) and because of the high extent of purity. With chromic trioxide, the anhydrides came in yields of about 65%.

The condensation of the isatoic anhydride (V*a*), or any of its derivatives (V*b–h*), with 2-amino-5-nitrothiazole failed under different experimental conditions. But it readily occurred with 2-aminothiazole, and the products were *N*-(2-thiazolyl)-*o*-aminobenzamides (VI*a–f*). In the presence of nitro groups on the aromatic parts of the anhydrides (V*g–h*), the condensation reaction between 2-aminothiazole and the corresponding anhydride failed to occur.

EXPERIMENTAL[3]

4,6-Dichloro-*m*-tolyl Chloride (I)—A solution of 5 g. (0.024 mole) of pure 4,6-dichloro-*m*-toluic acid (12) in 10 ml. of dry benzene was treated with 3 g. (0.025 mole) of freshly distilled thionyl chloride. The reaction mixture was heated on a steam bath for 1 hr. and then allowed to cool at room temperature. The solvent and the unreacted thionyl chloride were removed by distillation. The liquid residue was distilled under reduced pressure at 150° (11 mm.) to give 3.2 g. (60%).

***N*-(5-Nitro-2-thiazolyl)-4,6-dichloro-3-methylbenzamide (II)**—To a suspension of 2.5 g. (0.015 mole) of 2-amino-5-nitrothiazole in 5 ml. of dry benzene was added, dropwise under stirring, 3 g. (0.013 mole) of I dissolved in 5 ml. of dry benzene. The mixture was refluxed on a steam bath for 3 hr.; then the solvent was distilled, and the residue was poured on ice-cold water with stirring. The solid product was collected, washed with water, and dried. After recrystallization from methanol, it provided 3.2 g. (74%) as yellow crystals, m.p. 210–212°.

Anal.—Calc. for $C_{11}H_7Cl_2N_3O_3S$: C, 39.75; H, 2.10; N, 12.55. Found: C, 39.65; H, 2.24; N, 12.87.

4,6-Dichloro-*m*-toluamide (III)—A stream of dry ammonia was passed through a cold solution of 2 g. (0.0089 mole) of the acid chloride, I, in 20 ml. of dry benzene for a few minutes. The solid material that separated was filtered, washed with water, dried, and recrystallized from an ethanol–water mixture to yield 1.58 g. (83%) as shiny white needles, m.p. 164–165°; IR: 1675 cm.$^{-1}$ (—CO·NH_2).

Anal.—Calc. for $C_8H_7Cl_2NO$: C, 47.05; H, 3.43. Found: C, 46.82; H, 3.61.

4,6-Dichloro-*m*-tolunitrile (IV)—To a suspension of 1 g. (0.005 mole) of the amide III in 2 ml. of dry pyridine was added 1 g. of phosphorus oxychloride under good cooling. The mixture was left at room temperature for 2 hr. and then heated on a steam bath for 20 min. Ice-cold water was added, and the formed precipitate was filtered, washed with cold water, and recrystallized from ethanol. The obtained white crystals were further purified through sublimation to give 0.75 g. (80%), m.p. 111–112°; IR: 2232 cm.$^{-1}$ (—CN).

Anal.—Calc. for $C_8H_5Cl_2N$: C, 51.61; H, 2.70; N, 7.52. Found: C, 51.34; H, 2.87; N, 7.18.

Isatoic Anhydrides (V*a–h*)—These anhydrides were prepared through the oxidation of the corresponding isatins by two different methods: one using chromic trioxide (11) and the other using monoperphthalic acid (13). The obtained melting points were: V*a*, 243° dec. [lit. (14) m.p. 240–243° dec.]; V*b*, 273° dec. [lit. (15) m.p. 277° dec.]; V*c*, 245° dec. [lit. (16) m.p. 245° dec.]; V*d*, 237° dec. [lit. (15) m.p. 232° dec.]; V*e*, 268° dec. [lit. m.p. (17) 268° dec.]; V*g*, 215° dec. [lit. (18, 19) m.p. 215° dec.]; and V*h*, 243° dec. [lit. (11) m.p. 244° dec.]. Compound V*f* was recrystallized from acetic acid and had m.p. 310° dec.

Anal.—Calc. for $C_9H_6ClNO_3$: C, 51.06; H, 2.87. Found: C, 51.43; H, 3.24.

[3] All melting points were taken in open glass capillaries, using a Gallenkamp melting-point apparatus, and are uncorrected. Microanalyses were performed by Micro-analytical Laboratory, National Research Centre, Cairo, U.A.R., and Spang Microanalytical Laboratory, Ann Arbor, Mich. IR spectra were determined with a Carl-Zeiss model IR 10 infracord spectrophotometer and were determined in chloroform.

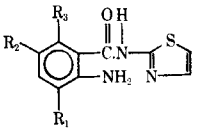


Table I—*N*-(2-Thiazolyl)-*o*-aminobenzamides (VI)

Compound	R_1	R_2	R_3	Yield, %	Melting Point[a]	Formula	Analysis, % Calc.	Analysis, % Found
VI*a*	H	H	H	73	164°	$C_{10}H_9N_3OS$	C, 54.79 H, 4.14 N, 19.17	C, 54.52 H, 4.18 N, 18.88
VI*b*	CH_3	H	H	83	192°	$C_{11}H_{11}N_3OS$	C, 56.56 H, 4.75 N, 18.02	C, 56.41 H, 4.80 N, 18.08
VI*c*	H	CH_3	H	79	198°	$C_{11}H_{11}N_3OS$	C, 56.65 H, 4.75	C, 56.35 H, 4.85
VI*d*	Cl	H	H	88	195°	$C_{10}H_8ClN_3OS$	C, 47.33 H, 3.18 N, 16.56	C, 47.28 H, 3.18 N, 16.76
VI*e*	H	Cl	H	80	210°	$C_{10}H_8ClN_3OS$	C, 47.33 H, 3.18 N, 16.56	C, 46.97 H, 3.16 N, 16.36
VI*f*	CH_3	H	Cl	81.5	243°	$C_{11}H_{10}ClN_3OS$	C, 49.34 H, 3.76 N, 15.69	C, 48.85 H, 3.63 N, 15.59

[a] Recrystallization solvent was ethanol.

***N*-(2-Thiazolyl)-*o*-aminobenzamides (VI*a–f*, Table I)**—A mixture of 0.005 mole from the isatoic anhydride and 0.43 g. (0.005 mole) of 2-aminothiazole in 5 ml. of isopropanol was refluxed for 10 hr. The alcohol then was distilled off and the residue crystallized from the proper solvent.

IR for VI*f*: 1640 cm.$^{-1}$ (—CO·NH—), 807 cm.$^{-1}$ (two adjacent ring hydrogen atoms in a 1,2,3,4-tetrasubstituted aromatic ring in the molecule), 1570 cm.$^{-1}$ (thiazole moiety) (20).

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