served for 10 min. The test drugs were given 20 min. prior to injection of phenylquinone.

Randall–Sellito Pressure Paw—The method employed was adapted from that of Randall and Sellito (8). Inflammation of the hindpaw of fasted Sprague-Dawley rats (body weight 100–125 g.) was induced by an injection of 0.1 ml. of 20% brewer's yeast suspension into the plantar surface. The ability of the subcutaneously administered test drugs (administered concomitantly with phlogistic agent) to affect the pressure pain interval was determined 1, 2, 3, and 4 hr. after drug administration. This test was modified to determine antipyretic activity; thus, rectal temperatures were taken prior to drug–phlogistic administration and at the designated time intervals after administration.

REFERENCES

(1) H. A. Luts, W. A. Zucarello, W. L. Nobles, and J. F. Grattan, *J. Pharm. Sci.*, **55**, 1459(1966).

(2) E. Palosiou, L. Szporny, and K. Nador, *ibid.*, **57**, 709(1968).

(3) W. A. Skinner, J. Kennedy, J. DeGraw, and H. Johnson, *J. Med. Chem.*, **12**, 715(1969).

(4) S. Irwin, "Gordon Research Conference on Medicinal Chemistry," 1959, p. 133.

(5) L. O. Randall and R. E. Baydon, *Ann. N. Y. Acad. Sci.*, **80**, 626(1959).

(6) W. L. Kuhn and E. F. Van Maanen, *J. Pharmacol. Exp. Ther.*, **134**, 60(1961).

(7) L. C. Hendershot and J. Forsaith, *ibid.*, **125**, 237(1959).

(8) L. O. Randall and J. J. Sellito, *Arch. Int. Pharmacodyn. Ther.*, **111** (9), 409(1957).

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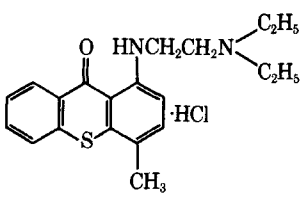
Condensed *p*-Toluidines with Aminothiazoles as Schistosomicidal Agents II

I. NABIH and M. ABBASI

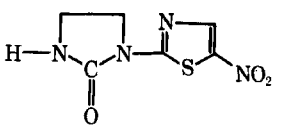
Abstract □ Compounds representing structural combinations between the two moieties necessary for the biological activity in both schistosomicidal agents, 1-(β-diethylaminoethylamino)-4-methylthiaxanthone and 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (*p*-toluidine and 5-nitrothiazole, respectively), have been synthesized. For the condensation reaction, aromatic azido acids were used followed by selective reduction of the azido groups through metallic hydrides.

Keyphrases □ *p*-Toluidines, 5-nitrothiazole—synthesis, potential schistosomicidal agents □ Schistosomicidal agents, potential—synthesis of condensed *p*-toluidines, aminothiazoles

Investigations carried out since the discovery of the schistosomicidal activity of 1-(β-diethylaminoethylamino)-4-methylthiaxanthone[1] (I) and its analogs showed that the presence of an amino side chain located on C-1 in *para*-position to the methyl group on C-4 is necessary for the biological activity of these agents (1, 2). In the recent schistosomicidal agent, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone[2] (II), the presence of the nitrothiazole group was confirmed to be an essential feature for its activity (3, 4).

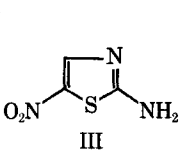


I

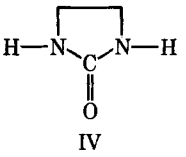


II

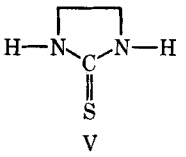
[1] Lucanthone or Miracil D.
[2] Ambilhar or Ciba 32644-Ba.



III



IV

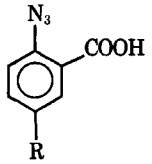


V

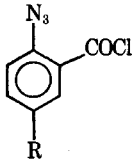
These considerations suggested the synthesis of compounds containing these necessary moieties. Both systems were designed to be connected through an amide linkage, because this may be biologically hydrolyzed to free both parts. Thus, the molecules may act as a whole or as separate components in the presence of one another.

Aromatic azido acids were used in the condensation reaction with 2-amino-5-nitrothiazole (III), 2-imidazolidinone (IV), and its thione analog, 2-imidazolidinethione (V). 2-Imidazolidinone is structurally included with 5-nitrothiazole in the schistosomicidal agent II.

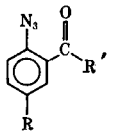
The azides of anthranilic acid (VI*a*) and its 3-methyl derivative (VI*b*) were prepared by a procedure involving the addition of hydrazoic acid to the corresponding diazonium salt. The azido acid chlorides (VII*a* and VII*b*) prepared through the action of thionyl chloride upon the acids VI*a* and VI*b*, respectively, reacted readily



VI*a*: R = H
VI*b*: R = CH_3

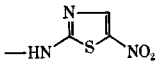
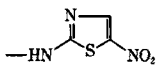
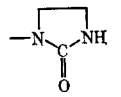
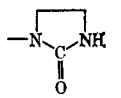
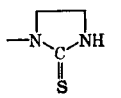
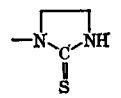


VII*a*: R = H
VII*b*: R = CH_3



VIII

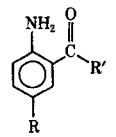
Table I—2-Azidobenzoyls

Number	R	R′	Yield, %	Melting Point (Recrystallization Solvent)[a]	Molecular Formula	Analysis, % Calc.	Analysis, % Found
a	H		64	208–210°(D)	$C_{10}H_6N_6O_3S$	C, 41.37 H, 2.08 N, 28.96 S, 11.03	C, 41.37 H, 2.36 N, 29.01 S, 11.14
b	CH_3		70	214–215°(D)	$C_{11}H_8N_6O_3S$	C, 43.42 H, 2.63 N, 27.63	C, 43.67 H, 2.34 N, 27.61
c	H		73	170–172°(E)	$C_{10}H_9N_5O_2$	C, 51.94	C, 51.99
d	CH_3		63	174–175°(E)	$C_{11}H_{11}N_5O_2$	C, 53.87 H, 4.52 N, 28.57	C, 54.19 H, 4.79 N, 28.62
e	H		50	176–177°(D)	$C_{10}H_9N_5OS$	C, 48.58 H, 3.64 N, 28.34	C, 48.59 H, 3.57 N, 28.04
	CH_3		53	170–171°(D)	$C_{11}H_{11}N_5OS$	C, 50.57 H, 4.24 N, 26.81	C, 50.79 H, 5.06 N, 26.81

[a] D = dioxane, E = ethanol.

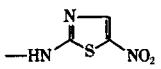
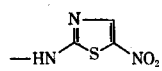
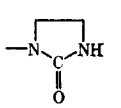
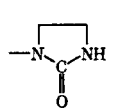
with III, IV, and V to give the azidobenzoyls (VIII*a–f*), respectively (Table I). The reaction was accelerated through the addition of dry sodium carbonate.

The lower reactivity of sodium borohydride compared to that of lithium aluminium hydride was advantageous in permitting the selective reduction of the azides. Although the former could reduce amides slowly (5), it was possible to reduce the azido groups in the amides VIII*a–d* selectively, giving the amines IX*a–d*, respectively (Table II). The reduction occurred readily in methanol or ethanol, provided the reaction mixture was kept at a temperature less than 25°.



IX

Table II—2-Aminobenzoyls

Number	R	R′	Yield, %	Melting Point (Recrystallization Solvent)[a]	Molecular Formula	Analysis, % Calc.	Analysis, % Found
a	H		34	127–130°(E–P)	$C_{10}H_8N_4O_3S$	C, 45.45 H, 3.05 N, 21.21 S, 12.12	C, 46.07 H, 3.40 N, 21.16 S, 12.84
b	CH_3		36	167–168°(E–P)	$C_{11}H_{10}N_4O_3S$	C, 47.48 H, 3.59 N, 20.14 S, 11.51	C, 47.16 H, 3.39 N, 19.88 S, 11.40
c	H		70	137–138°(B)	$C_{10}H_{11}N_3O_2$	N, 20.48	N, 20.29
d	CH_3		74	93–94°(B–P)	$C_{11}H_{13}N_3O_2$	N, 19.16	N, 18.77

[a] E–P = ethyl acetate–petroleum ether, B = benzene.

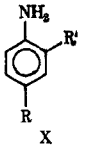


Table III—Amino Alcohols

Number	R	R′	Melting Point (Recrystallization Solvent)[a]	Molecular Formula	Analysis, % Calc.	Found
a	H	—CH_2OH	80–81°[b] (*n*-H)	C_7H_9NO	C, 68.29 H, 7.37 N, 11.38	C, 67.86 H, 7.79 N, 11.90
b	CH_3	—CH_2OH	121–122°[c] (*n*-H)	$C_8H_{11}NO$	C, 70.07 H, 8.08 N, 10.21	C, 69.66 H, 8.30 N, 10.10

[a] *n*-H = normal hexane. [b] Lit. (6) m.p. 82°. [c] Lit. (7) m.p. 122°.

Similar treatment of VIII*e* and VIII*f* caused hydrolysis of the amide linkage, along with the reduction of the azido groups, and yielded the alcohols X*a* and X*b*, respectively (Table III). Alternatively, the reduction of both azides was attempted through hydrobromic acid, which selectively reduced the azido groups, giving the corresponding amines XI*a* and XI*b*, respectively.

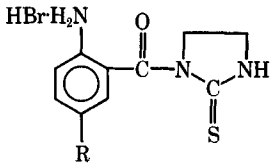
EXPERIMENTAL[3]

2-Azidobenzoyl Chloride (VII*a*) and 2-Azido-3-methylbenzoyl Chloride (VII*b*)—The azido acid (0.0023 mole) was mixed in 20 ml. of dry benzene with 0.025 mole of redistilled thionyl chloride. The mixture was gently heated on a steam bath with occasional shaking until the evolution of hydrogen chloride and sulfur dioxide ceased. The excess of thionyl chloride and benzene was distilled under reduced pressure, and the residual acid chloride was used without any further treatment due to explosion upon distillation.

(2′-Azidobenzoyl)-2-amino-5-nitrothiazole (VIII*a*), (2′-Azidobenzoyl)-2-imidazolidinone (VIII*c*), (2′-Azidobenzoyl)-2-imidazolidinethione (VIII*e*), and Their (3′-Methyl) Derivatives (VIII*b*, *d*, and *f*) (Table I)—To a solution of 0.018 mole of the azido acid chloride in 10 ml. of dry benzene was added 0.02 mole of the desired amine: III, IV, or V. The mixture was heated gently on a steam bath for 12 hr.; then the benzene was distilled, and the residue was poured into water. The product formed was collected, washed with water, and recrystallized from a proper solvent.

Reduction of the 2-Azidobenzoyls (VIII*a*–*f*) (Tables II and III)—To a cold suspension of 0.005 mole of the azidobenzoyl in 10 ml. of absolute ethanol was added 0.095 g. (0.0026 mole) of sodium borohydride portionwise, with stirring for 1 hr. Ethanol was then evaporated under reduced pressure, and the residue was decomposed by addition of 5 ml. of water followed by adjustment to pH 8.0 with diluted hydrochloric acid. The solution was extracted with hot ethyl acetate. The ester layer was separated, dried over sodium sulfate, and filtered; the filtrate was concentrated and then refrigerated. The product that separated was collected, dried, and recrystallized from a proper solvent.

(2′-Aminobenzoyl)-2-imidazolidinethione Hydrobromide (XI*a*)—To a suspension of 1.22 g. (0.005 mole) of VIII*e* in 10 ml. of absolute ethanol, 5 ml. of hydrobromic acid (48%) was added. This was refluxed for 3 hr. until the suspension went into solution. The solution was refrigerated overnight; the precipitated hydrobromide was collected, washed with cold alcohol, dried, and recrystallized from ethanol to give 0.6 g. (40% yield) as yellow crystals, m.p. 202–203°.



XI*a*: R = H
XI*b*: R = CH_3

Anal.—Calc. for $C_{10}H_{12}BrN_3OS$: N, 13.90; S, 10.59. Found: N, 14.50; S, 10.39.

(2′-Amino-5′-methylbenzoyl)-2-imidazolidinethione Hydrobromide (XI*b*)—Similar reaction of 1.5 g. (0.005 mole) of VIII*f* with hydrobromic acid gave 0.95 g. (50% yield) of XI*b*, which was recrystallized from ethanol as yellow crystals, m.p. 250–251°.

Anal.—Calc. for $C_{11}H_{14}BrN_3OS$: C, 41.45; H, 4.43; N, 13.29. Found: C, 40.90; H, 4.38; N, 12.84.

BIOLOGICAL TESTING

Compounds IX*a*, IX*b*, IX*d*, and XI*b*, in suspension or in water solution, were submitted to biological screening. Groups of mice, six each, of 29–31-g. average weight and infected with *Schistosoma mansoni*, were used for testings. All mice in each group were showing viable ova in their stools.

Group A was kept as the control. Group B was given oral doses of 75 mg./kg. of body weight from Compound IX*a*. Oral administration of the compound continued for 10 consecutive days. Three other groups (C, D, and E) were similarly given Compounds IX*b*, IX*d*, and XI*b*, respectively, at the same dosage levels as in Group B (75 mg./kg. of body weight) for the same period. After 1 week from the end of treatment, ova excretion in each group was examined once weekly for 6 weeks. Examinations showed a gradual decrease in the rate of ova excretion until it ceased in both Groups C and E given Compounds IX*b* and XI*b*, respectively.

In Groups B and D, given Compounds IX*a* and IX*d*, respectively, no remarkable decrease in the rate of ova excretion was observed compared to the control group A.

These biological findings suggest that the presence of the methyl group *para* to the amino group (*p*-toluidine type) is necessary for the activity, as shown by Compounds IX*b* and XI*b*.

REFERENCES

(1) H. Mauss, *Chem. Ber.*, **81**, 19(1948).
(2) E. J. Blanz and F. A. French, *J. Med. Chem.*, **5**, 185(1963).
(3) C. R. Lambert, M. Willhelm, H. Striebel, F. Kradolfer, and P. Schmidt, *Experientia*, **20**, 452(1964).
(4) A. Abdallah, M. Saif, M. Abdel-Meguid, A. Badran, and F. Abdel-Fattah, *J. Egypt. Med. Ass.*, **49**, 145(1966).
(5) N. G. Gaylord, "Reduction With Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp. 16, 118, 383, 533, 709, 917.
(6) T. Curties and A. Semper, *Chem. Ber.*, **46**, 1163(1915).
(7) F. Mayer, W. Schafer, and J. Rosenbach, *Arch. Pharm.*, **571**, 567(1929).

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[3] Melting points are uncorrected and were taken in open capillaries, using a Gallenkamp melting-point apparatus. Microanalyses were performed by the Microanalytical Laboratory, National Research Centre, Cairo, Egypt, and Spang Microanalytical Laboratory, Ann Arbor, Mich.