chloride itself has been found to be more effective than the rest of the compounds. The mixed ligand complexes are found to be less effective than the base monohydrochloride and its binary complex. All the compounds are found to be potent to kill the protozoa upto 0·001 M concentration within 24 hrs and higher concentration has proved to be more effective in shorter period.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF *a*, *a'*-THIOBISFORMAMIDINE DERIVATIVES: PART II

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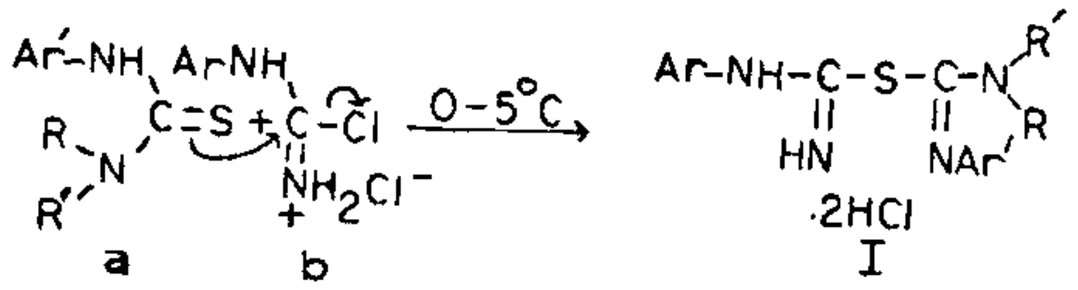
ABSTRACT

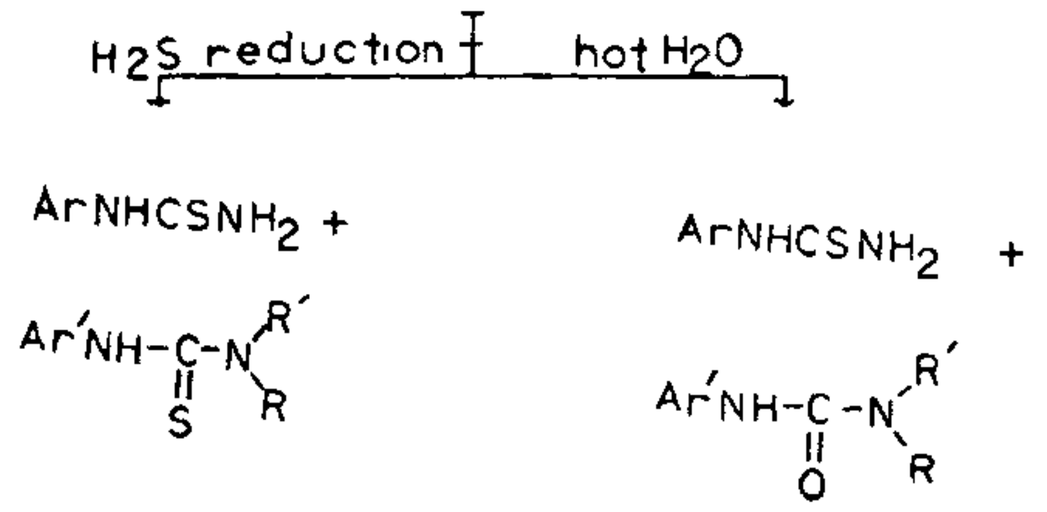
A series of N^1,N^4 diaryl/aryl alkyl-N^3,N^3 dialkyl/N^3 alkyl-*a*,*a'* thiobisformamidine salts have been prepared by the condensation of *a*-chloroarylformamidines with 1-aryl-3 alkyl/3,3 dialkyl thioureas in ether-acetone medium at 0–5° C. Their local anaesthetic, antifungal, larvicidal activities and chemical behaviour have been studied.

INTRODUCTION

INTERACTION of *a*-chloroarylformamidine hydrochlorides[1,2] with monosubstituted aryl[3], alkyl[4] or acylthioureas[5] has been investigated. The present study of the reaction with 1, 3 arylalkyl or 1, 3, 3-aryldialkylthioureas was undertaken to see the effect of substitution on the course of reaction and also to evaluate the biological potency of newly formed compounds.

At lower temperatures (0–5°) *a*-chloroarylformamidine hydrochlorides reacted with 1-aryl-3, 3-dialkyl/3-alkyl-thioureas in ether-acetone medium to afford corresponding *a*, *a'*-thiobisformamidine salts (I), as shown in scheme 1.

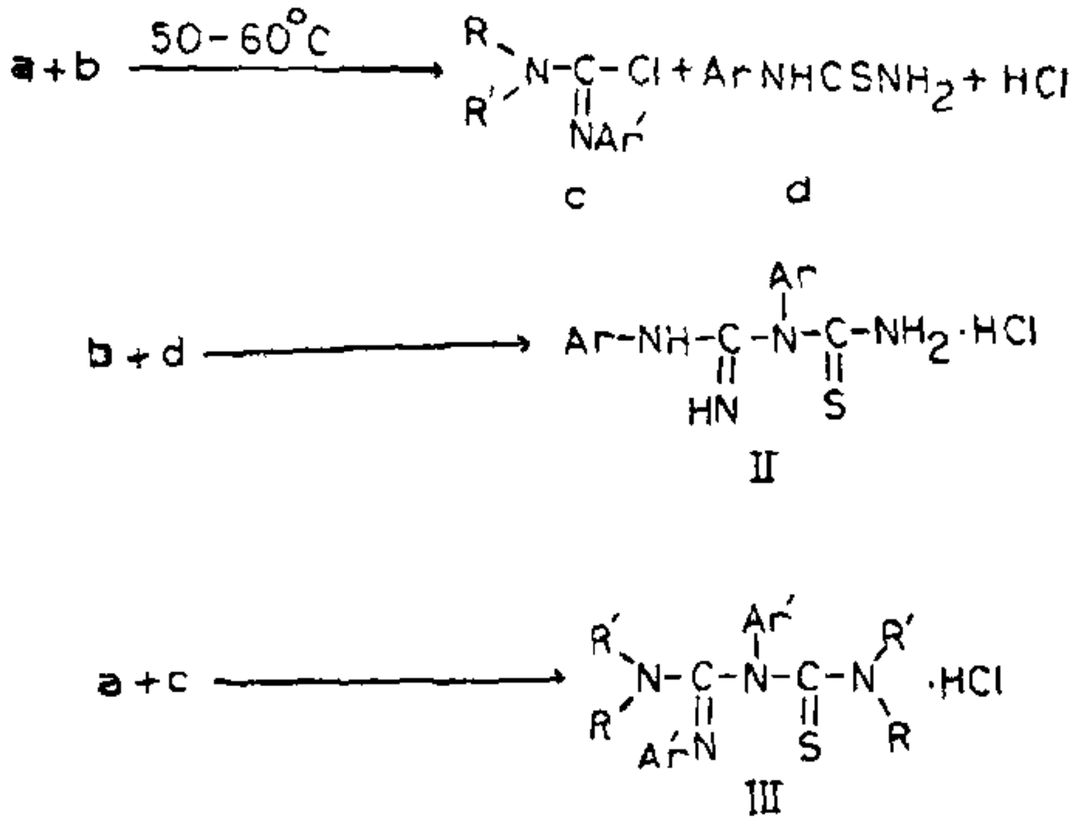




SCHEME I

The structure of I was confirmed on the basis of decomposition products and analysis of their picrates. On boiling with water compound (I) decomposed into mono-substituted arylthiourea corresponding to the *a*-chloroarylformamidine hydrochloride used and di- or tri-substituted arylalkyl urea corresponding to the thiourea used. Reduction of I with hydrogen sulphide in alcoholic ammonia gave arylthiourea and di- or tri-substituted arylalkylthioureas.

On raising the temperature of the reaction medium I could not be isolated, instead II and III were separated. The structures of II and III were confirmed by their elemental analysis, decomposition products and their synthesis by another method as described in the literature[3,6]. The sequence of formation of these products has been outlined under Scheme 2.



SCHEME 2

where R = CH_3, C_2H_5, R′ = H, CH_3, C_2H_5, Ar and Ar′ are aryl and benzyl groups.

EXPERIMENTAL

All melting points were taken by capillary method and are uncorrected. Biological activity was done according to the method as described earlier[5].

Interaction of α-chlorophenylformamidine hydrochloride with 1-phenyl-3-methylthiourea

(i) *At 0–5° C* : An acetone solution of 1-phenyl-3-methylthiourea (2·5 g, 0·02 mole) was added to an ethereal suspension of α-chlorophenylformamidine hydrochloride (2·5 g, 0·03 mole) under ice cold condition. Within few minutes a semisolid product was obtained which was solidified by washing several times with acetone. The compound was found to be highly hygroscopic and therefore not suitable for analysis. Its aqueous solution, on addition of picric acid, afforded a picrate, recrystallised from aqueous ethanol, m.p. 85°. Analysis : found C, 43·79; H, 2·61; N, 18·69%; $C_{15}H_{16}N_4S \cdot 2C_6H_3N_3O_7$ requires C, 43·66; H, 2·56, N, 18·86%. Similarly picrates of other derivatives were prepared (Table I).

(ii) *At 50·60° C* : When above reaction was carried out at 50–60°, a micro crystalline solid was obtained, m.p. 158°, picrate 142 which was identified as 1-phenylamidino-1-phenylthiourea hydrochloride (II, Ar = Ph). The solvent was evaporated out and a sticky solid was obtained. The aqueous solution on treatment with ethanol-acetone gave a crystalline solid m.p. 162°, gave picrate (m.p. 155°) with picric acid which was found in all respects identical with 1-(N-phenyl-N′ methylamidino)-1-phenyl-3-methylthiourea hydrochloride.

IIIa : Ar′ = Ph, R = H, R′ = CH_3; m.p. 162°, base, m.p. 83°; picrate m.p. 155°. The same reaction sequence was found in other cases.

IIIb : Ar′ = *p*-tolyl, R = Me, R′ = H, m.p. 113°, base m.p. 120°, picrate m.p. 140°.

IIIc : Ar′ = Ph, R = R′ = Me, m.p. 105°, base m.p. 118°, picrate m.p. 139°.

Decomposition Studies

(i) *Effect of water* : N^1, N^4 Diphenyl-N^3 methyl α, α′-thiobisformamidine dihydrochloride was boiled with water for half an hour and then cooled, crystals of phenylthiourea were separated out (m.p. 153°). The filtrate on basification yielded a solid, recrystallised from hot water m.p. 147°, identified as 1-phenyl-3-methylurea by mixed m.p. method. Similarly N^1, N^4 diphenyl-N^3, N^3 dimethyl α, α′-thiobisformamidine hydrochloride decomposed into phenylthiourea and 1-phenyl-3, 3 dimethylurea (m.p. 131°).

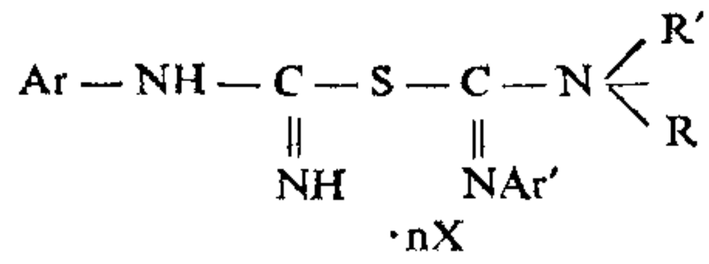
(ii) *Effect of hydrogen sulphide* : Hydrogen sulphide was bubbled through the solution of N^1, N^4 diphenyl-N^3 methyl α, α′-thiobisformamidine dihydrochloride (2 g) in strong alcoholic ammonia (200 ml) for about one hour. The resulting solution was filtered and excess of hydrogen sulphide was boiled off. A crude material was obtained. By fractional crystallisation method two compounds were identified as phenylthiourea (m.p. 153°) and 1-phenyl-3 methylthiourea (m.p. 114°). Similarly N^1N^4 diphenyl N^1, N^3 dimethyl α, α′-thiobisformamidine hydrochloride afforded phenylthiourea and 1-phenyl 3, 3 dimethylthiourea (m.p. 134°).

RESULTS AND DISCUSSION

The course of reaction seems to be according to our earlier observation. In the local anaesthetic testing they are not very promising as compared with the standard drug and also less active than previously synthesized drugs, while with respect to their antifungal and larvicidal activity they are potent. They inhibit the growth of test fungi *Curvularia lunata* and *Alternaria alternata* in the MIC range of 15–125 μg/ml and kill the III and IV instar of larvae at 200 ppm of the test drug. The most effective substituent in

TABLE I

Physical and Biological data of N^1, N^4 diaryl/arylalkyl-N^3N^3 dialkyl/N^3 alkyl α,α'-thiobisformamidine picrates/hydrochlorides



X = $C_6H_3N_3O_7$
n = 1,2

Sl. No.	Ar	Ar'	R'=H R	Picrate* m.p. (°C)	Molecular formula	△ Local anaesthetic activity (in min.) with 0·1 NHCl	△ Anti-fungal activity MIC (μg/ml) C.L.	A.A.	△ Larvicidal activity with (% mortality) 200 ppm	100 ppm
1.	C_6H_5	C_6H_5	CH_3	85	$C_{15}H_{16}N_4S.2X$	24·0	125	60	45	35
2.	$3CH_3C_6H_4$	C_6H_5	CH_3	79	$C_{16}H_{18}N_4S.2X$	21·0	125	60	50	35
3.	$4CH_3C_6H_4$	C_6H_5	CH_3	102	$C_{16}H_{18}N_4S.2X$	23·0	125	60	45	30
4.	$4C_2H_5OC_6H_4$	C_6H_5	CH_3	76	$C_{17}H_{20}N_4SO.2X$	25·0	60	15	45	40
5.	$4ClC_6H_4$	C_6H_5	CH_3	107	$C_{15}H_{15}N_4SCl.2X$	24·0	60	15	65	55
6.	C_6H_5	$4CH_3C_6H_4$	CH_3	105	$C_{16}H_{18}N_4S.2X$	26·0	125	60	40	30
7.	$4CH_3C_6H_4$	$4CH_3C_6H_4$	CH_3	115	$C_{17}H_{20}N_4S.2X$	25·0	125	60	50	40
8.	$4C_2H_5OC_6H_4$	$4CH_3C_6H_4$	CH_3	118	$C_{18}H_{22}N_4SO.2X$	29·0	60	15	50	45
9.	$3CH_3C_6H_4$	$4CH_3C_6H_4$	CH_3	101	$C_{17}H_{20}N_4S.2X$	22·0	125	60	40	35
10.	$3ClC_6H_4$	$4CH_3C_6H_4$	CH_3	118	$C_{16}H_{17}N_4SCl.2X$	22·0	60	15	60	55
11.	C_6H_5	$3ClC_6H_4$	CH_3	125	$C_{15}H_{15}N_4SCl.2X$	24·0	125	60	60	50
12.	$4ClC_6H_4$	$3ClC_6H_4$	CH_3	130	$C_{15}H_{14}N_4SCl_2.2X$	25·0	60	15	65	50
13.	$4CH_3C_6H_4$	$3ClC_6H_4$	CH_3	135	$C_{16}H_{17}N_4SCl.2X$	23·0	60	15	65	50
14.	$4C_2H_5OC_6H_4$	$3ClC_6H_4$	CH_3	106	$C_{17}H_{19}N_4SOCl.2X$	28·0	60	15	65	65
15.	C_6H_5	$C_6H_5CH_2$	CH_3	89	$C_{16}H_{18}N_4S.2X$	20·0	60	15	50	40
16.	$4CH_3C_6H_4$	$C_6H_5CH_2$	CH_3	95	$C_{17}H_{20}N_4S.2X$	22·0	125	60	45	35
17.	$4ClC_6H_4$	$C_6H_5CH_2$	CH_3	139	$C_{18}H_{17}N_4SCl.2X$	21·0	125	60	55	50
18.	$3CH_3C_6H_4$	$C_6H_5CH_2$	CH_3	129	$C_{17}H_{20}N_4S.2X$	26·0	60	15	45	35
19.	$4C_2H_5OC_6H_4$	$C_6H_5CH_2$	CH_3	131	$C_{18}H_{22}N_4SO.2X$	26·0	60	15	45	35
20.	$4CH_3OC_6H_5$	$C_6H_5CH_2$	CH_3	136	$C_{16}H_{20}N_4SO.2X$	27·0	125	60	40	30
21.	C_6H_5	C_6H_5 R=R'	CH_3	128	$C_{16}H_{18}N_4S.X$	24·0	125	125	50	40
22.	C_6H_5	$4CH_3C_6H_5$	CH_3	110	$C_{17}H_{20}N_4S.X$	30·0	125	125	50	35
23.	$4C_2H_5OC_6H_4$	$4CH_3C_6H_5$	CH_3	103	$C_{19}H_{24}N_4SO.X$	32·0	60	15	45	40
24.	$4ClC_6H_4$	C_6H_5	C_2H_5	78	$C_{18}H_{21}N_4SCl.X$	24·0	60	15	55	50
25.	C_6H_5	$4CH_3C_6H_4$	C_2H_5	79	$C_{19}H_{24}N_4S.X$	25·0	125	125	40	30
26.	C_6H_5	C_6H_5	C_2H_5	101	$C_{18}H_{22}N_4S.X$	24·0	125	125	45	40

* The compounds gave satisfactory elemental analysis and were within the range of ± 04%

△ for the respective hydrochlorides. C.L. = *Curvularia lunata.* A.A. = *Alternaria alternata.*

fungicidal activity was found to be *p*-ethoxy and para/meta chloro. These substituents in the phenyl ring greatly enhance the activity in the present series.

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