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SYNTHESIS OF SOME NEW SULPH-HYDRAZONES AS POSSIBLE POTENTIAL TUBERCULAR COMPOUNDS

by

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SYNTHESIS OF SOME NEW SULPH-HYDRAZONES AS POSSIBLE POTENTIAL TUBERCULAR COMPOUNDS

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3–Nitro-4-acetylsulphanilylhydrazide (I) was syntheesized, and the unsubstituted nitrogen of the hydrazine moiety was incorporated in reactions with several aldehydes and ketones, 1,2 or 1,3 diketones, oc -oxoacids, α -keyoacids, and certain acyl or sulphonyl chloride compounds to give different sulphydrazones that were excepted to show high antitubercular activity.

INTRODUCTION

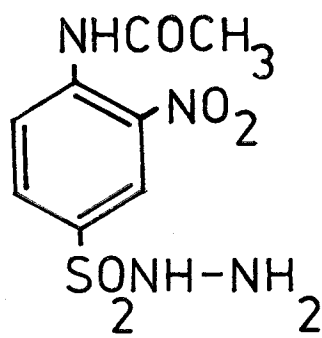
Isonicotinic acid hydrazide and its N-isopropyl derivative are effective drugs in the treatment of human tuberculosis[1]. With a view to reduce toxocity due to free amino group, the condensation products of a number of hydrazides with various aldehydes and ketones were also examined[2]. Hydrazones have been found to possess antibacterial activity[3,4]. In addition they also been reported to possess antifungal[5,6,7] as well as insecticidal activity[8,9,10,11]. On other the hand, it is known that sulphonamide drugs were the first effective chemotherapeutic agents employed for prevention and cure of tuberculosis[12] and that those containing a sulphanilyl or potential sulphanilyl group act as antimetabolites competing with normal metabolites in bacterial growth[13,14]. Also, several sulph-hydrazones were prepared and proved to be potential tuberculostatic drugs[15,16].

In isoniazide the position of the hydrazide group, in relation to the tertiary nitrogen atom, has a critical importance, as well as the shifting from the gamma to the beta position abolishes the activity.

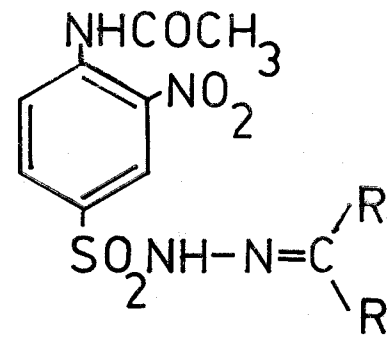
Therefore, it was suggested in this work to synthesize some hydrazones of 3-nitro-4-acetylsulphanilylhydrazide, in which the acetomino-nitrogen, although not incorporated in the nucleus but it is still para to the sulph-hydrazono-group as in case if isoniazide.

RESULTS AND DISCUSSION:

A number of 3-nitro-4-acetylsulphanilyl-hydrazones (II a-j) have been synthesized, as described by Cremyln[17], by the reaction of 3-Nitro-4- acetylsulphanilylhydrazide[18] (I) with a variety of monocarbonyl compounds, namely, crotonaldehyde, cinnamaldehyde, pyridine-2-carbaldehyde, butan-2-one, 4-acetyl-pyridine, 2-acetylfuran, 2-acetylindol, 2-oxobutyric acid, 2-oxoglutaric acid and phenylpyruvic acid.



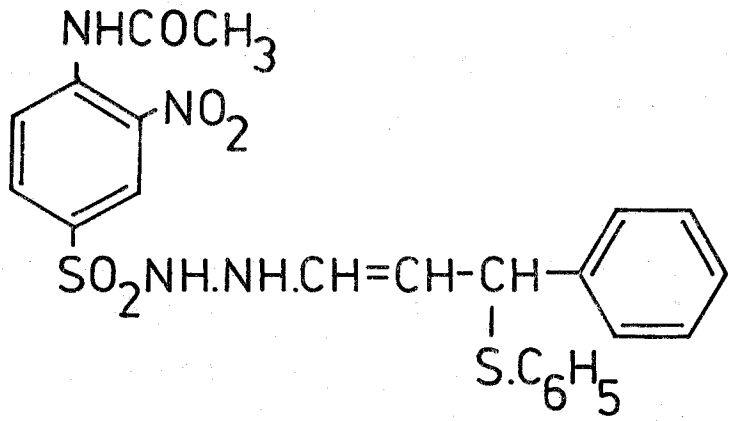
(I)



(II)

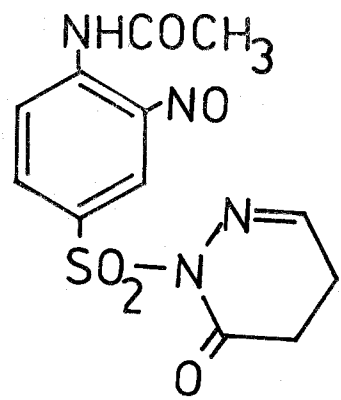
II a;	H	$CH=CH.CH_3$	II f;	CH_3	2-Furyl
b;	H	$CH=CH.C_6H_5$	h;	CH_3	2-Indolyl
c;	H	2-Pyridyl	h;	C_2H_5	COOH
d;	CH_3	C_2H_5	i;	$COOH.(CH_2)_2$	COOH
e;	CH_3	4–Pyridyl	j;	$C_6H_5.CH_2$	COOH

The activity of the exocyclic C=C conjugated with the C=N group in IIb promoted us to investigate its behaviour towards the action of thiophenol. Thus, when II_b is fused with excess thiophenol, the sulphide (III) is obtained through a 1, 4-addition mechanism.



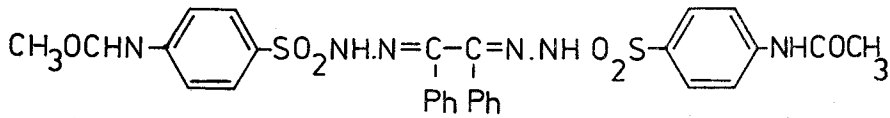
(III)

Cyclization of II_i refluxing in NaOH media gives 2-(3′-nitro-4′-acetyl sulphanilyl-4-carboxy-pyridazinone (IV).



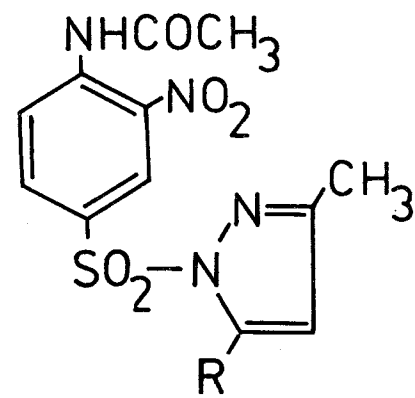
(IV)

Dicarbonyl reagents, where the two carbonyl groups are adjacent such as 1,2-diphenylethanedione react with (I) in absolute ethanol producing the dihydrazone (V).



(V)

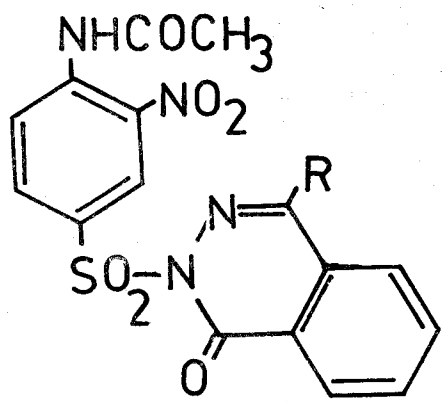
On the other hand, B-dicarbonyl reagents lead to the direct formation of pyrazoles by acid catalysed reaction with (I). Thus, when (I) is treated with acetylacetone and benzoylacetone in glacial acetic acid, the corresponding 1(3′-nitro-4′-acetylsulphanilyl)-3-5-disubstituted pyrazoles ($VI_{a,b}$) are produced.



(VI)

	R		R
VIa	CH_3	VIb	C_6H_5

The reaction of (I) with keto-acids, namely, o-acetobenzoic acid and o-benzoylbenzoic acid in absolute ethanol or glacial acetic acid under reflux gives 2-(3-nitro-4′acetylsulphanilyl-4-substituted phthalazinione ($VII_{a,b}$) respectively.



(VII)

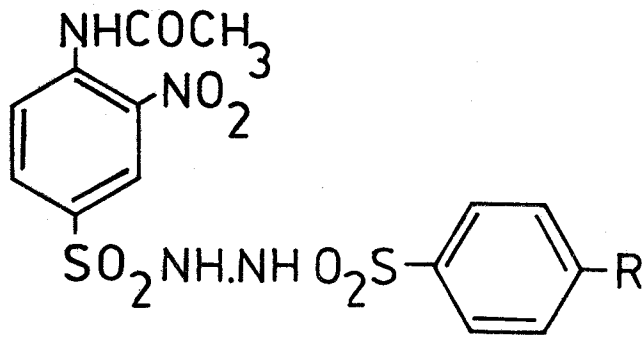
	R		R
VIIa	CH_3	VIIb	C_2H_5

(VIIa, R=CH_3; VIIb, R=C_6H_5)

Acylation of (I) with different acylating agents including benzenesulphonyl chloride, touenesulphonyl chloride and 4-acetic-aminobenzenesulphonyl chloride has also been examined where the sulphonyl derivatives ($VIII_{a-c}$) were obtained as a result of substitution at the unsubstituted nitrogen.

The author also, investigated the reaction of (I) with acid anhydrides, namely, succinic anhydride and phthalic anhydride, where 2-(3′nitro-4′-acetyl-sulphanilyl)-dihydropyridazine-1,4- dione (IX) and 2-(3′-nitro-4′-acetylsulphanilyl)-(2H)-phthalazine-1,4-dione (X) were obtained.

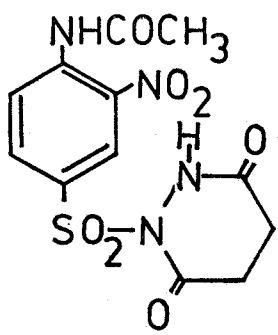
Compound (I), undergoes nucleophillic aromatic substitution which takes place preferentially at the unsubstituted nitrogen[19] of the hydrazine moiety. Thus, when (I) is subjected to the action of 3-chloro-5, 6- diphenyl -1,2,4- triazine we have obtained the stable 5, 6-diphenyl -3-(3′-nitro-4′-acetylsulphanilyl)-hydrazotriazine (IX).



(VIII)

	R
VIIIa	H
b	CH_3
c	$NH.COCH_3$

(VIIa, R=H; b,R = CH_3; VIIIc, R=NH.CO.CH_3)



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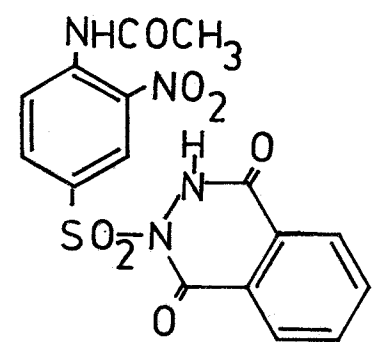

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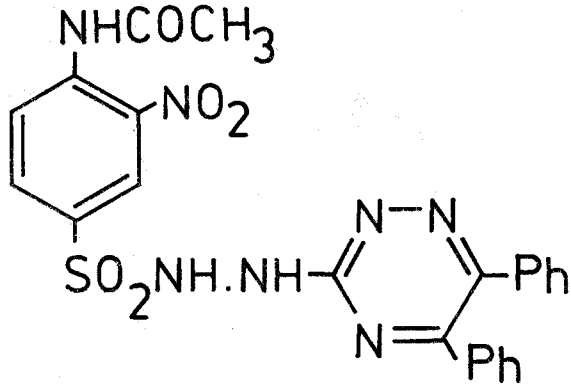
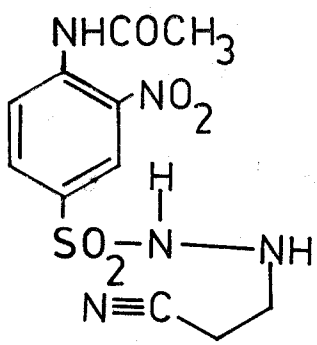
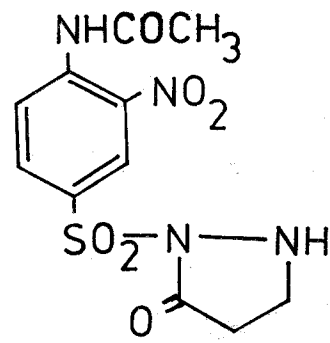


(XI)

Alkanes which have strongly electron-withdrawing substituents react rapidly with hydrazine and its derivatives, where the normal monoalkylation product is formed in high yield[20]. Thus, when (I) is subjected to the action of acrylonitrille, cyanoethylation takes place affording 1-(3′-nitro-4′-acetylsulphanilyl)-2-cyanoethyl-hydrazine (XII) which on acid hydrolysis yielded 1-(3′-nitro-4′-acetylsulphanilyl) pyrazol-5-one (XIII).



(XII)



(XIII)

The structure of the compounds newly prepared in this investigation is confirmed by elemental analysis and infrared spectral studies.

The IR spectra of the above compounds are listed in Table (1).

All the compounds show the four 4-nitro-3-acetylsulphanilyl skeletal bands in the regions of 1700—1680, 3350—3200, 1080—1400, and 1500 and 1340 cm^{-1} due to the amide C=O, both free-NH and hydrogen-bonded N-H, S=O, and the conjugated nitro strecthing frequencies respectively.

In compounds V and XI the diminution in size and functional activity of the C=N absorption band may be rendered to symmetry considerations[21,22].

The results of testing of such compounds, its significance, if positive, and its correlation with molecular structure will be investigated and reported elsewhere.

EXPERIMENTAL

The IR spectra were recorded with a Beckmann IR 4 spectrophotometer using KBr pellet technique.

All melting points are not corrected.

3-nitro-4-acetylsulphanilylhydrazide was prepared after the procedure described by Lester Friedman et al.,[17].

Reactions of I with monocarbonyl compounds: Formation of Arylidene and Alkylidene derivatives (II a-j).

A mixture of I (0.01 mole) and the appropriate aldehyde, ketone, and / or 2-oxoacid (0.15 mole), in abs. ethanol (30 ml.) was heated under reflux for 30 minutes, cooled, poured into water, filtered and the solid obtained recrystallized from a proper solvent to give II a-j (Table 2).

Action of thiophenol on II b: Formation of Sulphide III.

A mixture of II b (0.01 mole) and excess thiophenol (0.015 mole), was heated at 150° (oil-bath) for 6 hr. The solid obtained was triturated with petroleum ether (60–80) to give III which was crystallized from toluene as yellow crystals (Table 2).

Table 1 I.R. Spectra of Compounds II—XIII (KBr; cm^{-1})

Compound	(OH)	(NH)	(C≡N)	(C=O)	(C=N)	(CNH)	(SO_2)
II c	—	3310	—	—	1610 (cyclic)	—	—
d	—	3380	—	—	1580 (exocyclic)	—	—
e	—	3500	—	—	1610	—	—
f	—	3380	—	—	1610 (cyclic) 1570 (exocyclic)	— —	—
g	—	3320	—	—	1620 1580	—	—
h	3430	3320	—	1720	1620	—	—
i	3420	3320	—	1730	1610 (cyclic) 1575 (exocyclic)	—	—
j	3440	3320	—	1680	1600	—	—
V	—	3380	—	—	1620 1605 1580 1570	—	—
VI a	—	3380	—	—	1580	—	—
VI b	—	—	—	—	1580	—	—
VII a	—	—	—	1665 (cyclic amide)	1610	—	—
VII b	—	—	—	1650 (cyclic amide)	1580	—	—
VIII b	—	—	—	—	—	—	1380
X	—	3200	—	1720 (condensed a1,4—dione)	—	—	—
XI	—	3400 3320	—	—	1600	~1510	—
XII	—	3460	2260–2240	—	—	—	—
XIII	—	3210	—	1680	—	1520	—

Reaction of I with α-diacrbonyl reagents: Formation of (V)

A mixture of I (0.02 mole) and 1,2-diphenyl-ethanedione (0.01 mole) in absolute ethanol (20 ml.) was heated under reflux for 1 hr., cooled, poured into water and filtered. The solid obtained was recrystallized from chlorobenzene to give V as yellow crystals (Table 3).

Table 2

Compound	Yield %	Solvent	M.P. °C	Mol. Formula	Analysis (Found/Required) %			
					C	H	N	S
II a	60	Acetic acid	168–169	$C_{12}H_{14}N_4O_5S$	44.45	4.32	17.62	9.44
					44.17	4.29	17.18	9.82
b	75	Acetic acid	178–179	$C_{17}H_{16}N_4O_5S$	52.69	4.18	14.68	8.40
					52.58	4.12	14.43	8.25
c	80	Dioxane	178–179	$C_{14}H_{13}N_5O_5S$	46.35	3.76	18.50	8.80
					46.28	3.58	19.28	8.82
d	70	Ethanol	149–150	$C_{12}H_{16}N_4O_5S$	43.76	5.40	17.40	9.82
					43.90	4.88	17.07	9.76
e	80	Dioxane	122–123	$C_{15}H_{15}N_5O_5S$	47.53	3.66	19.10	7.90
					47.75	3.98	18.56	8.49
f	70	Acetic acid	205–206	$C_{14}H_{14}N_4O_6S$	46.10	4.10	15.45	8.60
					45.90	3.83	15.30	8.74
g	80	Ethanol	164–165	$C_{18}H_{16}N_5O_5S$	52.90	4.12	17.20	6.90
					52.17	3.86	16.91	7.73
h	95	Ethanol	154–155	$C_{12}H_{14}N_4O_7S$	40.30	4.15	15.31	8.86
					40.22	3.91	15.64	8.94
i	95	Acetic acid	145–146	$C_{13}H_{14}N_4O_9S$	38.64	3.61	14.24	8.20
					38.81	3.48	13.93	7.96
j	75	Dioxane	174–175	$C_{17}H_{16}N_4O_7S$	48.82	3.75	13.72	7.67
					48.57	3.81	13.33	7.62
III	65	Toluene	55	$C_{23}H_{22}N_4O_5S_2$	55.27	4.51	11.31	13.00
					55.42	4.42	11.24	12.85
IV	70	Methanol	135–136	$C_{12}H_{12}N_4O_6S$	42.18	3.68	16.15	9.62
					42.35	3.53	16.47	9.41

Table 3

Compound	Yield %	Solvent	M.P. °C	Mol. Formula	Analysis (Found/Required) %			
					C	H	N	S
(V)	90	Chlorobenzene	119–120	$C_{13}H_{14}N_4O_5S$	45.50	4.70	16.63	8.80
					46.15	4.14	16.57	9.47
VI a	85	Dil. acetone	204–205	$C_{18}H_{16}N_4O_5S$	53.86	4.80	14.12	8.26
					54.00	4.00	14.00	8.00
VI b	90	Methanol	204–205	$C_{30}H_{26}N_8O_{10}S_2$	49.80	3.50	15.30	8.60
					49.86	3.60	15.51	8.86

Reaction of I with B-dicarbonyl reagents: Formation of VI a, b.

A mixture of I (0.01 mole) and acetylacetone or benzoylacetone (0.015 mole), in abs. ethanol (30 ml.) was heated under reflux for 1–2 hr. The reaction mixture was washed as usual to give VI a or VI b as yellow crystalls (Table 3).

Reaction of I with ketoacids: Formation of VII a, b.

A mixture of I (0.01 mole) and o-acetobenzoic acid or o-benzoylbenzoic acid (0.01 mole), in glacial acetic acid (20 ml.), was heated under reflux (steam-bath) for 2 hr., cooled, poured into water and filtered. The solid obtained was recrystallized from ethanol to give VII_a or VII_b as yellowish crystals. (Table 4).

Table 4

Compound	Yield %	Solvent	M.P. °C	Mol. Formula	Analysis (Found/Required) % C	H	N	S
VII a	90	Ethanol	210–211	$C_{17}H_{16}N_4O_7S$	48.32 48.57	3.85 3.81	13.56 13.33	7.81 7.62
VII b	80	Ethanol	98–99	$C_{22}H_{18}N_4O_7S$	54.83 54.77	3.62 3.73	11.94 11.62	6.50 6.69

Acylation reactions of I:

(a) *Formation of VIII a-c.*

A mixture of I (0.01 mole) and the appropriate aryl sulphonyl chloride (0.015 mole), in dry pyridine (10 ml.), was heated under reflux for 15 min., cooled, triturated with dil. HCl and extracted with pet. ether (40—60°C). The solid obtained was recrystallized to give VIII a-c (Table 5).

Table 5

Compound	Yield %	Solvent	M.P. °C	Mol. Formula	Analysis (Found/Required) % C	H	N	S
VIII a	70	Benzene	155–156	$C_{14}H_{14}N_4O_7S_2$	40.83 40.58	3.43 3.38	13.64 13.53	15.50 15.46
VIII b	60	Benzene	190–192	$C_{15}H_{16}N_4O_7S_2$	41.89 42.06	3.62 3.74	12.92 13.08	15.16 14.95
VIII c	80	Benzene	180–181	$C_{16}H_{17}N_5O_8S_2$	40.56 40.76	3.69 3.61	14.64 14.86	13.92 13.59
IX	80	Ethylaectate	255	$C_{12}H_{12}N_4O_7S$	40.63 40.45	3.29 3.37	15.94 15.73	9.05 8.99
X	75	Ethylacetate	285	$C_{23}H_{19}N_7O_5S$	54.32 54.65	3.85 3.76	20.06 19.41	6.39 6.34
XI	80	Ethanol	99–100	$C_{23}H_{19}N_7O_5S$	54.82 54.65	3.70 3.76	19.63 19.41	6.22 6.34
XII	60	Ethanol	194–195	$C_{11}H_{13}N_5O_5S$	40.65 40.37	3.50 3.98	21.84 21.41	9.66 9.79
XIII	60	Ethanol	135–136	$C_{11}H_{12}N_4O_6S$	40.60 40.24	3.70 3.66	17.28 17.07	9.86 9.76

(b) *Formation of IX and X.*

A mixture of I and succinic anhydride or phthalic anhydride (0.012 mole), in glacial acetic acid (50 ml.), was heated under reflux for 2 hrs., cooled, poured into water and filtered. The solid obtained recrystallized to give IX or X respectively. (Table 5).

Reaction of I with 3-chloro-5,6-diphenyl-1,2,4-triazine: Formation of XI.

A mixture of I (0.01 mole), 3-chloro-5,6-diphenyl-1,2,4-triazine (0.01 mole) and triethylamine (0.01 mole) in pyridine (15 ml.) was heated under reflux (steam-bath) for 1 hr. The reaction mixture was cooled washed with water and the organic layer was separated and dried over anhydrous sodium sulphate, filtered and evaporated to dryness to give XI. which recrystallized from ethanol as brownish yellow crystals (Table 5).

Reaction of I with actylonitrile: Formation of XII.

A mixture of I (0.01 mole), acrylonitrile (3 ml.) and water (10 ml.) in pyridine (30 ml.) was heated under reflux for 2 hrs., cooled. washed with dil. HCl and extracted with ether. The solid obtained after the removal of solvent was crystallized from ethanol to give XII as yellov crystals (Table 5).

Acid Hydrolysis of XII: Formation of XIII.

A mixture of XII (0.01 mole) and 20 % HCl (20 ml.) was heated under reflux (hot plote) for 1 hr., cooled and filtered. The solid obtained was recrystallized from the ethanol to give XIII as orange crystals (Table 5).

Cyclization of II i: Formation of IV:

Compound IIi (0.01 mole) in sodium hydroxide (2N) (40 ml.) was refluxed for one hour, cooled, neutralized with dilute HCl and the solid precipitated was filtered, washed with cold water and crystallized from methanol to give IV as golden-yellow crystals (Table 2).

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