# SYNTHESIS OF N-(2-NAPHTHYLOXYACETYL)THIOSEMICARBAZIDES AND 2-ARYLAMINO-5-(2-NAPHTHYLOXYMETHYL)-1,3,4-THIADIAZOLES/OXADIAZOLES AS ORAL HYPOGLYCEMIC AGENTS

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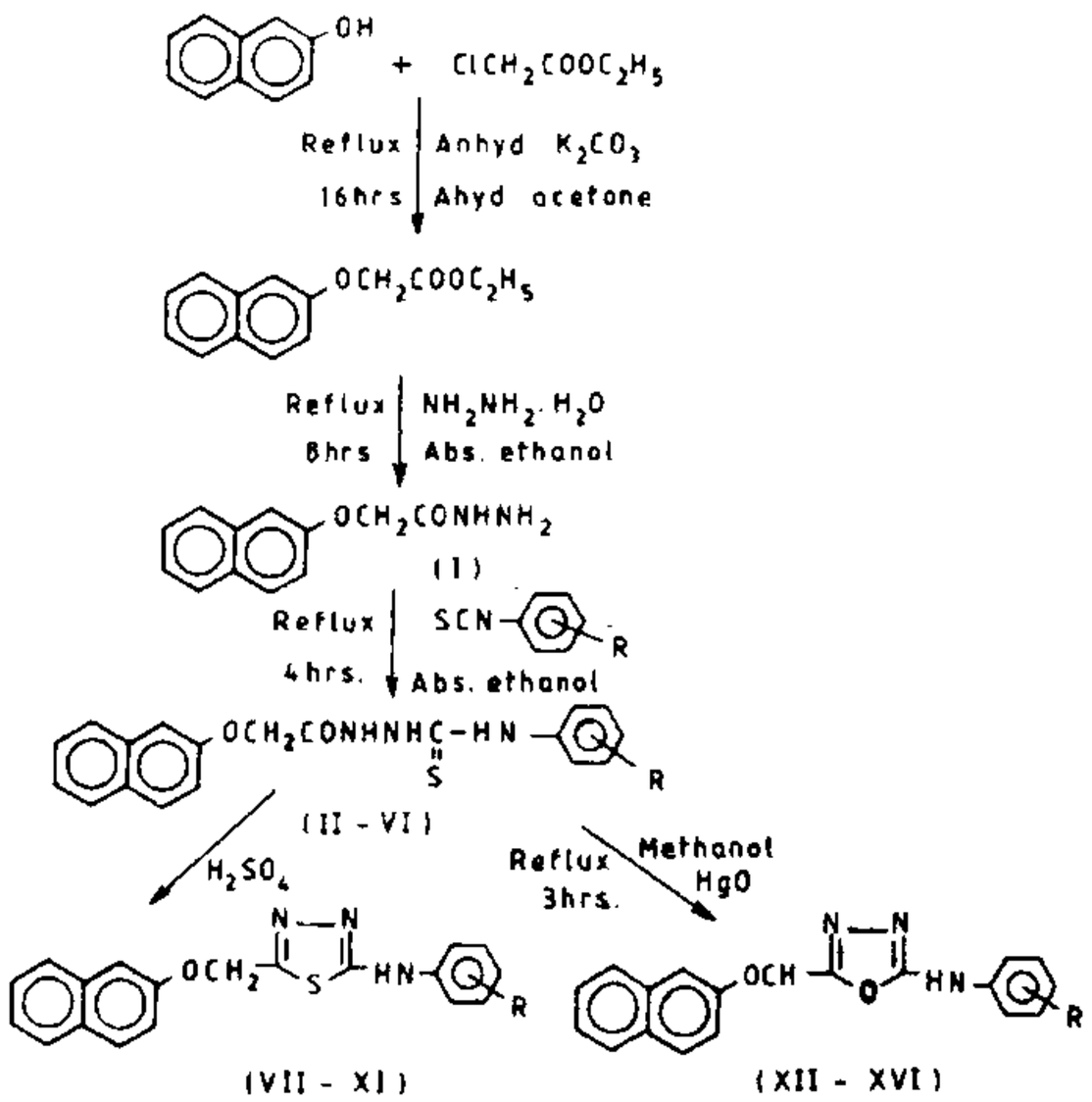
## ABSTRACT

N-(2-Naphthyloxyacetyl)thiosemicarbazides on treatment with conc. $H_2SO_4$ or mercuric oxide afforded 2-arylamino-5-(2-naphthyloxymethyl)-1,3,4-thiadiazoles/oxadiazoles respectively. Ten of these compounds on being screened reduced the blood sugar in rats up to 21% at a dose of 250 mg/kg body weight.

## INTRODUCTION

THIADIAZOLES[1–3] and oxadiazoles[4–5] derivatives possess a high order of hypoglycemic activity. Some thiosemicarbazides as well as naphthyloxyalkylamino benzoic acid[7] and naphthyloxyacetic acid[8] derivatives have also been known to exhibit marked hypoglycemic activity. In view of these findings, it was, therefore, considered worthwhile to synthesize the title compounds and evaluate their hypoglycemic activity.

The synthesis was accomplished along the following route (scheme 1).




(SCHEME - 1)

## EXPERIMENTAL PROCEDURE

The melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on Perkin-Elmer spectrometer using KBr and PMR spectra in $CDCl_3$ on a Varian AC 60-D instrument using TMS as an internal standard (chemical shift in $\delta$ppm). The purity of the compounds was checked by TLC using plates coated with silica gel G.

*N-(2-Naphthyloxyacetyl)hydrazine (I):*

2-Naphthol 2.7 g (0.02 mol) was refluxed with ethylchloroacetate 2.8 ml (0.02 mol) in the presence of anhydrous acetone (50 ml) and anhydrous $K_2CO_3$ 3.9 g (0.03 mol) for 16 hr on a water bath. Thereafter, the reaction mixture was filtered and the solvent distilled off from the filtrate. The solid ester obtained was refluxed with hydrazine hydrate 2 ml (0.04 mol) in absolute ethanol (20 ml) for 8 hr. On cooling the reaction mixture a solid was obtained. It was filtered and recrystallized from ethanol.
m.p. 185–86°. Yield 50%. Anal. for $C_{12}H_{12}N_2O_2$; Calcd.; C, 66.66%; H, 5.55%; N, 12.96%. Found; C, 66.23%; H, 5.32%, N, 12.54%
IR (KBr): 1700–1690 $cm^{-1}$ (C = 0 of amide), 1220–1140 $cm^{-1}$ ($-OCH_2$) and 3450–3300 $cm^{-1}$ ($-NH_2$)

*N-(2-Naphthyloxyacetyl)thiosemicarbazide (II–VI):*

N-(2-Naphthyloxyacetyl)hydrazine 4.32 g (0.02 mol) was refluxed with benzene isothocyanate 3 ml (0.02 mol) in absolute ethanol (30 ml) for 4 hr. On cooling, a solid compound (II) was obtained. It was recrystallized from ethanol, yield 2 g. Other compounds of the series were similarly prepared (table 1).

**Table 1** *N-(2-Naphthyloxyacetyl)thiosemicarbazides*

| Compd. No. | R | m.p.°C | Molecular formula | Found (%) (Calc.) C | H | N | Hypoglycemic potency (% reduction in blood sugar |
|---|---|---|---|---|---|---|---|
| II* | H | 156 | $C_{19}H_{17}N_3O_2S$ | 64.58 (64.95) | 4.65 (4.84) | 11.72 (11.96) | 8 |
| III* | $CH_3$ | 163–4 | $C_{20}H_{19}N_3O_2S$ | 65.52 (65.75) | 5.48 (5.20) | 11.28 (11.50) | 16 |
| IV | $CH_3O$ | 160 | $C_{20}H_{19}N_3O_3S$ | 62.75 (62.99) | 4.64 (4.98) | 11.42 (11.02) | 13 |
| V* | Cl | 174 | $C_{19}H_{16}N_3O_2SCl$ | 59.45 (59.14) | 4.65 (4.15) | 10.45 (10.89) | 12 |
| VI | Br | 185–6 | $C_{19}H_{16}N_3O_2SBr$ | 53.45 (53.03) | 3.42 (3.72) | 9.42 (9.76) | — |

*Showed IR spectral bands at 1720–1690 $cm^{-1}$ (C=O) 1140 $cm^{-1}$ ($-OCH_2$) and 3300–3150 $cm^{-1}$ ($-NHNH$). PMR ($CDCl_3$) $\delta$: Compound No. II: 6.85–73 (m, 12 ArH), 4.55 (s, 2H $-OCH_2$), 7.4 (bs, 1H $-CONH$) 8.7 (bs 1H of

), 6.2 (s, 1H, ArNH). The yields ranged from 40 to 50%.

**Table 2** *2-Arylamino-5-(2-naphthyloxymethyl)-1,3,4-thiadiazoles/oxadiazoles*

| Compd No. | R | m.p. °C | Molecular formula | Found % (Calc.) C | H | N | Hypoglycemic potency (% reduction in blood sugar) |
|---|---|---|---|---|---|---|---|
| VII* | H | 183 | $C_{19}H_{15}N_3OS$ | 68.15 (68.46) | 4.25 (4.50) | 12.25 (12.61) | — |
| VIII* | $CH_3$ | 194 | $C_{20}H_{17}N_3OS$ | 69.58 (69.16) | 4.32 (4.89) | 12.52 (12.10) | 21 |
| IX | $CH_3O$ | 189 | $C_{20}H_{17}N_3O_2S$ | 66.54 (66.11) | 4.32 (4.68) | 11.12 (11.57) | 14 |
| X | Cl | 204 | $C_{19}H_{14}N_3OSCl$ | 62.54 (62.04) | 3.50 (3.80) | 11.62 (11.42) | 18 |
| XI | Br | 213 | $C_{19}H_{14}N_3OSBr$ | 55.0 (55.35) | 3.62 (3.39) | 10.42 (10.19) | — |
| XII** | H | 175 | $C_{19}H_{15}N_3O_2$ | 71.64 (71.92) | 4.46 (4.73) | 13.48 (13.24) | — |
| XIII** | $CH_3$ | 182–3 | $C_{20}H_{17}N_3O_2$ | 72.80 (72.50) | 5.45 (5.13) | 12.10 (12.68) | 12 |
| XIV | $CH_3O$ | 187–8 | $C_{20}H_{17}N_3O_3$ | 69.48 (69.16) | 4.52 (4.89) | 12.55 (12.10) | 15 |
| XV** | Cl | 197 | $C_{19}H_{14}N_3O_2Cl$ | 64.28 (64.86) | 3.42 (3.98) | 11.60 (11.94) | 10 |
| XVI | Br | 205 | $C_{19}H_{14}N_3O_2Br$ | 57.12 (57.59) | 3.10 (3.53) | 10.25 (10.60) | — |

*Showed IR spectral bands at 3420 $cm^{-1}$ ($-NH$), 1620 (C=N), 1120 $cm^{-1}$ ($-OCH_2$).
**Showed IR spectral bands at 3400 $cm^{-1}$ ($-NH$), 1610 (C=N), 1140 $cm^{-1}$ ($-OCH_2$), 1230, 1020 $cm^{-1}$ (C–O–C–)
PMR ($CDCl_3$)$\delta$ : compound No. VII: 7.5 (m, 12H, Ar-H), 5.6 (s, 2H, $-OCH_2$), 6.2 (s, 1H, NH)
PMR ($CDCl_3$)$\delta$ : Compound No. XII: 6.9–7.3 (m, 12H, Ar-H), 5.8 (s, 2H, $-OCH_2$), 6.5 (s, 1H, NH)
The yields ranged from 50–55%

### 2-(*Arylamino*-5-(2-*naphthyloxymethyl*)-1,3,4-*thiadiazoles* (*VII–XI*)

N-(2-Naphthyloxyacetyl)thiosemicarbazide (II) 3.5 g (0.01 mol) was dissolved in conc. $H_2SO_4$ acid (10 ml). The solution was kept at room temperature for 3 hr and subsequently stirred at intervals. It was poured into crushed ice. The solid compound (VII) thus separated was recrystallized from ethanol, Yield – 1.5 g. Other compounds of the series were similarly prepared (table 2).

*2-Arylamino-5-(2-naphthyloxymethyl)-1,3,4-oxadiazoles (XII-XVI)*

To a methanolic solution of thiosemicarbazide (II), 3.5 g (0.01 mol) was added mercuric oxide 2.6 g (0.012 mol). The mixture was refluxed for 3 hr and filtered. Distilling off the solvent from the filtrate gave a solid compound (XII) which was recrystallized from ethanol, yield 1.8 g. Other compounds of the series were similarly prepared (table 2).

## BIO-ASSAY

The hypoglycemic activity of ten compounds was determined according to the method of Somagyi[9]. From the results recorded in tables 1 and 2, it is difficult to arrive at a definite trend in SAR of compounds synthesized. Nevertheless, in case of thiosemicarbazides (table 1) an increasing trend in the reduction of blood glucose was found in the following order of phenyl substituents (R): $H < Cl < OCH_3 < CH_3$. Moreover, in a series of thiodiazoles and oxadiazoles, a maximum reduction of 21 % blood glucose was shown by compound No. VIII with $R = CH_3$.

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# ANNOUNCEMENT

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The International Symposium on 'Bioindicators of Industrial and Mining Environment' will be held at the Department of Bioscience, Bhopal University, Bhopal, during December 4–7, 1986.

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