CYCLISATION REACTION OF N-SUBSTITUTED MANDELHYDRAZIDE WITH FORMALDEHYDE

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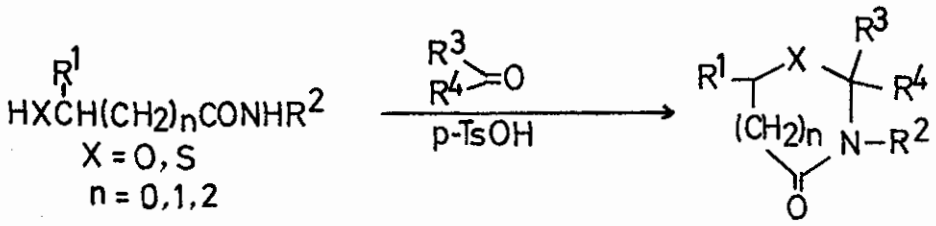
Acid-catalysed cyclisation of N-substituted mandelhydrazides II and X with paraformaldehyde gave hexahydro-1,2,4,5-tetrazine derivatives. Furthermore, the acetyl group on the nitrogen rearranged to alcoholic oxygen during the reaction of X to give VI.

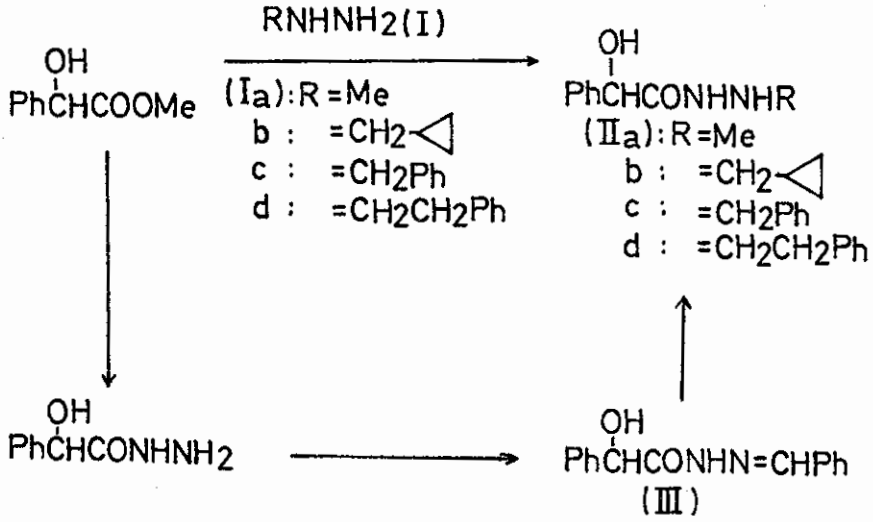
We have previously reported[1] that the secondary amides possessing a hydroxyl or a mercapto group at α-,β- or γ-position reacted with various carbonyl compounds in the presence of an acidic catalyst to give cyclisation products, oxazolidine, tetrahydro-1,3-oxazine, hexahydro-1,3-oxazepine, thiazolidine, tetrahydro-1,3-thiazine and hexahydro-1,3-thiazepine derivatives.



Scheme 1

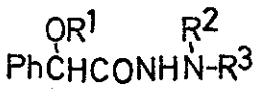
As an extention of our studies, we wish to report an acid catalysed cyclisation of the N-substituted mandelhydrazides, possessing a hydroxyl group at α-position, with formaldehyde.

The starting N-substituted mandelhydrazides (II) have been prepared by a condensation of N-substituted hydrazines (I) with methyl mandelate by heating at 110 - 115° for 3∿7 h, whose results are shown in Table I. The structure of II was verified from microanalyses, spectral consideration and an alternative synthesis of this compound (IIc) as shown in Scheme 2.



Scheme 2

Table I Syntheses of N-Substituted Mandelhydrazides



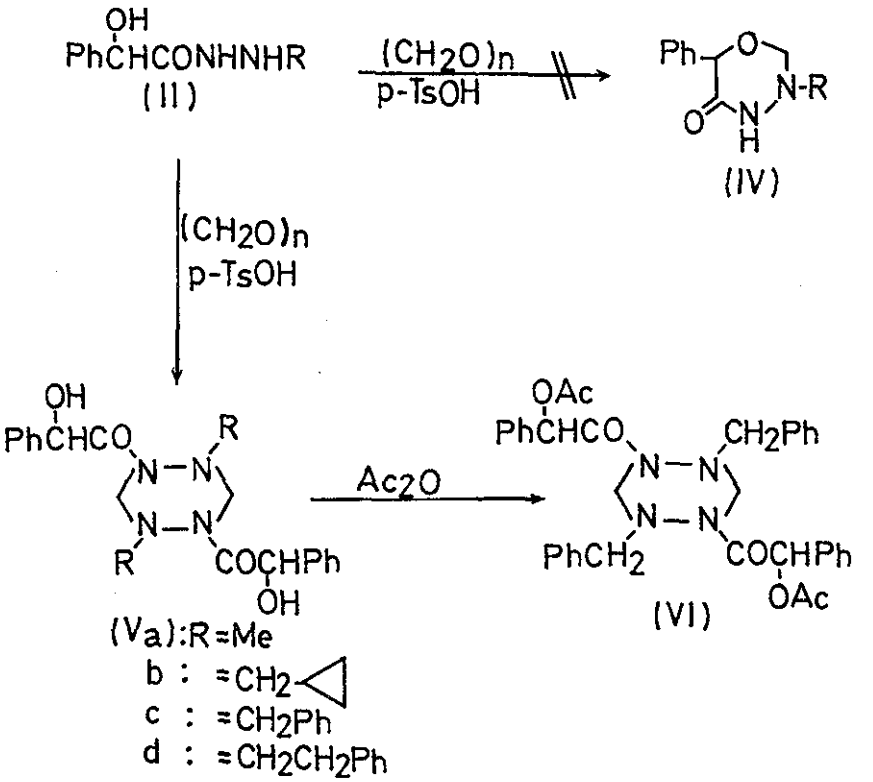
	R^1	R^2	R^3	Reaction Conditions Heating Time(h)	Temp(°C)	mp °C/Solvent	Yield(%)
IIa	H	H	-Me	3	90-100	115-116/AcOEt	70
IIb	H	H	$-CH_2-$◁	3	90-100	148.5-150.5/AcOEt	42
IIc	H	H	$-CH_2Ph$	7	110-125	133-135/EtOH	57
IId	H	H	$-CH_2CH_2Ph$	4	140-150	159-160/EtOH	46
IX*1	Ac	Ac	$-CH_2Ph$	3	140-150	157-159/EtOH	83
X*2	H	Ac	$-CH_2Ph$	0.5	100	122-123/C_6H_6	67.5
XII*3	Ac	H	$-CH_2Ph$	0.3	130	92-93/Et_2O-pet. ether	46

*1) Diacetylated compound (IX) was obtained by heating IIc with acetic anhydride.

*2) N-Acetylhydrazide (X) was synthesised by a partial hydrolysis of IX with the borate buffer at pH 9.95.

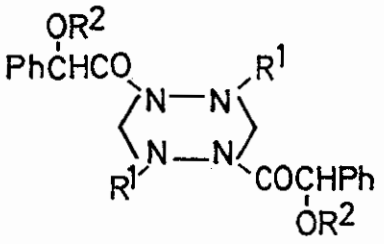
*3) Acetate (XII) was prepared from X by heating in the presence of p-toluenesulphonic acid.

The cyclisation was carried out by refluxing a solution of the hydrazides II or X with paraformaldehyde in the presence of p-toluene-sulphonic acid in xylene under the removal of water formed. After cooling, precipitate in the reaction mixture was collected with filtration, washed by 2-propanol, aqueous sodium hydrogen carbonate solution and water, and purified by recrystallisation from dimethyl-formamide to give the cyclisation products. These results are shown in Table II.



Scheme 3

Table II Synthesis of Hexahydro-1,2,4,5-tetrazines from N-Substituted Mandelhydrazides

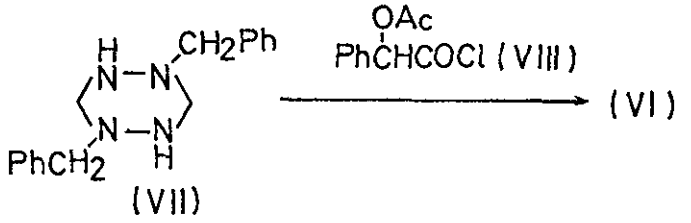


	R^1	R^2	Refluxing Time(h)	mp°C/Solvent	Yield(%)
Va	-Me	H	1.0	281-283/DMF	12
Vb	$-CH_2$-cyclopropyl	H	1.5	246.5-248.5/DMF	15.2
Vc	$-CH_2Ph$	H	1.5	287-290/DMF	40.7
Vd	$-CH_2CH_2Ph$	H	1.5	257-259/DMF	28.4
VI	$-CH_2Ph$	Ac	5 min*1) 1.5 h*2)	255-257/EtOH	63.4 48.0

*1) By acetylation of Vc with acetic anhydride and pyridine; *2) By cyclisation of X with paraformaldehyde in the presence of p-toluenesulphonic acid in xylene.

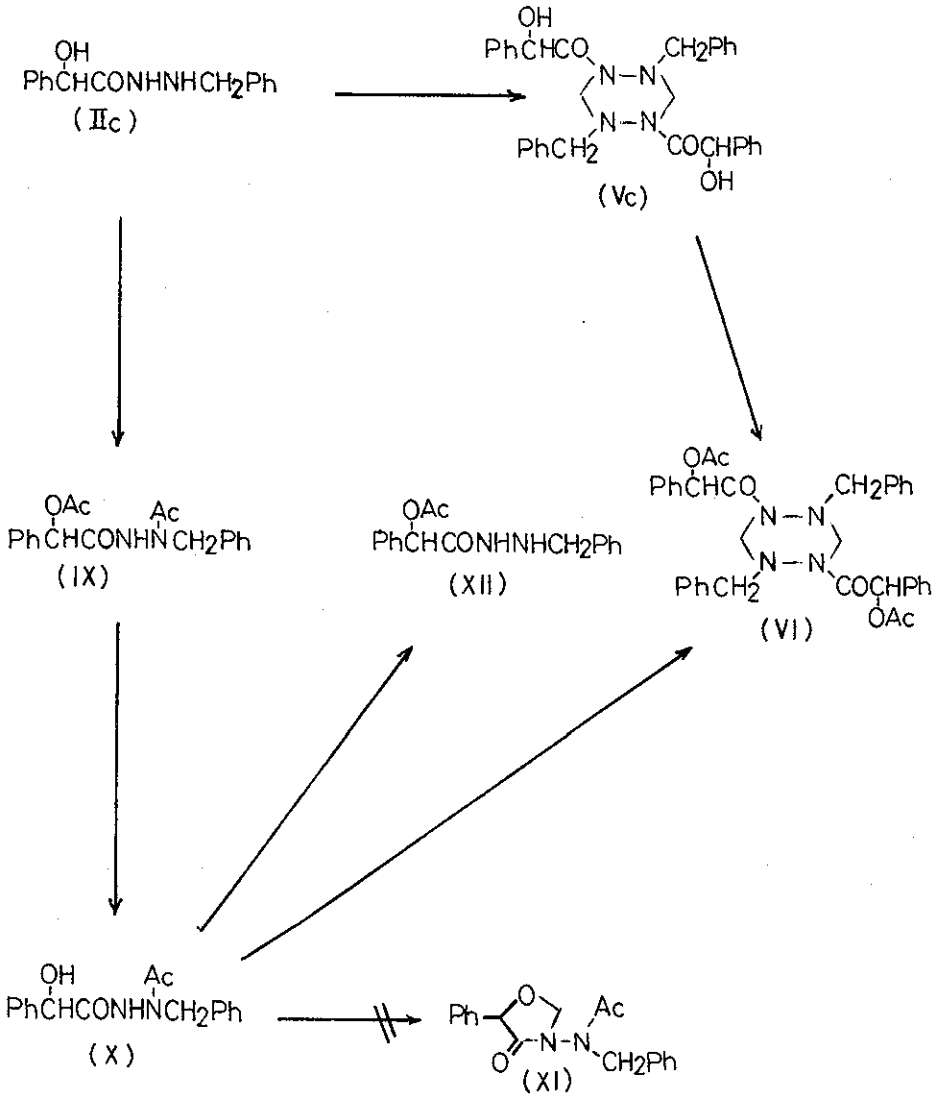
The reaction did not form the expected 1,3,4-oxadiazine derivatives (IV)[2] but hexahydro-1,2,4,5-tetrazine derivatives (V) by a double condensation of the hydrazide (II) with formaldehyde.

Microanalysis and mass spectrum [m/e 536 (M^+)] of the product (Vc) revealed that this compound had a dimeric structure, which was strongly supported by *ir and nmr spectra* as shown in Table III. Moreover, this fact was proved by an alternative synthesis of the acetylated derivative VI of Vc, which was carried out by the reaction of VII[3] with acetylmandelic chloride (VIII).[4]



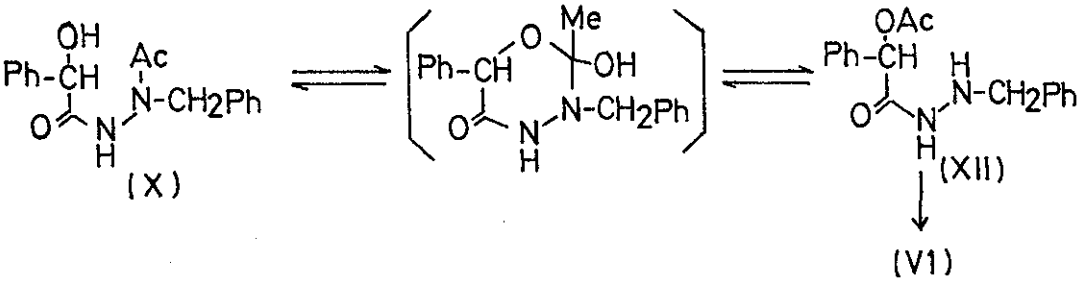
Scheme 4

The same reaction of X with parafomaldehyde gave VI, the unexpected product, identical with the authentic sample described above, but no the oxazolidinone (XI). This fact suggested that acetyl group on the nitrogen atom migrated to an alcoholic oxygen atom during the reaction. The same rearrangement as above is also observed during the reaction of X with p-toluenesulphonic acid in xylene to form the O-acetyl compound (XII).


OH
PhCHCONHNHCH2Ph
(IIc)
OH
PhCHCO
CH2Ph
N–N
N–N
PhCH2
COCHPh
OH
(Vc)
OAc
PhCHCONHNHCH2Ph
(XII)
OAc
PhCHCO
CH2Ph
N–N
N–N
PhCH2
COCHPh
OAc
(VI)
OAc
Ac
PhCHCONHNCH2Ph
(IX)
OH
Ac
PhCHCONHNCH2Ph
(X)
Ph
O
Ac
N–N
O
CH2Ph
(XI)

Scheme 5

In the nmr spectrum (in $CDCl_3$) of XII, a methine proton at the α-position which appeared at 5.05 ppm in X is shifted to 6.05 ppm. The ir spectrum (KBr) of XII showed carbonyl absorption of ester at 1730 cm^{-1}. The rearrangement is presumed to proceed through the formation of 1,3,4-oxadiazine ring[5] as shown in Scheme 6.



Scheme 6

Thus, it turned out that the acid-catalysed cyclisation reaction of the hydrazides (II) possessing a hydroxyl group with formaldehyde produced tetrahydro-1,2,4,5-tetrazine derivatives.

Table III Spectral Data of the Cyclisation Products

	ir ν_{max}^{KBr} cm^{-1}	nmr (CF_3COOH) δ
Va	3400 1650	2.6 (6H, s, N-C<u>H</u>$_3$x2), 3.35, 4.53 (each 2H, each d, <u>J</u> = 13.5 Hz, $C_{3,6}$-H_2), 5.83 (2H, s, PhC<u>H</u>O-x2).
Vb	3450 1650	2.65 (4H, d, <u>J</u> = 6 Hz, N-C<u>H</u>$_2$◁ x2), 3.25, 4.80 (each 2H, each d, <u>J</u> = 14 Hz, $C_{3,6}$-H_2), 6.1 (2H, s, PhC<u>H</u>O-x2).
Vc	3430 1650	3.4, 4.73 (each 2H, each d, <u>J</u> = 13 Hz, $C_{3,6}$-H_2), 3.8 (4H, s, N-C<u>H</u>$_2$Phx2), 5.56 (2H, s, PhCHO-x2).
Vd	3440 1650	2.8-3.1 (8H, m, NC<u>H</u>$_2$C<u>H</u>$_2$Phx2), 3.2, 4.75 (each 2H, each d, <u>J</u> = 13 Hz, $C_{3,6}$-H_2), 5.5 (2H, s, PhC<u>H</u>O-x2).
VI	1725 1670	2.25 (6H, s, N-COC<u>H</u>$_3$x2), 3.5, 4.85 (each 2H, each d, <u>J</u> = 13.5 Hz, $C_{3,6}$-H_2), 6.6 (2H, s, PhC<u>H</u>O-x2).

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