Lactam Acetals 4 : Reactions with Araldehydes

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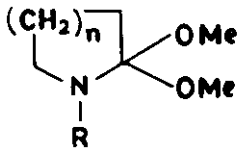
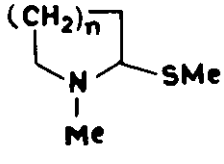
Summary : Lactam acetals undergo facile electrophilic substitution at 3 position with araldehydes to form benzhydrols. Both threo and erythro products are formed, their proportion depending upon the aldehyde; the threo products undergo facile dehydration to form (E)-3-benzylidene derivatives. The threo oamino benzhydrols obtained as the exclusive products by reaction of lactam acetals with o-aminobenzaldehyde undergo instantaneous cyclisation to give a novel one pot synthesis of 1-substituted azacycloalkano (2, 3-b)quinolines.

Lactams are practically inert towards electrophiles and nucleophiles because of the delocalization of the lone pair of electrons. However, they can be activated by conversion into lactim ethers and lactam acetals, which undergo a facile annellation reaction at positions 1,2 and 2,3 respectively. In view of the versatility of these compounds for the synthesis of condensed heterocycles, their chemistry has been under study in this laboratory.[1-4] In this communication the reaction of various aldehydes with lactam acetals of 1-alkyl pyrrolidone/piperidone/azepinone *1*-*5*, a comparison of the reactivity of lactam acetals with ketene S, N-acetals[5] *6*-*7*, the effect of the nature of the aldehyde on the stereochemistry of the benzhydrol formed, and the facile cyclisation of the product obtained from o-aminobenzaldehyde to give a novel one pot synthesis of 1-substituted azacycloalkano-[2, 3-b]quinoline are reported.

Benzaldehyde on reaction with lactam acetal *1* gave a mixture of the threo-benzhydrol *8* (vide infra) and the (E)-benzylidene derivative[6] *9*, as shown by NMR; the mixture on treatment with 50% H_2SO_4 gave exclusively *9*. Similarly the benzylidene compounds *10*-*12* were obtained from the lactam acetals *2*-*4* respectively. A similar reaction of *1* with o-aminobenzaldehyde gave the benzhydrol *13* along with the cyclised product *14*, which were separated either by chromatography or by fractional crystallization. The NMR of *13* showed resonance signals for OH proton as a doublet (J = 6 Hz) at 5.51 and for 3α-H as a quartet at 4.4, which were converted into a singlet and doublet ($J_{3H,\ 3\alpha\text{-}H}$ = 12Hz) respectively on D_2O treatment. The benzhydrol *13* easily cyclised to the 2, 3-fused quinoline *14* on acid treatment. Similarly the lactam acetals *2*, *4* and *5* on reaction with o-aminobenzaldehyde gave the 2, 3-condensed quinolines *15*-*17* respectively.



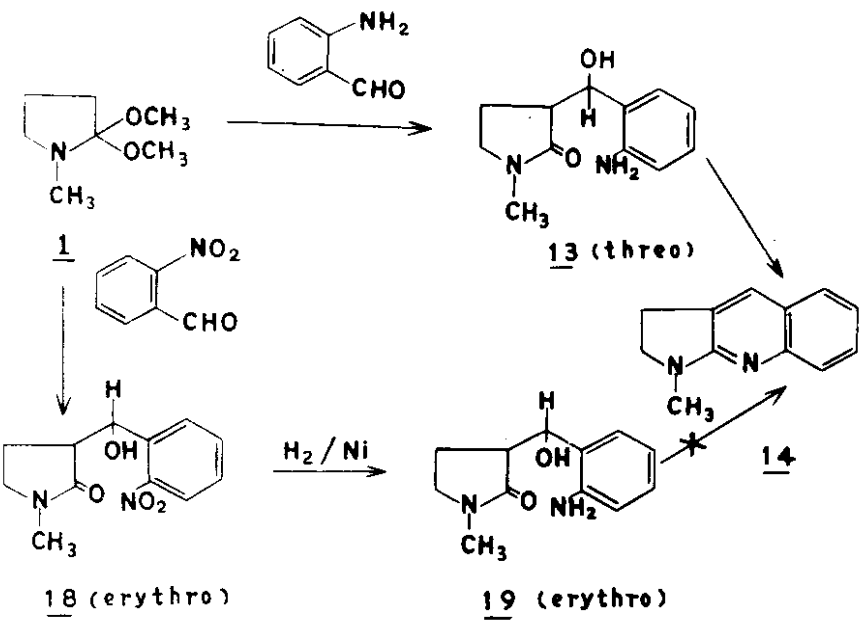


1 n = 1, R = CH_3
2 n = 1, R = CH_2 ph
3 n = 1, R = n-C_4H_9
4 n = 2, R = CH_3
5 n = 3, R = CH_3

6 n = 1
7 n = 2

Reaction of the acetal *1* with o-nitrobenzadehyde gave exclusively the erythro-benzhydrol *18*. Its NMR (DMSO-d_6) showed 3α-H and 3α-OH signals merged together at 5.61 which converged into a doublet ($J_{3H,\ 3\alpha\text{-}H}$ = 2.5 Hz) on D_2O treatment. *18* was not dehydrated by acid treatment. Reduction of *18* in presence of Raney Ni gave the corresponding aminobenzhydrol *19* ($J_{3H,\ 3\alpha\text{-}H}$ = 2.5 Hz), different from the aminobenzhydrol *13* obtained above. On acid treatment *19*, unlike *13*, did not cyclise to the quinoline, thus showing that *13* and *19* are diastereoisomers.

As the stereochemistry of the benzhydrol formed appeared to depend upon the nature of the aldehyde used, which in turn determined its propensity to dehydration, the reaction of acetal *1* with various aldehydes was next studied and the results are summarised in Table — I. Phthalaldehyde gave the erythro hemiacetal



SCHEME 1

23. Reaction with indole-3-aldehyde gave N-methylindole-3-aldehyde as the major product. This appears to be the first reported instance of N-alkylation by lactam acetals, though Lewis acid catalysed glycosidation with amide acetals has been reported recently by Hanessian *et al*[7]

To obtain a comparative picture of the reactivity of acetals and their thio analogs towards aldehydes, reaction of benzaldehyde, o-nitrobenzaldehyde and o-aminobenzaldehyde with the ketene acetals *6* and *7* was studied. The reaction of *6* with benzaldehyde gave a mixture of the erythro and threo-benzhydrols *25* and *8* and the benzylidene compound *9* in a ratio of 1:2:2, as shown by NMR. Chromatography of the mixture on alumina column gave only the erythro-benzhydrol *25* and the dehydrated product *9* confirming that the threo isomer dehydrates readily. o-Nitrobenzaldehyde on reaction with *6* gave exclusively the erythro-benzhydrol *18* identical to that obtained from the lactam acetal, along with a small amount of an unidentified product, while with *7* it gave a mixture of the erythro benzhydrol *26* and the dehydrated product *27* in a ratio of 1:2, thus indicating the initial formation of the threo-benzhydrol. The reaction of *6* with o-aminobenzaldehyde gave only the azacycloalkanoquinoline as in the case of the lactam acetal. Although the overall reactivity of ketene S, N-acetal and lactam acetals with aldehydes is similar, there appears to be lesser stereoselectivity of the reactions with the ketene S, N-acetals.

Stereochemistry.: The stereochemical outcome of this addition reaction would be determined by the orientation of the aromatic group and the hydrogen atom of the aldehyde group in relation to the enamine double bond. In the transition state the π-bond of the enamine species and the carbonyl group of the aldehyde have to come in one plane in such a way that there is an effective overlap of the π-orbitals; the two possible orientations of the transition state, (*a*) and (*d*), are shown in Fig. 1. The orientation (*a*) would lead to the threo isomer, while (*d*) would give the erythro isomer. Of the transition states (*b*) and (*c*), the former, having two gauche interactions compared to three in the case of latter, would be more favoured. Thus, greater thermodynamic stability of the threo isomers over the erythro isomers, on account of lesser gauche interactions in the threo isomers in the hydrogen bonded state would explain their preferential formation. Although no clear-cut explanation can be given at this stage for the anomalous formation of the erythro isomer with o-nitrobenzaldehyde and o-phthalaldehyde, this could perhaps be

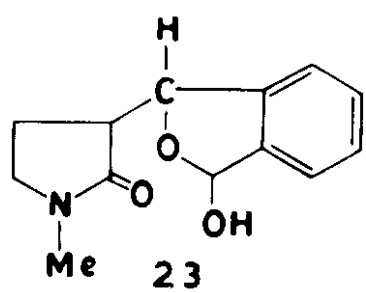


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TABLE – I

Reaction of 1-methyl-2, 2-dimethoxypyrrolidine (*1*) with various aldehydes

Aldehyde	Product Ratio Percent[a]			
	Erythro-	Threo		
	Benzhydrol %	Benzhydrol %	Dehydrated %	Total %
Benzaldehyde	0	32	68	100
o-Nitrobenzaldehyde	100	0	0	0
o-Aminobenzaldehyde	0	10[b]	90	100
	0	80[c]	20	100
α-Naphthaldehyde	0	5	95	100
β-Naphthaldehyde	0	0	100	100
Pyrrole-2-aldehyde	0	0	100	100
Salicylaldehyde	0	0	100	100
Phthalaldehyde	100		(as hemi-acetal *23*)	
o-Anisaldehyde[d]	20	55	25	80
Pyridine-3-aldehyde[d]	66	34	0	34
p-Nitrobenzaldehyde[d]	30	30	40	70

[a]In order to calculate the percentage of threo isomer formed, the amount of dehydrated product has been added since it is shown that only the threo isomer undergoes dehydration.
[b]Reaction at 35-38°C; [c]Reaction at 20-25°C. [d]Individual compounds were not isolated, the ratio of isomers is given on the basis of NMR of the mixture.

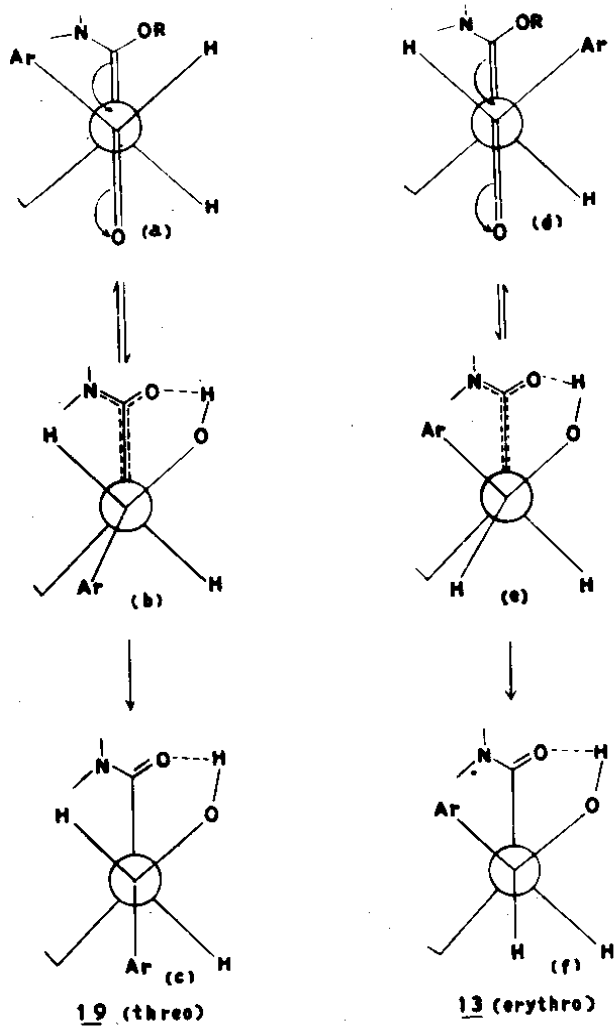
due to secondary dipolar interactions between the nitro or the second aldehyde group with the ring nitrogen in the erythro isomer (f). The electronic effect of the substituents per se does not appear to be the reason for this, as p-nitrobenzaldehyde gave both the threo and erythro isomers.

The J values of 3 α-H of the two sets of diastereo-isomers are 9.5 - 12.0 and 2.5 Hz respectively. An examination of the different rotamers of the threo and erythro isomers as shown in Fig. 2 would indicate that on account of internal hydrogen bonding and lesser gauche interactions, the rotamer (*a*) of the threo isomer would be the most favoured. In this rotamer 3 α-H on account of its coupling with the anti peri-planar proton, would have a high J value. Thus the isomers having J values of 9.5 - 12.0 have been assigned threo stereochemistry (R,S) while the isomers having J values of 2.5, erythro stereochemistry (R,R or S,S). The J values would indicate that in the case of threo isomers there is a preponderance of the rotamer (*a*) while in the erythro that of rotamers (*e*) or (f)

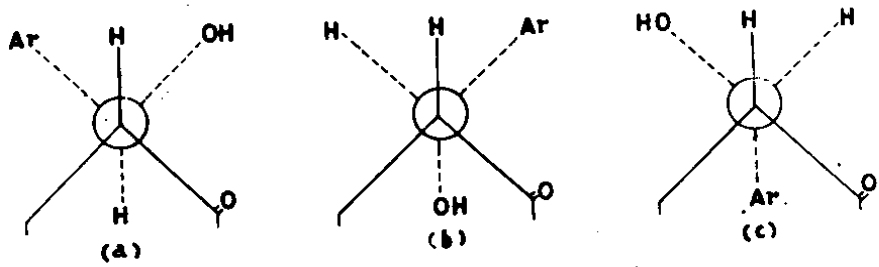
Experimental

Melting points were determined in an electrically heated apparatus (Townson and Mercer Ltd., Croydon, England) and are uncorrected. The compounds were routinely checked by IR on Perkin-Elmer 137, 177 or 337 spectrometer, and NMR on Varian A-60 D instrument using TMS as internal reference and chemical shift values are expressed in δ scale downfield from TMS. TLC carried out on silica gel and neutral alumina plates and spots were located by exposing in an iodine chamber and by $KMnO_4$ spraying. All the compounds were analysed for their C, H & N analysis, which were within 0.3% of the expected limit.

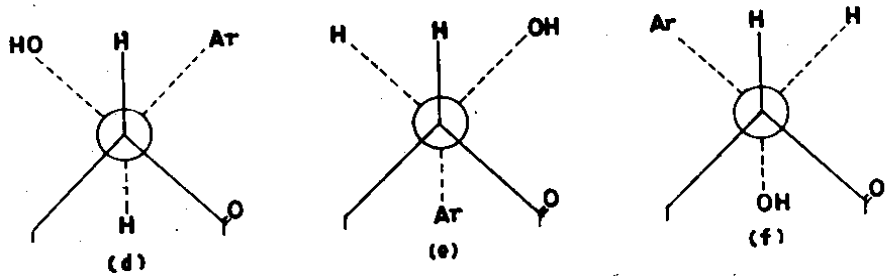
Preparation of lactam acetals 1-5 : *1*, *4* and *5* were synthesized by the procedure outlined in ref. 8. The boiling points and spectral data of acetals *2* and *3* generated by this procedure are given below.



19 (threo) 13 (erythro)



ROTAMERS OF 13 (Threo)



ROTAMERS OF 19 (Erythro)

1-Benzyl-2, 2-dimethoxypyrrolidine (2) : b.p. 54-56°/4 mm; yield 40%; NMR (CCl_4) : 1.90 (2, m, 4-CH_2), 2.73 (2, t, 5-CH_2), 3.13 (2, t, 3-CH_2), 3.25 (6, s, OCH_3), 4.40 (2, s, CH_2Ph) and 7.21 (5, s, PhH).

1-Butyl-2, 2-dimethoxypyrrolidine (3) : b.p. 72-73°/4 mm; yield 45%; NMR (CCl_4): 0.91 (3, m, CH_3), 1.40 (4,m, $(CH_2)_2CH_3$) 1.82 (2, m, 4-CH_2), 2.40 - 2.90 (4, m, NCH_2 and 5-CH_2) and 3.15 (6, s, OCH_3).

Preparation of ketene S, N-acetals (6 and 7) : 1-Methyl 2-methyl-thio- Δ^2-piperidine (7) were prepared by the general method outlined in ref. 9, by $KOBu^t$ treatment of the methyliodide adduct of the thiolactams.

(E)-1-Methyl-3-benzylidene-2-pyrrolidone (9) : Benzaldehyde (1.01 ml, 0.009 mole) was added to 1 (1.45 g, 0.01 mole) under cooling (exothermic reaction) and kept at room temperature for 24 hr. Methanol generated in the reaction was removed under reduced pressure to give a mixture of (8) and (9) in a ratio of 3.2 : 6.8 respectively as shwon by NMR ($CDCl_3$) : 1.71 (0.32, q, 4-CH_2 of 8), 2.61 (0.62, m, 4-CH_2 of 9), 2.93 (3, s, NCH_3), 3.45 (2, t, 5-CH_2), 4.71 (0.32, d, 3 α-H of 8, J = 9 Hz), 5.30 (0.32, b.s., OH, exchangeable with D_2O) and 7.36 (5.68, m, PhH and olefinic H of (9).

The crude mixture of 8 and 9 was warmed on the steam bath with aqueous sulphuric acid (5 ml of 50%) for 1 hr and left at room temperature for 18 hr, diluted with water, cooled, when 9 was obtained as a solid, which was filtered and crystallized from chloroform benzene; yield 0.98 g (68%), m.p. 126°; IR (KBr) : 2850, 1680, 1500, 1450, 1400, 1300, 762, 690. NMR ($CDCl_3$) : 3.00 (3, s, NCH_3), 3.01 (2, t, 4-CH_2) 3.50 (2, t, 5-CH_2). 7.38 (5, s, PhH), 7.38 [1, merged t, olefinic H, shifted downfield to 7.80 on adding 10 mg Eu $(fod)_3$].

When the reaction was carried out in dry ether as solvent, the ratio of 8 to 9 was 1:5.

Compounds 10-12 were prepared essentially by the same method using corresponding lactam acetals. Their physical data are given in Table - II.

(R.S.)-1-Methyl-3-(α-o-aminophenyl) hydroxymethyl-2-pyrrolidone 13 : o-Aminobenzaldehyde (1.1 g, 0.009 mole) was added to 1 (1.45 gm, 0.01 mole) in dry ether in small amounts under cooling. The reaction mixture was left at room temperature for 30 hr. The solvent was removed in vacuo, the residue treated with hexane ether, and the solid obtained was crystallized from chloroform-methanol, yield 0.85 g (58%); m.p. 169-70°. IR (KBr) : 3350, 2890, 1635, 1485, 1130, 1050, 770. NMR(DMSO-d_6) : 2.00 (2, m, $4CH_2$), 2.86 (3, s, NCH_3), 3.33 (4, t, 5-CH_2 and NH_2, exchangeable with D_2O). 4.40 (1, g, 3 α-H, after D_2O shake, d, J = 12 OHz), 5.51 (1, d, 3 α-OH exchangeable with D_2O) and 6.90 - 7.30 (4, m, ArH).

Treatment of the mixture of 13 and ether-hexane soluble residue with aqueous 50% sulphuric acid gave 14. IR (KBr) : 2915, 2850, 1635, 1590, 755, 710. NMR ($CDCl_3$) : 3.03 (2, m, 3-CH_2), 3.06 (3, s, NCH_3), 3.53 (2, t, 2-CH_2) and 7.36 (5, m, PhH and 4-H). Mass — M^+ 184; U.V. λ max. 252, 345.

TABLE — II

Compound No.	R	R_1	n	m.p. °C	Yield %	Molecular Formula
(9)	Me	C_6H_5	1	126	70	$C_{12}H_{13}NO$
(10)	$CH_2C_6H_5$	C_6H_5	1	114	50	$C_{18}H_{17}NO$
(11)	C_4H_9	C_6H_5	1	61	50	$C_{15}H_{19}NO$
(12)	Me	C_6H_5	2	71	50	$C_{13}H_{15}NO$
(20)	Me	α-naphthyl	1	94	50	$C_{16}H_{15}NO$
(21)	Me	β-naphthyl	1	143	55	$C_{16}H_{15}NO$
(22)	Me	o-hydroxyphenyl	1	118	50	$C_{12}H_{13}NO_2$
(24)	Me	2-pyrrolyl	1	212	55	$C_{10}H_{12}N_2O$

Similarly, *15*-*17* were prepared by reaction of the corresponding lactam acetals with o-aminobenzaldehyde, and subsequent treatment of the crude product with sulphuric acid, without isolating the hydroxy products. The physical data of these compounds is given in Table — III.

(R, R/S,S)-1-Methyl-3-(α-o-nitrophenyl)hydroxymethyl-2-pyrrolidone (18) : o-Nitrobenzaldehyde (1.30 g, 0.01 mole) was added to a solution of *1* (1.45 g, 0.01 mole) in dry benzene (15 ml) when an exothermic reaction set in. The mixture was left at room temperature for 18-20 hr. The solid which separated was filtered, washed thoroughly with benzene and crystallized from ethanol, yield 1.42 g (60%), m.p. 171-72°. IR (KBr) : 3290, 2850, 1650, 1575, 1520, 1450, 1350, 860, 800, 750, 710, NMR (DMSO-d_6) : 1.80 (2, m, 4-CH_2), 2.71 (3, s, NCH_3), 3.28 (2, t, 5-CH_2), 5.61 (2, bs, 3 α-H and 3 α-OH, after D_2O shake, 1, d, 3 -H, J = 2.5 Hz) and 7.66 (4, m, ArH).

(R, R/S)-1-Methyl-3-(α-o-aminophenyl)hydroxymethyl-2-pyrrolidone (19) : A solution of *18* (200 mg) in dry methanol (20 ml) was hydrogenated in presence of Raney-Ni catalyst at 45 psi. The catalyst was removed by filtration, the filtrate concentrated to give (*19*) as a solid, yield 0.12 g (70%), m.p. 138°. IR (KBr) : 3360, 2890, 1650, 1605, 1500, 1450, 1400, 1310, 1040, 750. NMR ($CDCl_3$) : 2.05 (2, m, 4-CH_2), 280 (3, s, NCH_3), 3.26 (2, t, 5-CH_2), 3.86 (3, bs, NH_2 and OH, exchangeable with D_2O), 5.40 (1, d, 3 -H, J = 2.5 Hz) and 6.96 (4, m, ArH).

1, 3Dihydro-3-hydroxy-1-[3'-(N-methyl-2'-oxo)pyrrolidinyl] isobenzofuran (23) : Phthalaldehyde (1.2 g, 0.009 mole) was added to *1* (1.45 gm, 0.01 mole) when an exothermic reaction set in. The mixture was left at room temperature for 18 hr, concentrated *in vacuo*, and the residue treated with hexane-ether mixture. The solid thus obtained was filtered and crystallized from methanol-chloroform, yield 0.52 gm (38%), m.p. 220°. IR (KBr) : 3300, 2800, 1490, 755. NMR (DMSO-d_6) : 1.96 (m, 2H, 4 CH_2), 2.7 (diffused, 1, 3H), 2.78 (s, 3, NCH_3), 3.28 (m, 4, 5-CH_2, OCH-OCH) and 7.25 (s, 4, ArH and OH). Mass : M^+ 233 and other major fragments at m/e 215, 204, 186, 158, 128, 110.

Compounds (*20*-*22*) and (*24*) were obtained similarly by reactions of lactam acetal with salicylaldehyde, 1, and 2-naphthaldehyde, and pyrrole-2-aldehyde respectively.

Reaction of 1-methyl-2-methylthio- Δ^2-pyrroline (6) with benzaldehyde : Benzaldehyde (1.01 ml, 0.009 mole) was added to *6* (1.29 gm, 0.01 mole) and the mixture left at room temperature for 48 hr. The reaction mixture was dried *in vacuo* and the residue chromatographed on neutral alumina column. Elution with benzene gave *8* (0.5 gm, 45%) and with benzene-ethylacetate gave (*25*), (0.5 gm, 45%), m.p. 94°C. IR (KBr) : 3210, 2850, 1660, 1495, 1450, 752, 700 NMR ($CDCl_3$) : 1.91 (2, q, 4-CH_2), 2.80 (3, s, NCH_3), 3.15 (2, t, 5-CH_2), 3.61 (1, bs-OH, exchangeable with D_2O), 5.20 (1, d, 3 -H, J = 2.5 Hz), 7.26 (5, m, PhH).

Reaction of o-nitrobenzaldehyde with 1-methyl-2-methyl-thio- Δ^2-pyrroline (7) : o-Nitrobenzaldehyde (2.2 g, 0.145 mole) was added to cooled solution of (*7*) (2.2 g, 0.15 mole) in dry benzene and left at room temperature for 48 hr. The solid (*26*, 100 mg) which separated was filtered and washed with hexane-benzene mixture. The filtrate was concentrated and the residue triturated with hexane-ether giving a mixture (600 mg) of (*26*) and (*27*) in 1:2 ratio; NMR ($CDCl_3$) of mixture of (*26*) and (*27*) 1.80 (m, 2.6, 4-CH_2 and 5CH_2), 2.5 (t, 1.4, 4-CH_2 of *27*) 2.90 (s, .9, NCH_3 of *26* 3.10 (s, 2.1 NCH_3 of *27*), 6.08 (d, .4, 3 α-H, J = 2.5 Hz) and 7.65 (m, 4.0 ArH and .7, olefenic H); Compound (*26*) m.p. 195° (5%), IR (KBr) : 3350, 1610, 1505, 1330, 1090, 850, 795, 720, NMR (DMSOd_6) : 1.60 (4, m, 4 and 5-CH_2), 2.80 (3, s, NCH_3), 3.2 (2, t, 6 CH_2), 5.55 (1, d, OH exchangeable with D_2O), 5.95 (1, d, 3 α-H, J = 2.5 Hz) and 7.68 (4, m, ArH).

TABLE — III

Compound No.	n	R	m.p. °C	Yield %	Molecular Formula
14	1	Me	101	60	$C_{12}H_{12}N_2$
15	1	CH_2-Ph	105	50	$C_{18}H_{16}N_2$
16	2	Me	120-25	40	$C_{13}H_{14}N_2$
17	3	Me	156-60	40	$C_{14}H_{16}N_2$

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References

1. K. Joshi, V.A. Rao and N. Anand, *Indian J. Chem.*, **11**, 1222 (1973).
2. K. Bhandari, V. Virmani, V.A. Murti, P.C. Jain and N. Anand, *Indian J. Chem.*, 17 B, 107 (1979).
3. K. Bhandari, V. Virmani, V.A. Murti, P.C. Jain and N. Anand, *Indian J. Chem.* (In press).
4. V. Virmani, V.A. Murti, P.C. Jain and N. Anand, *Indian J. Chem.*, **13**, 1335 (1975).
5. T. Mukaiyama, S. Aizawa and T. Yamaguchi, *Bull. Chem. Soc. (Japan)*, **40**, 2641 (1967).
6. V. Virmani, B.B.P. Srivastava and P.C. Jain, *Indian J. Chem.*, **15B**, 981 (1977).
7. S. Hanessian and J. Banoub, *Tetrahedran Lett.*, 657 (1976).
8. H. Bredereck, F. Effenberger and H.P. Bayerlin, *Chem. Ber.*, **97**, 3081 (1964).
9. R. Gompper and W. Elser, *Org. Synth.*, 48, 98 (1968).