J. Indian Oem. Soc.,
Vol. ,66, August-October 1989, pp. 681-685

Formation of 3-Amino-l ,5,6,7-tetrahydro-4H-indol..4-ones from 2-(2..0xo-2-arylethyl)..1,3-cyclohexanediones ancd N,N..Disubstituted..hydrazinest

KUPP,USWAMY NAGARAJAN* and RASHMJ K. SHAH

Hindustan Ciba-Gelgy Ltd"oResearoh Oentre, Bombay-ilOO 098

Phenacyldimedones (ia-d) undergo an anomalous reaction with *N,N*-dlsubstitut'ed-hydrazines to afford 3-amino-I,5.6,7-tetrahYdro-4H-iDdol-4-olle's (3), with only Id, the (\ mechanism is for reaction of la with N.N-dirnel:hylhydrazine illvolving species 16 and 17 as intermediates. This is substan- of Ia with *N,N* dimethylhydrazine aDd excess of other <,a'niines likernorpholine, N,N·dibenzylamine. a.niline aDd n-propylamine ilea,d'iog to products 3d, 3f, 3j and 4 respectively_ 3f is to 3,j,andf;heнce deaw,illated to,kn!>wo.2-pheoyltetrahyd,roindole (9a). tWo of withphenylglyoxal affords ,3.!l, reac!s the acyclic triketone (7)to<afford only Jhe product 8, whIle WIth 18, ketotetrahydrofndoles 9b and 23 through a complex sequence of reactions,

tbat while 2-phe;Qaqyl- o

> hyd!azrnes

to form'

a few

, .bY:drazlD,es -WaS anomalous. ThepJ;'P9ucts the l:swbst.ituted-perhydroindoles (2), and

3 wer.e on analyti- of t]le

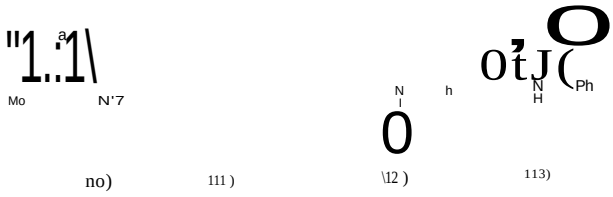
j,.QP.wn (9a)

3d" from,atDtnoketone :(ilO), phenyl glyoxal and ,morphQ'!ine.iWe'have subsequently explored the scope'8(this bbvd(reaction with a variety of *N,N*-ketones la an,d7. into the possiblec6urse allowed us' to devise a"n; inter<sting yield further examples :W,e,present,in full Qetails 9f. o,llr

M. aHa Ph

(71

(9 al'$I = H
(9b) R = Mq



no) 111) \12) 113)

Phenacyldimedone (1a) and six N,N-disubstituted-hydrazines afforded the ketotetrahydroindoles (3a - f ; Table 1). Yields were in the range 43 - 66% Witl,lOut effort at optimisation. Mother liquors fr.om ,'larger runs of the :reaction between 1a and were carefully investigated for material balance. Chromatography gave small amounts of methylene-bis-dimedone (5) and a cololired -'product, $C_{11o}H$"llsil)l<l0.- tively to be 6 on the basis of ir and nmr data. The reaction of 4-bromophenyl (lb) and 4-fiuorophenyl (lc),k.etoпes w!th N-aminomorptioline ,andN--aiIiinopiperidine' w'Mfaciteyielding 3g"(60%) and 3h (55%). In contrast, in one study with 2-phenacylcyclohe:xane-l,3-dione (ld) and No·amino-;piperidine, 3k W'as obtained only in 17% yield, whikt:be 'normal' product 2a was formed to the extent of 31%. From the reaction of acetonyl dimedone (Ie) and N,N-dimethylhydrazine, only small of 5 could be obtained. The origin ofS .in ,involving

Rf, , ":' 0. , ,R

(1a) R: Ph ı ,R_t = MQ'
(1bI.R: 4,-,Br'CSH4' Rl =1M
.'1CI:R'14 R, ;M.
i!,dlR ;,Ph, .:R;"H
i,,,iR: R,=Mı'

(21
qa}R,Ph. R,.,H
)N =1-

, 0

it"
Pr(n)'

(4) (5) (S)

t No. 779 from oentre.'

.Present Address: B & D Oentre, Searle (India) Ltd., Thane..400 601.

hydrazine is not easily understood. Lastly, the acyclic triketone, phenacyl acetylacetone (**7**) and *N*-aminopiperidine gave a poor yield of 1-piperidinopyrrole (**8**). 1-Unsubstituted-3-aminotetrahydroindoles of this study were characterised by the presence in the ir spectrum of a very broad NH band around 3 100 – 3 200 cm^{-1} and C=O band between 1 610 and 1 630 cm^{-1}, and a broad singlet signal due to NH in the ^1H nmr spectrum at around δ 11.2 ppm which disappeared with D_2O. 1-Amino compounds **2a** and **8** on the other hand were readily identified by the presence in their ^1H nmr spectra of a singlet due to the proton on the β-carbon atom at δ 6.30 and 5.83 ppm respectively.

Structures **3** were proved in two ways. Dibenzylamino derivative **3f** was hydrogenolysed to the 3-aminoindole (**3i**) which was deaminated to the known 2-phenyltetrahydroindole (**9a**)[2]. Secondly, aminoketone (**10**) was allowed to react with phenyl glyoxal and morpholine to afford **3d** although only in 6% yield.

In contrast to the phenacyldimedone (**1a**), 2-phenacylcyclohexanone (**11**) and *N*-aminopiperidine afforded only the 1-piperidino derivative (**12**) and not the 3-piperidinoindole (**13**)[3]. Taking this fact into account, we visualise the formation of **3a** from **1** (Chart 1) to occur through the enaminone (**14**) wherein the hydrazine *N,N*-bond is weakened to facilitate an intramolecular transfer of the disubstituted amino group as shown to form **15**. The latter can lead to the formation of **3a** via **16**, which

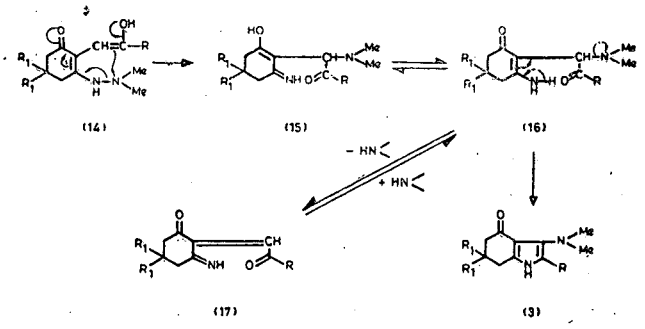


Chart 1

in turn will be in a reversible equilibrium with **17**. The formation of **3d** from **10**, phenyl glyoxal and morpholine must be occurring through **17** and the morpholine analogue of **16** as intermediates. Reaction of **17** with excess *N,N*-dimethylhydrazine, followed by oxidation would account for the formation of **6** as a byproduct in the reaction of **1a** with this hydrazine.

The mechanism proposed (Chart 1) would predict that the presence of an excess of a new amine during the reaction of **1a** with *N,N*-disubstituted-hydrazine to form **16** would lead to incroporation of the amine in **17** and hence into the final products **3**. We were pleased to find that the reaction of **1a** with 3 molar equivalents of *N,N*-dimethylhydrazine and 10 molar equivalents of morpholine indeed gave a mixture of **3a** and **3d** approximately in the ratio of 3 : 10 (^1H nmr). Pure **3d** was isolated from this mixture in 55% yield and identified. When excess morpholine was replaced by *N,N*-dibenzylamine or aniline, **3f** and **3j** were isolable although yields were unsatisfactory (12% and 6%). Excess n-propylamine led to double incorporation, both at positions 1 and 3 to give **4** in 30% yield along with a little **3a**. Its formation can be rationalised by assuming that **17** not only adds n-propylamine but also suffers an exchange of the imino group with the primary amine to give an analogue of **16** carrying two n-propyl groups.

Lastly, we studied the action of *N*-aminopiperidine with α-dimedonylpropiophenone (**18**). The reaction was sluggish and gave a complex mixture of products from which **9b** and **23** were obtained in 12% and 4% yield respectively. The structure of **9b** rested on analytical and spectral data. Identity was further established by comparison with a sample obtained by fusing **18** with ammonium carbonate. The structure of **23** was deduced from analytical as well as ir, nmr and mass spectral data. The ^1H nmr spectrum was particularly diagnostic, showing the indole α-H as a singlet at δ 7.60 ppm. Signals were lacking for both NH and β-protons. We propose the tentative mechanism shown in Chart 2.

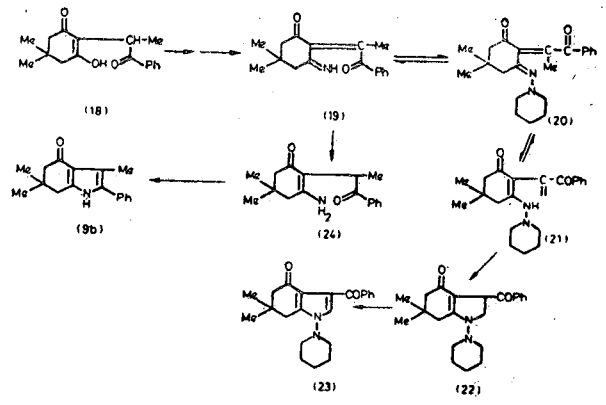


Chart 2

In the reaction of **18** with *N*-aminopiperidine, species **19** analogous to **17** is formed initially, but in the presence of excess of the reagent, **19** is transformed into **20**. The dienamine tautomer **21** of **20** can undergo intramolecular addition to form **22**. The observed final product **23** could arise by the oxidation of **22** by species **19** which in turn gets reduced to **24** leading to **9b** by cyclodehydration.

Physical and spectral data of compounds are given in Tables 1 and 2.

Experimental

*3-Amino-1,5,6,7-tetrahydro-4*H*-indol-4-ones* (**3**). *Method A :* A mixture of the ketone (**1a** ; 10 mmol) with *N,N*-disubstituted-hydrazine (30 mmol) produced an exothermic reaction. After it subsided,

J. Indian Chem. Soc.,
Vol. 66, August—October 1989, pp. 681-685

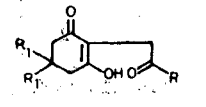
Formation of 3-Amino-1,5,6,7-tetrahydro-4*H*-indol-4-ones from 2-(2-Oxo-2-arylethyl)-1,3-cyclohexanediones and *N,N*-Disubstituted-hydrazines†

KUPPUSWAMY NAGARAJAN* and RASHMI K. SHAH

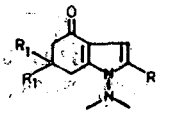
Hindustan Ciba-Geigy Ltd., Research Centre, Bombay-400 063

Phenacyldimedones (1a–d) undergo an anomalous reaction with *N,N*-disubstituted-hydrazines to afford 3-amino-1,5,6,7-tetrahydro-4*H*-indol-4-ones (3), with only 1d, additionally yielding the 'normal' product 2a. A mechanism is postulated for the novel reaction of 1a with *N,N*-dimethylhydrazine involving species 16 and 17 as intermediates. This is substantiated by reaction of 1a with *N,N* dimethylhydrazine and excess of other amines like morpholine, *N,N*-dibenzylamine, aniline and n-propylamine leading to products 3d, 3f, 3j and 4 respectively. 3f is hydrogenolysed to 3i and thence deaminated to known 2-phenyltetrahydroindole (9a). Reaction of aminocyclohexenone (10) with phenylglyoxal and morpholine affords 3d. *N*-Aminopiperidine reacts with the acyclic triketone (7) to afford only the 'normal' product 8, while with 18, ketotetrahydroindoles 9b and 23 are formed through a complex sequence of reactions.

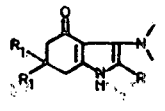
SOME years ago, we reported that while 2-phenacyldimedone (**1a**) and analogues underwent reaction with hydrazine and monosubstituted hydrazines to form 5-keto-1,4,5,6,7,8-hexahydrocinnolines[1,2], their behaviour towards a few *N,N*-disubstituted-hydrazines was anomalous. The products were not the expected 1-substituted-perhydroindoles (**2**), and were identified as 3-amino-1,5,6,7-tetrahydro-4*H*-indol-4-ones (**3**). Structures **3** were based on analytical and spectroscopic data, deamination of **3i** to the known ketotetrahydroindole (**9a**) and synthesis of **3d** from aminoketone (**10**), phenyl glyoxal and morpholine. We have subsequently explored the scope of this novel reaction with a variety of *N,N*-disubstituted-hydrazines and ketones **1a–e** and **7**. We have also gained insight into the possible course of the reaction which in turn allowed us to devise an interesting modification to yield further examples of **3**. We present in this paper full details of our studies.



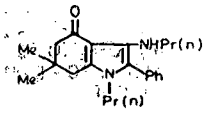
(1a) R = Ph, R_1 = Me
(1b) R = 4-Br-C_6H_4, R_1 = Me
(1c) R = 4-F-C_6H_4, R_1 = Me
(1d) R = Ph, R_1 = H
(1e) R = R_1 = Me



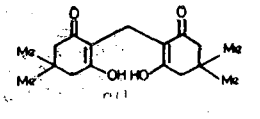
(2)
(2a) R = Ph, R_1 = N
N = 1-piperidinyl



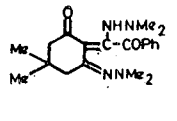
(3)



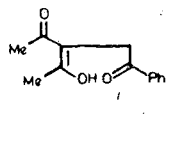
(4)



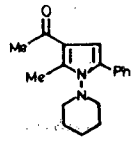
(5)



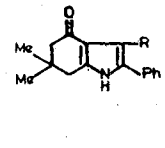
(6)



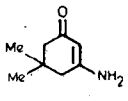
(7)



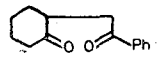
(8)



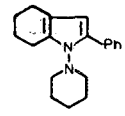
(9a) R = H
(9b) R = Me



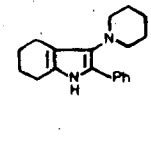
(10)



(11)



(12)



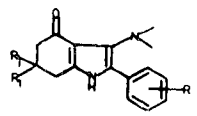
(13)

Phenacyldimedone (**1a**) and six *N,N*-disubstituted-hydrazines afforded the ketotetrahydroindoles (**3a–f**; Table 1). Yields were in the range 43–66% without any effort at optimisation. Mother liquors from larger runs of the reaction between **1a** and *N,N*-dimethylhydrazine were carefully investigated for material balance. Chromatography gave small amounts of methylene-bis-dimedone (**5**) and a coloured product, $C_{20}H_{28}N_4O_2$, considered tentatively to be **6** on the basis of ir and nmr data. The reaction of 4-bromophenyl (**1b**) and 4-fluorophenyl (**1c**) ketones respectively with *N*-aminomorpholine and *N*-aminopiperidine was facile yielding **3g** (60%) and **3h** (55%). In contrast, in one study with 2-phenacylcyclohexane-1,3-dione (**1d**) and *N*-aminopiperidine, the 'anomalous' product **3k** was obtained only in 17% yield, while the 'normal' product **2a** was formed to the extent of 31%. From the reaction of acetonyl dimedone (**1e**) and *N,N*-dimethylhydrazine, only small amounts of **5** could be obtained. The origin of **5** in reactions involving *N,N*-dimethyl-

† Contribution No. 779 from Research Centre.

*Present Address: R & D Centre, Searle (India) Ltd., Thane-400 601.

TABLE 1—PHYSICAL AND SPECTRAL DATA OF COMPOUNDS (3)‡



Compd. no.	R	R_1	N<	Yield* %	M.p** °C	Mol. formula (Mol. weight)	ν_{max} (nujol) cm^{-1}	δ†
3a	H	Me	NMe_2	66[a]	250–52[c]	$C_{16}H_{22}N_2O$ (282.4)	3 210, 1 600	[m]1.07 (6H, s, $2CH_3$), 2.27 (2H, s, C–$5H_3$), 2.67 (8H, s, C–$7H_3$, $2NCH_3$), 7.10–7.60 (m, 3ArH), 7.6–7.80 (m, 2ArH), 11.20 (br s, NH)
3b	H	Me	1-Piperidinyl	51[a]	273–75[d]	$C_{21}H_{26}N_2O$ (322.4)	3 160, 1 630	[m]1.07 (6H, s, $2CH_3$), 1.30–1.70 (6H, m, $CH_2CH_2CH_2$), 2.23 (2H, s, C–$5H_3$), 2.65 (2H, s, C–$7H_3$), 2.80–3.10 (4H, m, CH_2NCH_2), 6.90–7.50 (m, 3ArH), 7.45–7.95 (m, 2ArH), 11.17 (br s, NH)
3c	H	Me	1-Hexahydro-azepinyl	48[a]	249–50[e]	$C_{22}H_{26}N_2O$ (336.5)	3 200, 1 610	[m+n]1.07 (6H, s, $2CH_3$), 1.70–1.90 (8H, m, $(CH_2)_4$), 2.28 (2H, s, C–$5H_3$), 2.67 (2H, s, C–$7H_3$), 2.95–3.30 (4H, m, CH_2NCH_2), 7.00–7.60 (m, 3ArH), 7.90–8.15 (m, 2ArH), 10.70 (br s, NH)
3d	H	Me	4-Morpho-linyl	53[a] 55[b]	297–98[f]	$C_{20}H_{24}N_2O_2$ (324.4)	3 160, 1 610	[m+n]1.07 (6H, s, $2CH_3$), 2.27 (2H, s, C–$5H_3$), 2.68 (2H, s, C–$7H_3$), 3.00 (4H, m, CH_2–NCH_2), 3.65 (4H, m, CH_2OCH_2), 7.00–7.60 (m, 3ArH), 7.80–8.10 (m, 2ArH), 11.33 (br s, NH)
3e	H	Me	1-Methyl-4-piperazinyl	65[a]	272–74[g]	$C_{21}H_{27}N_3O_2$ (337.5)	3 160, 1 630	[m]1.03 (6H, s, $2CH_3$), 2.17 (3H, s, NCH_3), 2.20 (2H, s, C–$5H_3$), 2.23–2.40 (4H, m, CH_2–NCH_2), 2.70 (2H, s, C–$7H_3$), 6.95–7.48 (m, 3ArH), 7.50–7.90 (m, 2ArH), 11.15 (br s, NH)
3f	H	Me	$N(CH_2C_6H_5)_2$	43[a] 12[b]	203–05[h] (Chloro-form–hexane)	$C_{30}H_{30}N_2O$ (434.6)	3 220, 1 620	[n]1.05 (6H, s, $2CH_3$), 2.30 (2H, s, C–$5H_3$), 2.62 (2H, s, C–$7H_3$), 4.22 (4H, s, $2ArCH_2$), 6.90–7.50 (m, 5ArH), 7.10 (10H, s, $2C_6H_5CH_2$), 9.00 (br s, NH)
3g	4-Br	Me	4-Morpho-linyl	60[a]	>300[i]	$C_{20}H_{23}BrN_2O_2$ (403.3)	3 140, 1 610	[m]1.08 (6H, s, $2CH_3$), 2.28 (2H, s, C–$5H_3$), 2.70 (2H, s, C–$7H_3$), 3.00 (4H, m, CH_2NH_2), 3.70 (4H, m, CH_2OCH_2), 7.55 (m, 2ArH), 7.90 (m, 2ArH), 11.40 (br s, NH)
3h	4-F	Me	1-Piperi-dinyl	55[a]	287–88[j] (Ethanol–(methanol)	$C_{21}H_{25}FN_2O$ (340.4)	3 160, 1 610	[m]1.05 (6H, s, $2CH_3$), 1.30–1.80 (6H, m, $CH_2CH_2CH_2$), 2.20 (2H, s, C–$5H_2$), 2.63 (2H, s, C–$7H_2$), 2.75–3.15 (m, 4H, CH_2NCH_2), 7.10 (m, 2ArH), 7.87 (m, 2ArH), 11.17 (br s, NH)
3i	H	Me	NH_2	50	221–23[d]	$C_{16}H_{18}N_2O$ (254.3)	3 440, 3 330, 3 240, 1 620	[m]1.08 (6H, s, $2CH_3$), 2.18 (2H, s, C–$5H_3$), 2.60 (2H, s, C–$7H_3$), 4.80 (br s, NH_2), 6.80–7.60 (m, 5 ArH), 10.92 (br s, NH)
3j	H	Me	NHC_6H_5	6[b]	270–72[d]	$C_{22}H_{22}N_2O$ (330.4)	3 380, 3 200, 1 610	[m]1.07 (6H, s, $2CH_3$), 2.17 (2H, s, C–$5H_3$), 2.68 (2H, s, C–$7H_3$), 6.30–7.70 (m, 10 ArH), 6.65 (br s, ArNH), 11.22 (br s, pyrrole NH)
3k	H	H	1-Piperi-dinyl	17[a]	207–09[k]	$C_{19}H_{22}N_2O$ (294.4)	3 220, 1 610	[n]1.20–1.80 (6H, m, $CH_2CH_2CH_2$), 2.08 (2H, q, C–$6H_2$), 2.45 (2H, t, C–$5H_2$), 2.80 (2H, t, C–$7H_2$), 2.85–3.20 (4H, m, CH_2NCH_2), 7.00–7.60 (m, 3ArH), 7.60–8.00 (m, 2ArH), 9.00 (br s, NH)

‡All compounds gave satisfactory C, H and N analyses.

*[a]Method-A ; [b]Method-B, **Solvent for crystallisation : [c]Acetone–EtOH, [d]EtOH, [e]$CHCl_3$–EtOH, [f]THF–EtOH, [g]aq. EtOH, [h]$CHCl_3$–hexane, [i]acetone, [j]EtOH–MeOH, [k]MeOH, [l]acetone–MeOH.

†In [m]DMSO-d_6, [n]$ODCl_3$, [p]CCl_4.

hydrazine is not easily understood. Lastly, the acyclic triketone, phenacyl acetylacetone (**7**) and *N*-aminopiperidine gave a poor yield of 1-piperidinopyrrole (**8**). 1-Unsubstituted-3-aminotetrahydroindoles of this study were characterised by the presence in the ir spectrum of a very broad NH band around 3 100 – 3 200 cm^{-1} and C=O band between 1 610 and 1 630 cm^{-1}, and a broad singlet signal due to NH in the ^1H nmr spectrum at around δ 11.2 ppm which disappeared with D_2O. 1-Amino compounds **2a** and **8** on the other hand were readily identified by the presence in their ^1H nmr spectra of a singlet due to the proton on the β-carbon atom at δ 6.30 and 5.83 ppm respectively.

Structures **3** were proved in two ways. Dibenzylamino derivative **3f** was hydrogenolysed to the 3-aminoindole (**3i**) which was deaminated to the known 2-phenyltetrahydroindole (**9a**)[2]. Secondly, aminoketone (**10**) was allowed to react with phenyl glyoxal and morpholine to afford **3d** although only in 6% yield.

In contrast to the phenacyldimedone (**1a**), 2-phenacylcyclohexanone (**11**) and *N*-aminopiperidine afforded only the 1-piperidino derivative (**12**) and not the 3-piperidinoindole (**13**)[3]. Taking this fact into account, we visualise the formation of **3a** from **1** (Chart 1) to occur through the enaminone (**14**) wherein the hydrazine *N,N*-bond is weakened to facilitate an intramolecular transfer of the disubstituted amino group as shown to form **15**. The latter can lead to the formation of **3a** via **16**, which

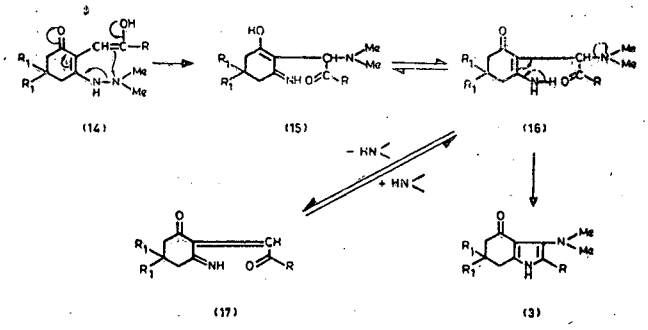


Chart 1

in turn will be in a reversible equilibrium with **17**. The formation of **3d** from **10**, phenyl glyoxal and morpholine must be occurring through **17** and the morpholine analogue of **16** as intermediates. Reaction of **17** with excess *N,N*-dimethylhydrazine, followed by oxidation would account for the formation of **6** as a byproduct in the reaction of **1a** with this hydrazine.

The mechanism proposed (Chart 1) would predict that the presence of an excess of a new amine during the reaction of **1a** with *N,N*-disubstituted-hydrazine to form **16** would lead to incroporation of the amine in **17** and hence into the final products **3**. We were pleased to find that the reaction of **1a** with 3 molar equivalents of *N,N*-dimethylhydrazine and 10 molar equivalents of morpholine indeed gave a mixture of **3a** and **3d** approximately in the ratio of 3 : 10 (^1H nmr). Pure **3d** was isolated from this mixture in 55% yield and identified. When excess morpholine was replaced by *N,N*-dibenzylamine or aniline, **3f** and **3j** were isolable although yields were unsatisfactory (12% and 6%). Excess n-propylamine led to double incorporation, both at positions 1 and 3 to give **4** in 30% yield along with a little **3a**. Its formation can be rationalised by assuming that **17** not only adds n-propylamine but also suffers an exchange of the imino group with the primary amine to give an analogue of **16** carrying two n-propyl groups.

Lastly, we studied the action of *N*-aminopiperidine with α-dimedonylpropiophenone (**18**). The reaction was sluggish and gave a complex mixture of products from which **9b** and **23** were obtained in 12% and 4% yield respectively. The structure of **9b** rested on analytical and spectral data. Identity was further established by comparison with a sample obtained by fusing **18** with ammonium carbonate. The structure of **23** was deduced from analytical as well as ir, nmr and mass spectral data. The ^1H nmr spectrum was particularly diagnostic, showing the indole α-H as a singlet at δ 7.60 ppm. Signals were lacking for both NH and β-protons. We propose the tentative mechanism shown in Chart 2.

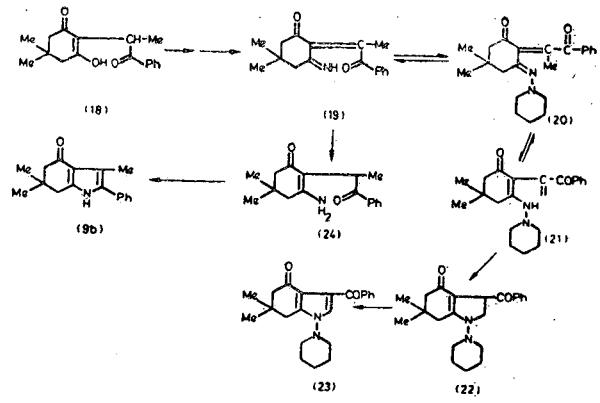


Chart 2

In the reaction of **18** with *N*-aminopiperidine, species **19** analogous to **17** is formed initially, but in the presence of excess of the reagent, **19** is transformed into **20**. The dienamine tautomer **21** of **20** can undergo intramolecular addition to form **22**. The observed final product **23** could arise by the oxidation of **22** by species **19** which in turn gets reduced to **24** leading to **9b** by cyclodehydration.

Physical and spectral data of compounds are given in Tables 1 and 2.

Experimental

*3-Amino-1,5,6,7-tetrahydro-4*H*-indol-4-ones* (**3**). *Method A :* A mixture of the ketone (**1a** ; 10 mmol) with *N,N*-disubstituted-hydrazine (30 mmol) produced an exothermic reaction. After it subsided,