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α,β-Epoxy Sulfoxides as Useful Intermediates in Organic Synthesis. III.[1] A Novel Synthesis of α-Amino Ketones and α-Amino Aldehydes by Aminolysis of α,β-Epoxy Sulfoxides

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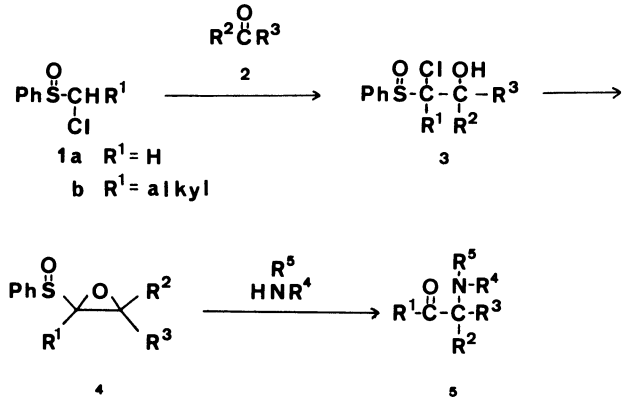
Aminolysis of α,β-epoxy sulfoxides, easily prepared from 1-chloroalkyl phenyl sulfoxides or chloromethyl phenyl sulfoxide and carbonyl compounds, with alkyl- or arylamines afforded α-amino ketones or α-amino aldehydes in good yields. Treatment of thus obtained α-arylamino ketones with weak Lewis acid led to 2,3-disubstituted indoles.

α-Amino ketones (**5**) are valuable synthetic intermediates for drugs[2,9] or useful as building blocks for nitrogen containing heterocyclic compounds.[3] In contrast to the impressive development of the methods for the synthesis of β-amino ketones, such as Mannich reaction[4] or Michael addition of amines to α,β-unsaturated carbonyl compounds,[5] only limited numbers of methods for the preparation of α-amino ketones (**5**) are reported. Five main methods have so far been reported but they have some drawbacks. The S_N2 type displacement of α-halo ketones with amines[3,6] is useful only when regioselectively halogenated carbonyl compounds are easily available and at the same time, this reaction usually gives relatively poor yields. Reduction of acyl cyanides[7] gives only α-acylmethylamines and the Neber rearrangement[8] gives only α-amino ketones having no substituent on the nitrogen atom. Aminolysis of enediol silyl ethers[2] was reported to give less than 45% yield of α-amino ketones. Aminolysis of α,β-epoxy ethers,[9] which are synthesized from α-halo ketones, seems to be a relatively good method but only synthesis of phenyl α-amino ketones was reported.

As a consequence of the usefulness of α-amino ketones, exploration of a new procedure for the synthesis of them from readily available precursors is still required. Recently we have reported a method for the synthesis of ketones, aldehydes, and α-sulfenylated carbonyl compounds from α,β-epoxy sulfoxides (**4**).[1,10] Here we report, in detail, a new and efficient method for a synthesis of α-amino ketones and α-amino aldehydes[11] from α,β-epoxy sulfoxides and an application of this method to a synthesis of 2,3-disubstituted indoles.



Scheme 1.

Results and Discussion

Synthesis of α-Alkylamino Ketones and α-Alkylamino Aldehydes. α,β-Epoxy sulfoxides (**4**)[12] are very easily prepared in good overall yields from chloromethyl phenyl sulfoxide (**1a**) or 1-chloroalkyl phenyl sulfoxides (**1b**) and carbonyl compounds (**2**) through chlorohydrins (**3**). Few synthetic methods have already been reported[13] by using α,β-epoxy sulfoxides. We have found that the β-carbon of α,β-epoxy sulfoxides (**4**) is highly reactive to various alkyl- and arylamines to afford α-amino ketones (**5**) in good to excellent yields.[11]

Seven types of α,β-epoxy sulfoxides (**4a—g**) are selected to clarify the reactivity of **4** with various amines. The epoxides **4a—c** and **4g** have two isomers, which are expressed as L and P,[14] respectively, but the stereochemistries have not yet been determined. The epoxide (**4g**) used in this study is a mixture of L and P.

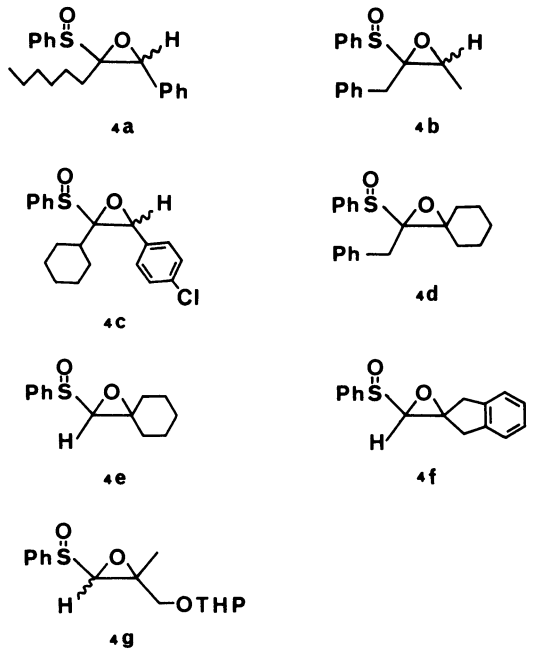


Table 1. α-Amino Ketones and Aldehydes from α,β-Epoxy Sulfoxides with Aliphatic Amines

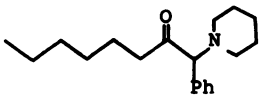
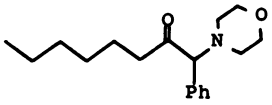
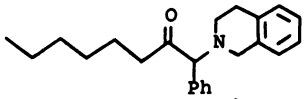
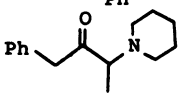
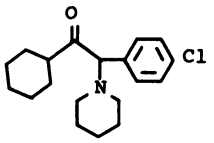
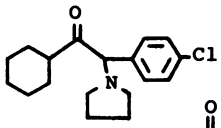
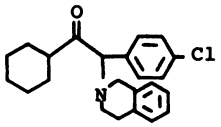
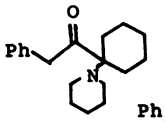
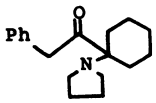
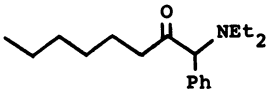
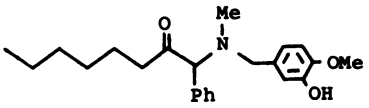
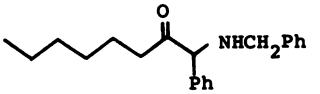
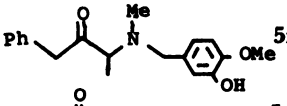
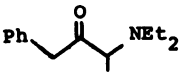
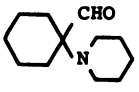
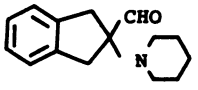
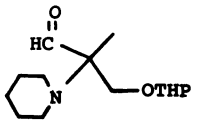
Run	Epoxy Sulfoxide	Amine[a]	Solvent	Temp	Time	α-Amino Ketone	Yield[b] %
1	**4a** L	A	—	r.t.	3 h	 **5a**	97
	P	A	—	r.t.	21 h		100
2	**4a** L	B	—	r.t.	4 h	 **5b**	100
	P	B	—	r.t.	23 h		99
	P	B	—	80°C	90 min		90
	P	B	DMSO	80°C	100 min		100
	P	B	HMPA	80°C	150 min		94
3	**4a** L	C	HMPA	r.t.	27 h	 **5c**	89
	P	C	HMPA	110°C	40 min		100
4	**4b** L	A	—	r.t.	20 min	 **5d**	92
	P	A	—	r.t.	2.5 h		100
5	**4c** L	A	—	100°C	2 h	 **5e**	97
	P	A	—	100°C	12 h		85
6	**4c** L	D	—	80°C	1 h	 **5f**	100
	P	D	—	80°C	6 h		85
7	**4c** L	C[c]	DMSO	100°C	7 h	 **5g**	94
	P	C[c]	DMSO	100°C	20 h		80
8	**4d**	A	—	100°C	6 h	 **5h**	76
9	**4d**	D	—	80°C	4 h	 **5i**	100
10	**4a** L	E	—	r.t.	8 d	 **5j**	96
	P	E[d]	DMSO	50°C	31 h		44
11	**4a** L	F[e]	DMSO	60°C	3 h	 **5k**	53
	P	F[e]	DMSO	60°C	5 h		52
12	**4a** L	G[d]	DMSO	55°C	1 h	 **5l**	72
	P	G[d]	DMSO	55°C	1 h		73
13	**4b** P	F[f]	DMSO	r.t.	8 h	 **5m**	80
14	**4b** P	E	—	r.t.	3 d	 **5n**	96
15	**4e**	A	—	90°C	2 h	 **5o**	78
16	**4f**	A	—	90°C	1 h	 **5p**	83

Table 1. (Continued)

Run	Epoxy Sulfoxide	Amine[a]	Solvent	Temp	Time	α-Amino Ketone	Yield[b] %
17	**4g**	A	—	r.t.	1 d		**5q** 71

a) A: piperidine, B: morpholine, C: 1,2,3,4-tetrahydroisoquinoline, D: pyrrolidine, E: diethylamine, F: *N*-methyl-3-hydroxy-4-methoxybenzylamine, G: benzylamine. b) Isolated yields after silica gel column chromatography. c) Forty equivalents of amine was used and the concentration of the epoxy sulfoxide was 0.07 M. d) Forty-five equivalents of amine was used. e) Three equivalents of amine was used. f) Five equivalents of amine was used.

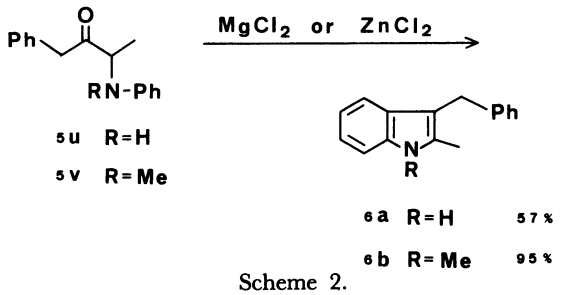
The reaction was simply conducted in an amine without solvent or in dimethyl sulfoxide (DMSO) or hexamethylphosphoric triamide (HMPA) as a solvent (0.5M† concentration of epoxy sulfoxide and 10 equivalents of amines are used unless otherwise noted) under nitrogen atmosphere.

The results of the reaction of α,β-epoxy sulfoxides (**4**) with aliphatic amines are summarized in Table 1. As shown in Table 1, aliphatic amines especially cyclic amines are very reactive to α,β-epoxy sulfoxides (**4**) giving α-amino ketones under the mild conditions in good to excellent yields. Isomers L and P showed some differences in the reactivity toward the amines but these differences are not essential problem for the practical use of this method. The epoxide having a cyclohexane ring in R^1 (**4c**) reacted slowly with amines than those having normal alkyl groups in R^1 (**4a** and **b**) due to a steric hindrance on the β-carbon of the epoxide by cyclohexyl group (see runs 1—7). The dipolar aprotic solvents known to be effective for nucleophilic bimolecular reactions[15] were used but we did not observe any solvent effect. The other conditions reported to be effective for opening of epoxides, such as the reaction with aminosilanes[16] or the reaction at alumina surface[17] were not effective in this reaction.

The results of the reaction of α,β-epoxy sulfoxides with acyclic alkylamines are summarized in runs 10 to 14. As acyclic amines are known to be less nucleophilic than cyclic amines, these reactions required much longer reaction time than those in cyclic amines and the yields were moderate to good (compare runs 1—4 with runs 10—14). The amine having a phenolic hydroxyl group, *N*-methyl-3-hydroxy-4-methoxybenzylamine, also reacted with **4a** and **b** to afford **5k** and **5m**, respectively, in moderate to good yields (runs 11 and 13). Monoalkylamines usually gave a complex mixture but only benzylamine afforded an α-benzylamino ketone (**5l**) in about 70% yield (run 12). Runs 15 to 17 show the results of the reaction of α-unsubstituted α,β-epoxy sulfoxides (**4e—g**) with piperidine to afford α-piperidino aldehydes (**5o—q**). Such complex amino aldehydes are usually very difficult to obtain but the present procedure gave α-piperidino aldehyde under the mild conditions without any problem in 70—80% yields.

Synthesis of α-Arylamino Ketones, Aldehydes and an Application of the Procedure to a Synthesis of 2,3-Disubstituted Indoles. Table 2 shows the results of the reaction of **4a**, **b**, **e**, **f** with arylamines. Since usually arylamines have a lower nucleophilic property than that of alkylamines, the reaction of arylamines with **4** required a higher temperature but the yields are still very good. α-Anilino aldehydes (**5x**) and (**5y**) were also obtained in excellent yields. In these cases it is noteworthy that aniline was very reactive to **4e** and **4f** (see Table 1, runs 15 and 16)

The present procedure has proved of value by transforming the products to heterocyclic compounds according to Scheme 2. α-Arylamino ketones have already been transformed to tetrahydrocarbazoles[3b] or substituted indoles[3c,18] but in these cases, α-arylamino ketones were derived from α-chloro ketones in about 50% yield. In our study, *N*-(1-methyl-2-oxo-3-phenylpropyl)aniline (**5u**) was heated with magnesium

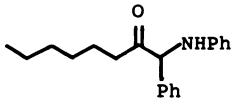
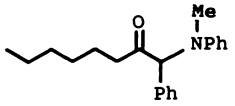
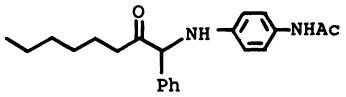
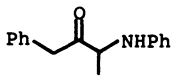
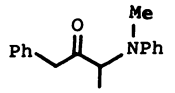
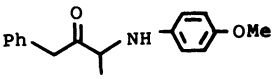
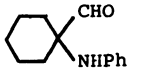
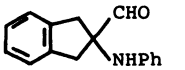


Scheme 2.

chloride in Ethylcellosolve at 130°C for 1.5 h to afford 3-benzyl-2-methylindole (**6a**; mp 89—90°C)[19] in 57% yield. Similarly, **5v** was heated with zinc chloride (in this case magnesium chloride was not effective) in Ethylcellosolve at 120°C for 3 h to give 3-benzyl-1,2-dimethylindole (**6b**; mp 54—55°C)[20] in 95% yield. Since, the α,β-epoxy sulfoxide (**4b**) was synthesized from benzyl bromide, chloromethyl phenyl sulfoxide, and acetaldehyde in three steps in over 90% yield[10a] the indole (**6b**) was synthesized from these three components and *N*-methylaniline in five steps overall

† 1 M = 1 mol dm^{-3}.

Table 2. α-Arylamino Ketones and Aldehydes from α,β-Epoxy Sulfoxides with Arylamines[a)]

Run	Epoxy sulfoxide	Amine[a)] (equiv)	Temp	Time	α-Arylamino Ketone or Aldehyde	Yield[b)] %
1	**4a** L	H (50)	100°C	1 h	 **5r**	97
	P	H (50)	100°C	2 h		81
2	**4a** L	I (90)	100°C	2 h	 **5s**	73
	P	I (90)	100°C	2 h		56
3	**4a** L	J (5)	100°C	3 h	 **5t**	63
	P	J (5)	100°C	5 h		47
4	**4b** L	H (5)	100°C	20 min	 **5u**	99
	P	H (5)	100°C	30 min		96
5	**4b** L	I (5)	100°C	1 h	 **5v**	95
	P	I (5)	100°C	2.5 h		88
6	**4b** L	K (5)	100°C	15 min	 **5w**	81
	P	K (5)	100°C	30 min		70
7	**4e**	H (50)	r.t.	2 d	 **5x**	84
8	**4f**	H (50)	r.t.	3 h	 **5y**	100

a) H: aniline, I: *N*-methylaniline, J: *p*-aminoacetanilide, K: *p*-anisidine. All reactions were conducted in HMPA under nitrogen atmosphere. b) Isolated yields after silica-gel chromatography.

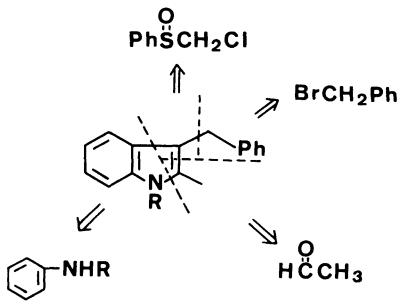


Fig. 1.

in about 80% yield (see Fig 1).

In conclusion a novel and versatile procedure for a synthesis of α-amino ketones and α-amino aldehydes has been developed from α,β-epoxy sulfoxides. In regard to the accessibility of the starting materials, the simplicity and mildness of the operation, and high yields of the products, the present method offers a simple and useful approach to α-amino ketones and α-amino aldehydes and at the same time this process contributes to the nitrogen containing heterocyclic chemistry.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured directly on a NaCl plate or in KBr disks with a Hitachi 215 spectrometer. ^{1}H Nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ solution with a JEOL FX-100 spectrometer using Me_4Si as an internal standard. Electron impact mass spectra (MS) were obtained on a Hitachi M-80 double focusing spectrometer at 70 eV by direct insertion. Silica gel BW-127ZH (Fuji-Devison) containing 2% fluorescence reagent 254 and quartz column were used for column chromatography and the products having ultraviolet (UV) absorption were detected by UV irradiation.

Materials. All α,β-epoxy sulfoxides (**4**) used in this study were reported in references 1 and 10. DMSO, HMPA, and all amines except *N*-methyl-3-hydroxy-4-methoxybenzylamine were dried over CaH_2 and distilled before use.

General Procedure for the Preparation of α-Amino Ketones and α-Amino Aldehydes by Aminolysis of α,β-Epoxy Sulfoxides with Amines. Method A: The α,β-epoxy sulfoxide (**4**) (0.1 mmol) was dissolved in 2 ml of an amine in dry flask under N_2 atmosphere. This reaction mixture was stirred at the appropriate temperature till the starting

material disappeared. The amine was distilled off under reduced pressure at room temperature and the residue was purified by silica-gel column chromatography with a mixture of hexane and ethyl acetate as an eluent.

Method B: The α,β-epoxy sulfoxide (**4**) (0.1 mmol) was dissolved in 0.2 ml of DMSO or HMPA in dry flask under N_2 atmosphere. To the solution was added an amine (1 mmol) and the reaction mixture was stirred at the appropriate temperature till the starting material disappeared. The reaction mixture was diluted with 50 ml of ethyl acetate and the solution was washed twice with water followed by sat. aq NaCl. The solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography with a mixture of hexane and ethyl acetate as an eluent. In the cases of arylamines, usually the R_f values of the amines are very close to the products. The products were purified by silica-gel column chromatography followed by preparative thin-layer chromatography (Merck Kieselgel 60 F_{254}; 0.25 mm).

1-Phenyl-1-piperidino-2-octanone (5a). Colorless oil; IR (neat): 1710 (CO) cm^{-1}; ^1H NMR δ=0.82 (3H, t, J=6 Hz), 1.0—1.8 (14H, m), 2.1—2.6 (6H, m), 4.87 (1H, s), 7.1—7.5 (5H, m); MS m/z (%): 287 (M^+, trace), 286 ([M−H]$^+$, trace), 174 ([M−$C_7H_{13}O$]$^+$, 100); Found: m/z 286.2160. Calcd for $C_{19}H_{28}NO$: ([M−l]$^+$) 286.2169.

1-Phenyl-1-morphorino-2-octanone (5b). Colorless oil; IR (neat): 1720 (CO) cm^{-1}; ^1H NMR δ=0.82 (3H, t, J=6 Hz), 1.0—1.6 (8H, m), 2.3—2.5 (4H, m), 3.6—3.8 (4H, m), 3.93 (1H, s), 7.2—7.4 (5H, m); MS m/z (%): 289 (M^+, trace), 288 ([M−H]$^+$, 0.1), 176 ([M−$C_7H_{13}O$]$^+$, 100); Found: m/z 288.1947. Calcd for $C_{18}H_{26}NO_2$: ([M−l]$^+$) 288.1961.

***N*-(2-Oxo-1-phenyloctyl)-1,2,3,4-tetrahydroisoquinoline (5c).** Colorless oil; IR (neat): 1710 (CO) cm^{-1}; ^1H NMR δ=0.82 (3H, t, J=6 Hz), 1.0—1.6 (8H, m), 2.4—3.0 (6H, m), 3.59 (2H, s), 4.10 (1H, s), 6.78—7.12 (4H, m), 7.2—7.5 (5H, m); MS m/z (%): 335 (M^+, trace), 334 ([M−H]$^+$, trace), 305 (trace), 222 ([M−$C_7H_{13}O$]$^+$, 100).

1-Phenyl-3-piperidino-2-butanone (5d). Colorless oil; IR (neat): 1720 (CO) cm^{-1}; ^1H NMR δ=1.11 (3H, d, J=7 Hz), 1.3—1.8 (6H, m), 2.3—2.6 (4H, m), 3.29 (1H, q, J=7 Hz), 3.82, 3.94 (each 1H, d, J=15 Hz), 7.24 (5H, bs); MS m/z (%): 230 ([M−H]$^+$, trace), 218 (6), 112 ([M−C_8H_7O]$^+$, 100); Found: m/z 230.1541. Calcd for $C_{15}H_{20}NO$: ([M−l]$^+$) 230.1543.

2-(4-Chlorophenyl)-1-cyclohexyl-2-piperidinoethanone (5e). Colorless oil; IR (neat): 1720 (CO) cm^{-1}; ^1H NMR δ=1.0—1.8 (16H, m), 2.2—2.6 (5H, m), 4.04 (1H, s), 7.27 (4H, s); MS m/z (%): 319 (M^+, trace), 318 (trace), 208 ([M−$C_7H_{11}O$]$^+$, 100).

2-(4-Chlorophenyl)-1-cyclohexyl-2-(1-pyrrolidinyl)ethanone (5f). Colorless crystals; mp 136—137 °C (AcOEt-hexane); IR (KBr): 1720 (CO) cm^{-1}; ^1H NMR δ=0.7—1.9 (14H, m), 1.1—1.7 (5H, m), 4.05 (1H, s), 7.31 (4H, s); MS m/z (%): 304 ([M−H]$^+$, trace), 194 ([M−$C_7H_{11}O$]$^+$, 100).

***N*-(1-(4-Chlorophenyl)-2-cyclohexyl-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline (5g).** Colorless crystals; mp 113—114 °C (AcOEt-hexane); IR (KBr): 1720 (CO) cm^{-1}; ^1H NMR δ=0.8—1.9 (10H, m), 1.4—2.0 (5H, m), 3.61 (2H, bs), 4.31 (1H, s), 6.8—7.2 (4H, m), 7.41 (4H, s); MS m/z (%): 367 (M^+, trace), 366 ([M−H]$^+$, trace), 256 ([M−$C_7H_{11}O$]$^+$, 100); Found: C, 74.89; H, 7.09; N, 3.84%. Calcd for $C_{23}H_{26}ClNO$: C, 75.08; H, 7.12; N, 3.81%.

1-Phenyl-2-(1-piperidinocyclohexyl)ethanone (5h). Colorless crystals; mp 79—82 °C (AcOEt-hexane); IR (KBr): 1715 (CO) cm^{-1}; ^1H NMR δ=0.8—2.1 (16H, m), 2.4—2.6 (4H, m), 3.90 (2H, s), 7.1—7.5 (5H, m); MS m/z (%): 284 ([M−H]$^+$, trace), 166 ([M−C_8H_7O]$^+$, 100).

1-Phenyl-2-[1-(1-pyrrolidinyl)cyclohexyl]ethanone (5i). Colorless oil; IR (neat): 1710 (CO) cm^{-1}; ^1H NMR δ=1.1—2.2 (14H, m), 2.5—2.8 (4H, m), 3.87 (2H, s), 7.1—7.4 (5H, m); MS m/z (%): 270 ([M−H]$^+$, trace), 152 ([M−C_8H_7O]$^+$, 100).

***N,N*-Diethyl-2-oxo-1-phenyloctylamine (5j).** Colorless oil; IR (neat): 1710 (CO) cm^{-1}; ^1H NMR δ=0.83 (3H, t, J=6 Hz), 0.98 (6H, t, J=7 Hz), 2.3—2.8 (6H, m), 4.36 (1H, s), 7.2—7.4 (5H, m); MS m/z (%): 275 (M^+, trace), 162 ([M−$C_7H_{13}O$]$^+$, 100); Found: m/z 275.2240. Calcd for $C_{18}H_{29}NO$: M, 275.2247.

***N*-Methyl-*N*-(2-oxo-1-phenyloctyl)-3-hydroxy-4-methoxybenzylamine (5k).** Colorless oil; IR (neat): 3420 (OH), 1710 (CO) cm^{-1}; ^1H NMR δ=0.83 (3H, t, J=6 Hz), 1.0—1.6 (8H, m), 2.15 (3H, s), 2.4—2.6 (2H, m), 3.34, 3.54 (each 1H, d, J=13 Hz), 3.93 (3H, s), 4.18 (1H, s), 6.80—6.96 (3H, m), 7.2—7.5 (5H, m); MS m/z (%): 256 ([M−$C_7H_{13}O$]$^+$, 2.5), 137 ([M−$C_{15}H_{22}NO$]$^+$, 6), 120 (100).

***N*-Benzyl-2-oxo-1-phenyloctylamine (5l).** Colorless oil; IR (neat): 3350 (NH), 1710 (CO) cm^{-1}; ^1H NMR δ=0.82 (3H, t, J=6 Hz), 1.0—1.6 (8H, m), 2.30 (2H, t, J=7 Hz), 3.61, 3.73 (each 1H, d, J=13 Hz), 4.39 (1H, s), 7.32, 7.36 (each 5H, s); MS m/z (%): 308 ([M−H]$^+$, trace), 202 ([M−C_7H_9N]$^+$, 2), 196 ([M−$C_7H_{13}O$]$^+$, 100).

***N*-Methyl-*N*-(1-methyl-2-oxo-3-phenylpropyl)-3-hydroxy-4-methoxybenzylamine (5m).** Colorless oil; IR (neat): 3340 (OH), 1720 (CO) cm^{-1}; ^1H NMR δ=1.09 (3H, d, J=7 Hz), 2.15 (3H, s), 3.42 (1H, q, J=7 Hz), 3.48, 3.52 (each 1H, d, J=13 Hz), 3.89 (3H, s), 3.90, 3.94 (each 1H, d, J=13 Hz), 6.79 (2H, d, J=1 Hz), 6.96 (1H, bt, J=1 Hz), 7.0—7.3 (5H, m); MS m/z (%): 312 ([M−H]$^+$, trace), 311 ([M−H_2]$^+$, trace), 194 ([M−C_8H_7O]$^+$, 42), 137 ([M−$C_{11}H_{14}NO$]$^+$, 100).

3-Diethylamino-1-phenyl-2-butanone (5n). Colorless oil; IR (neat): 1725 (CO) cm^{-1}; ^1H NMR δ=1.04 (6H, t, J=7 Hz), 1.05 (3H, d, J=7 Hz), 2.48 (4H, m), 3.49 (1H, q, J=7 Hz), 3.86, 3.99 (each 1H, d, J=15 Hz), 7.1—7.4 (5H, m); MS m/z (%): 219 (M^+, 3), 218 ([M−H]$^+$, 26), 100 ([M−C_8H_7O]$^+$, 100).

***N*-(1-Formylcyclohexyl)piperidine (5o).** Colorless oil; IR (neat): 1725 (CO) cm^{-1}; ^1H NMR δ=1.0—2.1 (14H, m), 2.4—2.7 (4H, m), 9.33 (1H, s); MS m/z (%): 166 ([M−CHO]$^+$, 100).

2-Piperidino-2-indancarbaldehyde (5p). Colorless crystals; mp 87—89 °C (AcOEt-hexane); IR (KBr): 1710 (CO) cm^{-1}; ^1H NMR δ=1.3—1.8 (6H, m), 2.4—2.6 (4H, m), 3.14, 3.28 (each 2H, d, J=16 Hz), 7.18 (4H, s), 9.75 (1H, s); MS m/z (%): 229 (M^+, trace), 200 ([M−CHO]$^+$, 100), 115 ([M−$C_6H_{12}NO$]$^+$, 19); Found: C, 78.34; H, 8.34; N, 6.03%. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11%.

2-Methyl-2-(*N*-piperidino)-3-tetrahydropyranyloxypropanal (5q). Colorless oil; IR (neat): 1740 (CO) cm^{-1}; ^1H NMR δ=1.14 (3H, s), 1.3—1.9 (12H, m), 2.4—2.6 (4H, m), 3.4—4.1 (4H, m), 4.60 (1H, m, $W_{1/2}$=6 Hz), 9.49 (1H, s); MS m/z (%): 254 ([M−H]$^+$, trace), 226 ([M−CHO]$^+$, 100).

***N*-(2-Oxo-1-phenyloctyl)aniline (5r).** Colorless crystals; mp 84—85 °C (AcOEt-hexane); IR (KBr): 3410 (NH), 1715 (CO) cm^{-1}; ^1H NMR δ=0.83 (3H, t, J=6 Hz), 1.0—1.7 (8H, m), 2.44 (2H, t, J=7 Hz), 5.00 (1H, s), 6.48—6.76 (3H, m), 6.98—7.22 (2H, m), 7.26—7.56 (5H, m); MS m/z (%): 295 (M^+, trace), 182 ([M−$C_7H_{13}O$]$^+$, 100); Found: m/z 295.1930. Calcd for $C_{20}H_{25}NO$: M, 295.1934.

***N*-Methyl-*N*-(2-oxo-1-phenyloctyl)aniline (5s).**

Colorless oil; IR (neat): 1720 (CO) cm^{-1}; ^1H NMR δ=0.84 (3H, t, J=6 Hz), 1.0—1.8 (8H, m), 2.49 (2H, t, J=7 Hz), 2.82 (3H, s), 5.49 (1H, s), 6.64—6.85 (3H, m), 7.0—7.4 (7H, m); MS m/z (%): 309 (M^+, trace), 105 ([M−$C_{14}H_{20}O$]$^+$, 100).

***N*-Acetyl-*N'*-(2-oxo-1-phenyloctyl)-*p*-phenylenediamine (5t).** Colorless crystals; mp 108—109 °C (AcOEt–hexane); IR (KBr): 3400, 3330 (NH), 1710 (CO) cm^{-1}; ^1H NMR δ=0.82 (3H, t, J=6 Hz), 1.0—1.7 (8H, m), 2.06 (3H, s), 2.43 (2H, t, J=7 Hz), 4.97 (1H, d, J=4 Hz, +D_2O gave singlet signal), 6.4—6.6 (2H, m), 6.8—7.5 (7H, m); MS m/z (%): 352 (M^+, 2), 239 ([M−$C_7H_{13}O$]$^+$, 100); Found: m/z 352.2134. Calcd for $C_{22}H_{28}N_2O$: M, 352.2148.

***N*-(1-Methyl-2-oxo-3-phenylpropyl)aniline (5u).** Colorless prisms; mp 71—72 °C (AcOEt–hexane); IR (KBr): 3420 (NH), 1715 (CO) cm^{-1}; ^1H NMR δ=1.41 (3H, d, J=7 Hz), 3.84 (2H, s), 4.19 (1H, q, J=7 Hz), 6.24—7.45 (10H, m); MS m/z (%): 239 (M^+, 4), 120 ([M−C_8H_7O]$^+$, 100); Found: C, 79.94; H, 7.18; N, 5.70%. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%.

***N*-Methyl-*N*-(1-methyl-2-oxo-3-phenylpropyl)aniline (5v).** Colorless oil; IR (neat): 1730 (CO) cm^{-1}; ^1H NMR δ=1.25 (3H, d, J=7 Hz), 2.74 (3H, s), 3.79 (2H, s), 4.46 (1H, q, J=7 Hz), 6.68—6.92 (3H, m), 7.04—7.40 (7H, m); MS m/z (%): 253 (M^+, 3), 134 ([M−C_8H_7O]$^+$, 100); Found: m/z 253.1440. Calcd for $C_{17}H_{19}NO$: M, 253.1465.

***N*-(1-Methyl-2-oxo-3-phenylpropyl)-*p*-anisidine (5w).** Colorless needles; mp 82—84 °C (AcOEt–hexane); IR (KBr): 3420 (NH), 1710 (CO) cm^{-1}; ^1H NMR δ=1.38 (3H, d, J=7 Hz), 3.75 (3H, s), 3.83 (2H, s), 4.12 (1H, q, J=7 Hz), 6.40—6.85 (4H, m), 7.08—7.40 (5H, m); MS m/z (%): 269 (M^+, 7), 150 ([M−C_8H_7O]$^+$, 100); Found: C, 75.46; H, 7.14; N, 5.06%; M^+, 269.1395. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%; M, 269.1413.

***N*-(1-Formylcyclohexyl)aniline (5x).** Colorless oil; IR (neat): 3390 (NH), 1735 (CO) cm^{-1}; ^1H NMR δ=1.1—2.0 (10H, m), 6.5—7.4 (5H, m), 9.67 (1H, s); MS m/z (%): 203 (M^+, 5), 174 ([M−CHO]$^+$, 100).

2-Anilino-2-indancarbaldehyde (5y). Colorless oil; IR (neat): 3410 (NH), 1725 (CO) cm^{-1}; ^1H NMR δ=3.38, 3.54 (each 2H, d, J=16 Hz), 6.4—7.2 (5H, m), 7.24 (4H, s), 9.76 (1H, s); MS m/z (%): 237 (M^+, 7), 208 ([M−CHO]$^+$, 100).

3-Benzyl-2-methylindole (6a). To a 20 ml dry flask was added 38 mg (0.4 mmol) of dry $MgCl_2$ and 0.5 ml of Ethylcellosolve followed by 18 μl (0.2 mmol) of aniline. The atmosphere of the flask was evacuated and replaced with nitrogen. The suspension was stirred and heated at reflux for 15 min to give colorless clear solution. To this solution was added a solution of *N*-(1-methyl-2-oxo-3-phenylpropyl)aniline (**5u**) (36 mg; 0.15 mmol) in 0.2 ml of Ethylcellosolve and the reaction mixture was stirred and heated at 130 °C for 1.5 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and the solvent was evaporated and the residue was chromatographed on a silica-gel column (hexane : AcOEt = 20:1) to afford 19 mg (57%) of **6a** as yellow crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 89—90 °C. IR (KBr): 3500 (NH) cm^{-1}; ^1H NMR δ=2.32 (3H, s), 4.09 (2H, s), 7.02—7.64 (10H, m); MS m/z (%): 221 (M^+, 100), 206 ([M−CH_3]$^+$, 27), 144 ([M−C_6H_5]$^+$, 43); Found: m/z 221.1194. Calcd for $C_{16}H_{15}N$: M, 221.1203.

3-Benzyl-1,2-dimethylindole (6b). To a 20 ml dry flask was added 230 mg (1.68 mmol) of dry $ZnCl_2$ and 1 ml of Ethylcellosolve and the atmosphere of the flask was replaced with nitrogen as described above. The suspension was stirred and heated at 100 °C for 10 min to give colorless clear solution. To this was added a solution of *N*-methyl-*N*-(1-methyl-2-oxo-3-phenylpropyl)aniline (**5v**) (62 mg; 0.24 mmol) in 0.5 ml of Ethylcellosolve and the reaction mixture was stirred and heated at 120 °C for 3 h. The work-up as described above gave a crude product, which was purified by silica-gel column chromatography (hexane:AcOEt=40:1) gave 55 mg (95%) of **6b** as light yellow crystals. Recrystallization from ethanol gave colorless prisms, mp 54—55 °C (lit,[20] 56.6—57 °C). IR (KBr): 740, 705 (aromatic) cm^{-1}; ^1H NMR δ=2.35 (3H, s), 3.65 (3H, s), 4.11 (2H, s), 6.92—7.50 (9H, m), MS m/z (%): 235 (M^+, 100), 220 ([M−CH_3]$^+$, 39), 158 ([M−C_6H_5]$^+$, 94); Found: m/z 235.1346. Calcd for $C_{17}H_{17}N$: M, 235.1360.

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