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BENZOLACTAMS—I

ALKYLATION OF 1,2,4,5-TETRAHYDRO-3-METHYL-3H-3-BENZAZEPIN-2-ONE WITH SODIUM HYDRIDE AND ALKYL HALIDE

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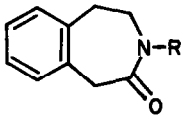
Abstract—Alkylation of 1,2,4,5-tetrahydro-3-methyl-3H-3-benzazepin-2-one **1a** with various halides and sodium hydride in tetrahydrofuran-dimethylformamide solvent system was studied. Primary halides predominantly provided the 1-mono-substituted products, such as alkyl (**2a–g, p, q**), allyl (**2j, k**), propargyl (**2l**) and benzyl (**2m–o**) derivatives, in satisfactory yields, and secondary halides resulted in lower yields (**2h, i**) than primary halides. In attempted dialkylations with ω, ω'-dibromoalkanes, 5- and 6-membered spiro products (**4c, d**) were obtained by this method. The Michael type addition reaction was also studied and it was found that acrylic acid esters gave the corresponding adducts (**2p, q**).

As a result of current interest in pharmacological activities† and also as skeletal feature of the rhoeadine, isopavine and cepharotaxine type alkaloids,[1] 3-benzazepines have received considerable attention. A number of routes to the synthesis of this azepine ring system has been studied, as documented well in a recent review.[2] Exploitation of efficient preparation of substituted 3-benzazepinones, as possible 3-benzazepine equivalents, would also be an alternative approach to the above interest. The C-functionalization reaction of amide group by a suitable trapping of carbanion generated on its α-carbon has been employed usually in use of a strong hydrogen-abstractor such as butyllithium, potassium or sodium amide, or dialkyl amide lithium.[3] On the contrary, despite its experimental ease, examples in use of sodium hydride as a base have been less often reported, especially with lack of the systematic studies for cyclic carboxamides, the so-called lactams, besides Zimmer's,[4] Wolfe's[5] or Hauck's[6] excellent works on cyclic imides. In this context, we intended to develop possible methods for use of sodium hydride in the chemistry of benzolactams, and wish to report a new procedure for the practical and convenient functionalization of 3-benzazepinones.

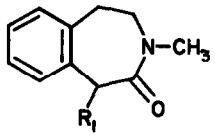
†Substituted 3-benzazepines have been found to have analgesic, anorexigenic, depressant, hypotensive, hypoglycemic, antidiabetic, antibacterial, antidepressant, antihypertensive, ganglion blocking activities and so on.[7]

RESULTS AND DISCUSSION

The new 3-benzazepinone **1a** was taken up as a simplest model possibly employed in the present research, and was easily prepared by the intramolecular Friedel–Crafts cyclization of N-chloroacetyl-N-methylphenethylamine in 70% yield, according to Nair and Malik's procedure.[8] With respect to the solvent, a mix-



1a: R = CH_3
1b: R = H



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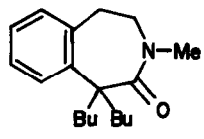

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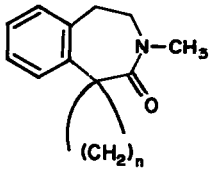
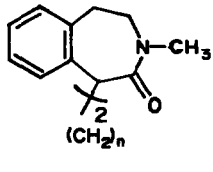


4a: n = 2
4b: n = 3
4c: n = 4
4d: n = 5



5a: n = 2
5b: n = 3
5c: n = 4
5d: n = 5

ture of dry THF and DMF (10:1 volume %)† was selected in the hope that the addition of DMF to THF could increase the ability of the metalation by NaH or the stability of carbanion formed, and a large ratio of THF to DMF could decrease the tar formation due to the side reaction of halides as well as the compounds. Solvent effect on alkylation of **1a** was examined followed by high pressure liquid chromatography (lc) and ^{1}H NMR analyses (Experimental). At the temperature of gently boiling THF which was set up by 80° oil bath, alkylation with n-butyl bromide in both mixed solvents of THF–DMF (10:1) and THF–DMSO (10:1) was examined. **1a** underwent smooth alkylation to lead to the monobutyl derivative **2d** (Table 1). Replacement of these mixed solvent system by the commonly used solvents, THF, dioxane, dimethoxyethane, benzene and toluene caused slower alkylation reaction by a factor of 2–70 times, respectively, as shown in Table 1. Results with THF–DMF (5:1) and THF–DMSO (5:1) were also in good agreement with the above assumption that polar solvent could be effective for the ready formation of carbanion. Table 2 exhibits that toluene or dioxane has good ability when it is boiling, and, further, it is noteworthy that vigorous boiling of these solvents (toluene at 140° bath and dioxane at 130°) provided the great enhancement of the reactivity, as shown in their relative rates. However, the increased amount of DMF or DMSO, and higher reaction temperature tends to leave a significant amount of polar material, which was observed on a silica gel tlc. In Table 3, the results of attempted dialkylation using the mono-n-butylbenzazepinone **2d** and 1.0 equiv. each of NaH and n-butyl bromide for 1.5 hr are summarized. Again, THF–DMF and THF–DMSO were found to be better solvent system for monoalkylation, showing little tendency toward the second alkylation into the mol ratio 0.09 of the produced di-n-butyl derivative **3** to the unchanged **2d** (0.02 for boiling toluene and 0.59 for boiling dioxane). It was clearly presented that dioxane was better solvent for dialkylation, at least on benzolactam **1a**. However, it was too early at this moment to expect that this fact would be also true for spiro ring formation on **1a** by interaction with ω,ω-dihaloalkanes, as described later.

Going back to the THF–DMF system, alkylation with a variety of halides was studied. Each reaction was performed with a little excess (1.1 equiv) of appropriate halides and NaH (2 equiv) in dry and gently boiling THF–DMF until all or most of **1a** was consumed. The methylation reaction was performed with much excess of the reagents, for instance, three folds of methyl iodide and two folds of NaH to **1a** at 50°. The resultant monomethylated benzazepinone **2a** was thus obtained from both **1a** and **1b**, respectively, in good yields (Table 4). However, this method was not acceptable for the production of **1a** from **1b**, since the methylation experiment of **1b** in use of one equiv of NaH revealed the formation of the compound due to C-methylation competitive to N-methylation (about 5:11, Experimental), as well as the presence of the unchanged starting material (**1b**), on the product distribution analysis by ^{1}H NMR. This result is very similar to Wolfe's observation‡ on the benzoylation of phenylacetamide.

Primary halides gave the corresponding alkyl, allyl, propargyl and benzyl derivatives **2** in satisfactory yields, even in case of bulky iso-butyl bromide in Table 4. In the preparation of **2d**, **h**, **i**, **j** or **m**, decreasing relative reactivities were observed in each practical reaction time by the expected order of iodide, bromide and chloride. The

Table 1. Interaction of **1a** with NaH and n-butyl bromide on 80° oil bath

Solvent	Weight of residue (mg)	Ratio of 2d to 2d + 1a (%)[c]
THF	103	24
THF-DMF (10:1)[b]	117	69
THF-DMSO (10:1)[b]	108	50
THF-DMF (5:1)[b]	113	91
THF-DMSO (5:1)[b]	114	95
DME	90	25
Dioxane	91	24
Benzene	83	5
Toluene	83	1

[a] All runs were performed by heating a mixture of 1a (88 mg, 0.5 mmol), NaH (24 mg, 1 mmol) and n-butyl bromide (76 mg, 0.55 mmol) in appropriate solvent (1 ml) in 80 °C oil bath for 1.5 hr.
[b] Volume %.
[c] Obtained on LC analyses.

Table 2. Reaction of **1a** with NaH and n-butyl bromide at the elevated temperature[a]

Solvent	Bath temp (°C)	Weight of residue[b] (mg)	Ratio of 2d to 2d + 1a (%)[c]
THF	80	103	24
DMF	100	98	31
Dioxane	120	109	70
Dioxane	130	116	98
Benzene	100	98	21
Toluene	130	110	73
Toluene	140	123	91

[a] Each reaction was performed in the same manner as that in Table 1 except reaction temp indicated.
[b] Weight of reaction residue obtained after work-up.
[c] Obtained on LC analyses.

Table 3. Reaction of **2d** with NaH and n-butyl bromide[a]

Solvent	Bath temp (°C)	Weight of residue (mg)	Ratio of 3 to 3 + 2d (%)[b]
THF-DMF (10:1)	80	124	8
THF-DMSO (10:1)	80	115	9
Toluene	130	128	17
Dioxane	120	128	37

[a] Reactions were effected in use of 2d (116 mg, 0.5 mmol), n-butyl bromide (137 mg, 1 mmol), NaH (24 mg, 1 mmol) and 1 ml of the appropriate solvent for 1.5 hr.
[b] Culculated from intensities of N-methyl signals on ^{1}H NMR spectra.

†This solvent system has been successfully used in N-methylation of amide groups.[9]

‡Wolfe and Trimitsis have proposed the mechanism that the two fold benzoylation of acetamide proceeds by C-benzoylation of the imide, N-benzoylacetamide, which is formed by initial N-benzoylation of acetamide. On the other hand, it has been also pointed out that phenylacetamide appears to react in a different way, since treatment of phenylacetamide with one mol equiv of methyl benzoate produced both 2-benzoyl- and N-benzoylphenyacetamides.[10]

Table 4. Reaction of 1,2,4,5 - tetrahydro - 3 - methyl - 3H - 3 - benzazepin - 2 - one **1a** with halides and NaH in THF–DMF (10:1 volume %)[a]

R_1-X	Reaction time (hr)	Product	Yield (%)	Bp., °C/mmHg Mp., °C (Solvent)
MeI[b]	2.5	**2a**	85	75-77 (Ether)
EtBr	3.0	**2b**	86	64-65 (Ether-Pet. Ether)
n-PrBr	4.0	**2c**	91	131-132/0.08
n-BuI	1.0	**2d**	92	147-149/0.2
n-BuBr	3.0	**2d**	93	
n-BuCl	4.0	**2d**	85	
iso-BuBr	3.0	**2e**	86	141-142/0.09, 47-50[c]
n-Pentyl Br	3.0	**2f**	89	146-147/0.1
n-Hexyl Br	3.0	**2g**	82	190-192/0.5, 46-47[c]
iso-PrI	1.0	**2h**	61	123-124/0.09, 51-53[c]
iso-PrBr	2.0	**2h**	63	
Cyclohexyl I	1.0	**2i**	7	157-158/0.09
Cyclohexyl Br	2.0	**2i**	44	
Allyl I	10 min	**2j**	88	190-191/0.5
Allyl Br	2.0	**2j**	89	
Allyl.Cl	4.0	**2j**	88	
C_6H_5-CH=CH-CH_2-Cl	3.0	**2k**	76	124-126 (Benzene-Ether)
HC≡C-CH_2Br	2.0	**2l**	84	94-95 (Ether)
$C_6H_5CH_2$Br	2.0	**2m**	85	128-129.5 (Benzene-Ether)
$C_6H_5CH_2$Cl	5.0	**2m**	86	
3,4-$OCH_2OC_6H_3CH_2$Br	3.0	**2n**	81	124-126 (Ether)
2,3-$(MeO)_2C_6H_3CH_2$Br	3.0	**2o**	91	144-145.5 (Ether)
MeOOC-CH_2CH_2Br	1.0	**2p**	78	170-171/0.4
EtOOC-CH_2CH_2Br	1.0	**2q**	73	172-173/0.3

[a]Each reaction was performed in use of 1.1 equiv of R_1X and 2 equiv of NaH, and in 80 °C oil bath, except the methylation reaction.

[b]The reaction mixture containing 3 equiv of MeI and 2 equiv of NaH was heated at 50 °C.

[c]Crystallized on standing.

method seems to be also useful for the preparation of the aromatic alkoxy substituted benzyl derivatives, **2n**, and **2o**, while the expected steric effect of *ortho*-substituent was not clearly observed in their relative reaction rates. Secondary halides resulted in lower yield than primary halides, for instance, in 63 or 61% yield with isopropyl bromide or iodide and in 44 or 7% with cyclohexyl bromide or iodide, respectively.

We also studied the reaction with ω-halo ester. When methy or ethyl β-bromopropionate was treated with **1a** in the same manner as the above alkylation, **2p** or **2q** was easily obtained in good yield. In case of ethyl γ-bromobutyrate, neither the expected alkylation nor the acylation with ester group due to the ester condensation reaction took place and most of the starting material **1a** was recovered. **2p** or **2q** was also prepared from the reaction with methyl or ethyl acrylate and NaH in 1.1:1.0 mol equiv to **1a** (Experimental). These results may suggest that the reaction of β-bromopropionate is not a direct displacement of Br atom by benzazepinone carbanion, but more plausibly due to the Michael type addition† onto the acrylate formed by the reaction of NaH and the β-halo ester. In fact, treatment of a mixture consisting of the same equiv of **1a**, methyl β-bromopropionate and NaH resulted in recovery of **1a** more than 90% together with none of **2p** detected.

The method was extended to the preparation of spiro type compounds **4**. Since second carbanion formation necessary for the dialkylation took place more readily in boiling dioxane or toluene as described above in Table 3, first, dioxane was selected as a solvent. The reaction was performed with **1a**, ω,ω'-dibromoalkane (1.1 mol equiv) and NaH (3 mol equiv) at the boiling temperature of the solvent, and the expected products with 5- and 6-membered spiro ring system, **4d** (55%) and **4e** (23%) were obtained, respectively. When the same reaction was undertaken in THF–DMF (10:1) on 80° oil bath (Table 5), it is however noteworthy that, **1a** was more effectively dialkylated even in the better yield, 63% for **4d** and 42% for **4e**, than in boiling dioxane. 1,2-Dibromoethane and 1,3-dibromopropane failed to give the corresponding spiro compounds depicted as **4a** or **4b**, even in dioxane, and the latter dibromide yeilded **2j** instead in 80% yield (71% in dioxane), which had been already obtained by the interaction with allyl halides. In the series of **e**, **d**, the compounds **4** were accompanied with significant amounts of dimeric benzazepinones **5**.

Thus, functionalization of 3-benzazepinone was found to be successfully performed under the combination of NaH and the suitable solvents.‡ It is reasonably said that the reaction might also be applicable to further functionalizations of certainly substituted 3-benzazepinones and, hopefully, to other benzolactams, too.

EXPERIMENTAL

M.ps were determined on a Labolatory Devices Meltemp and are uncorrected. B.ps are uncorrected. IR spectra were recorded on a Hitachi–Perkin–Elmer Model 125 spectrophotometer. ^{1}H NMR spectra were run on $CDCl_3$ solns with Me_4Si as an internal standard ($\delta = 0$ ppm) and registered on a 90 MHz Hitachi R-22 spectrometer. Mass spectrum was obtained on a Jeol JMS-D300 spectrometer. NaH (50% in mineral oil) was washed with dry n-hexane and dried *in vacuo*. Lc analysis was performed on a Jasco Familic-100 instrument using octadecylsilanoid (ODS) type column SC-01-05 and eluted with ether or ether-petroleum ether (1:1 volume %). Preparative tlc was run on Merck silica gel 60 PF-254 (Catalog No. 7749) and a 60 HF-254 (No. 7739) was used to follow the reaction.

1,2,4,5 - *Tetrahydro* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**1a**). Chloroacetyl chloride (15.7 g, 0.139 mol) in dry benzene (70 ml) was added dropwise to a stirred and cooled soln of N-methylphenethylamine (17.1 g, 0.126 mol) and pyridine (11.0 g, 0.139 mol) in dry benzene (150 ml). The mixture was allowed to

Table 5. Reaction of **1a** with ω,ω-dibromoalkanes[a]

Br$(CH_2)_n$Br	Reaction time (hr)	Product: Spiro compound (%)	Product: Others (%)
n=2	4	none	none
n=3	2	none	**2j** (80)[a] (71)[b]
n=4	4	**4c** (63)[a] (55)[b]	**5c** (32)[a]
n=5	4	**4d** (42)[a] (23)[b]	**5d** (26)[a]

[a]In dry THF and DMF (10:1 volume %) in 80 °C oil bath.

[b]In dry dioxane at 120 °C oil bath.

†Methyl or ethyl fumarate in preliminary experiment were found to also react with **1a** to give the corresponding diastereomeric Michael adducts.[11]

‡Attempted reactions with ketones (benzaldehyde, benzophenone) and halides (ethyl chloroacetate, chlorocyanomethane, 2-bromoethanol, ethylchloromethyl ether failed to introduce the appropriate functional groups on **1a** and most of the starting material was recovered instead.

stand at room temp for 1 hr and then heated on a boiling water-bath for an additional 1 hr. After cooling, the ppt was filtered off and the filtrate was washed with dil. Na_2CO_3aq, dil. HClaq and water. The benzene layer, after drying over Na_2SO_4, was distilled to afford 25.0 g (93%) of N-chloroacetyl-N-methylphenylethylamine, b.p. 137–149° (0.2 mm);† IR (Neat) 1650 cm^{-1}; ^1H NMR δ 2.90 and 2.96 (each s of about 1:1, 3 H, N–CH_3), 2.65–2.95 (m, 2H, ArCH_2), 3.35–3.65 (m, 2H, CH_2N), 3.66 and 4.01 (each s of about 1:1, 2H, CH_2Cl), 7.0–7.30 (m, 5H, aromatic H's). (Found: C, 62.67; H, 6.58; N, 6.64; Cl, 16.76. Calc. for $C_{11}H_{14}ONCl$: C, 62.41; H, 6.66; N, 6.61; Cl, 16.74%).

According to the method of Nair and Malik[8] for the preparation of **1b**, a mixture of the above chloroacetamide (23.0 g, 0.109 mol) and powdered anhyd. $AlCl_3$ (20.4 g, 0.153 mol) was stirred and heated at 140° for 15 hr. The mixture was treated with ice-water and conc HCl (18 ml), and then extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was treated with hot ether (500 ml). The ethereal layer separated from insoluble oily residue was decolorized with active carbon (Norit A) and passed through a thin layer of Celite powder. Concentration of this colorless soln gave 13.3 g (70%) of white crystals of **1a**, m.p. 114–116°, whose recrystallization from ether afforded an analytical sample, m.p. 114.5–116.5°; IR (Nujol) 1645 cm^{-1}; ^1H NMR δ 2.98 (s, 3H, N–CH_3), 2.85–3.15 (m, 2H, CH_2N), 3.50–3.75 (m, 2H, ArCH_2), 3.86 (s, 2H, ArCH_2CO), 7.10 (br s, 4H, aromatic H's). (Found: C, 75.34; H, 7.45; N, 7.99. Calc. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99%).

A general method for the preparation of **2** *from* 1,2,4,5-*tetrahydro*-3-*methyl*-3H-*benzazepin*-2-*one* (**1a**). To a stirred suspension of **1a** (350 mg, 2 mmol) and NaH (96 mg, 4 mmol) in a mixture (2 ml) of dry THF and DMF (10:1 volume %) was added a soln of the appropriate halide (1.1 mmol besides 3 mmol of MeI) in the same solvents (2 ml) as the above. The mixture was heated in a stream of dry N_2 in 80% oil bath (50° for **2a**), until all or most of starting benzazepinone was consumed, by following the reaction on silica gel tlc plate [developed with CH_2Cl_2], as specified in Table 4. The mixture, after removal of THF, was treated with ice-water and extracted with $CHCl_3$. The extract was thoroughly washed with brine, dried over Na_2SO_4, and evaporated. The residue was, if necessary, purified by preparative tlc on silica gel [developed with CH_2Cl_2 containing 3–5% MeOH and extracted with MeOH–CH_2Cl_2 (1:2 volume %)], and distilled through short-pass under reduced pressure or crystallized.

1,2,4,5-*Tetrahydro*-1,3-*dimethyl*-3H-3-*benzazepin*-2-*one* (**2a**). IR (Nujol) 1643 cm^{-1}; ^1H NMR δ 1.56 (d, 3H, J = 7 Hz, C_3–Me), 2.98 (s, 3H, N–Me), 3.0–4.2 (m, 4H, Ar–CH_2CH_2–N), 4.31 (q, 1H, J = 7 Hz, C_3–H), 7.1–7.3 (m, 4H, aromatic H's). (Found: C, 76.31; H, 8.14; N, 7.43. Calc. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40%).

1,2,4,5 - *Tetrahydro* - 1 - *ethyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2b**), IR (Nujol) 1645 cm^{-1}; ^1H NMR δ 1.02 (t, 3H, J = 7 Hz, CH_2CH_3), 1.6–2.5 (m, 2H, CH_2CH_3), 2.66 (s, 3H, N–Me), 3.0–4.2 (m, 5H, Ar–CH_2CH_2–N and C_3–H), 7.0–7.3 (m, 4H, aromatic H's). (Found: C, 76.91; H, 8.52; N, 6.83. Calc. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89%).

1,2,4,5 - *Tetrahydro* - 1 - *propyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2c**). IR (Neat) 1646 cm^{-1}; ^1H NMR δ 0.99(t, 3H, J = 7 Hz, $CH_2CH_2CH_3$), 1.1–2.5 (m, 4H, $-CH_2CH_2CH_3$), 2.98 (s, 3H, N–Me), 3.0–4.1 (m, 4H, ArCH_2CH_2N), 4.11 (dd, 1H, J = 6.5, 8 Hz, C_3–H), 7.0–7.3 (m, 4H, aromatic H's). (Found: C, 77.33; H, 8.93; N, 6.21. Calc. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45%).

1,2,4,5 - *Tetrahydro* - 1 - *butyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2d**). IR (Neat) 1652 cm^{-1}; ^1H NMR δ 0.94 (br t, 3H, J = 6 Hz, Me), 1.38 (m, 4H, 2 × CH_2), 1.5–2.0 (m, 2H, CH_2), 3.00 (s, 3H, N–Me), 3.0–4.1 (m, 4H, ArCH_2CH_2N), 4.08 (dd, 1H, J = 6, 8 Hz, C_3–H), 7.1–7.3 (m, 4H, aromatic H's). (Found: C, 77.86; H, 8.87; N, 5.94. Calc. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05%).

1,2,4,5-*Tetrahydro*-1-*isobutyl*-3-*methyl*-3H-3-*benzazepin*-2-*one* (**2e**). IR (Nujol) 1655 cm^{-1}; ^1H NMR δ 0.92 (d, 3H, J = 6 Hz, Me), 0.95 (d, 3H, J = 6 Hz, Me), 1.5–2.4 (m, 3H, CH_2CHMe_2), 3.0–4.1 (m, 4H, ArCH_2CH_2N), 4.17 (dd, 1H, J = 6, Hz, C_3–H), 7.0–7.2 (m, 4H, aromatic H's). (Found: C, 77.80; H, 9.15; N, 6.11. Calc. for $C_{15}H_{21}ON$: C, 77.85; H, 9.15; N, 6.05%).

1,2,4,5 - *Tetrahydro* - 1 - *pentyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2f**). IR (Nujol) 1650 cm^{-1}; ^1H NMR δ 0.89 (br t, 3H, J = 6 Hz, Me), 1.04 (br s, 6H, 3 × CH_2), 1.6–2.4 (m, 2H, CH_2), 2.97 (s, 3H, N–Me), 3.0–4.1 (m, 4H, CH_2), 4.07 (dd, 1H, J = 6, 8 Hz, C_3–H), 7.1–7.3 (m, 4H, aromatic H's). (Found: C, 78.31; H, 9.69; N, 5.44. Calc. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71%).

1,2,4,5 - *Tetrahydro* - 1 - *hexyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2g**). IR (Neat) 1652 cm^{-1}; ^1H NMR δ 0.85 (br t, 3H, J = 5.5 Hz, Me), 1.31 (br s, 8H, 4 × CH_2), 1.6–2.4 (m, 2H, CH_2), 2.92 (s, 3H, N–Me), 2.9–4.0 (m, 4H, 2 × CH_2), 4.02 (dd, 1H, J = 6, 8 Hz, C_3–H). (Found: C, 78.72; H, 9.61; N, 5.36. Calc. for $C_{17}H_{25}ON$: C, 78.71; H, 9.72; N, 5.40%).

1,2,4,5 - *Tetrahydro* - 1 - *isopropyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2h**). IR (Neat) 1644 cm^{-1}; ^1H NMR δ 0.92 (d, 3H, J = 7, Me), 1.13 (d, 3H, J = 7 Hz, Me), 2.1–2.7 (m, 1H, $CHMe_2$), 3.00 (s, 3H, N–Me), 3.0–4.2 (m, 5H, ArCH_2CH_2N and C_3–H), 7.16 (br s, 4H, aromatic H's). (Found: C, 77.33; H, 8.93; N, 6.21. Calc. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45%).

1,2,4,5 - *Tetrahydro* - 1 - *cyclohexyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2i**). IR (Neat) 1640 cm^{-1}; ^1H NMR δ 0.7–2.3 (m, 10H, cyclohexyl), 3.01 (s, 3H, N–Me), 3.0–4.2 (m, 5H, ArCH_2CH_2N and C_3–H), 7.0–7.3 (m, 4H, aromatic H's). (Found: C, 79.34; H, 9.19; N, 5.46. Calc. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44%).

1,2,4,5 - *Tetrahydro* - 1 - *allyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2j**). IR (Neat) 1656 cm^{-1}; ^1H NMR δ 2.93 (s, 3H, N–Me), 2.4–4.2 (m, 6H, 3 × CH_2), 4.17 (t, 1H, J = 7 Hz, C_3–H), 4.8–5.3 (m, 2H, $-CH=CH_2$), 5.6–6.2 (m, 1H, $-CH=CH_2$), 7.0–7.2 (m, 4H, aromatic). (Found: C, 77.86; H, 7.94; N, 6.37. Calc. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51%).

1,2,4,5 - *Tetrahydro* - 1 - *β* - *cinnamyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2k**). IR (Nujol) 1660 cm^{-1}; ^1H NMR δ 2.96 (s, 3H, N–Me), 2.6–4.2 (m, 7H), 4.27 (dd, 1H, J = 6, 8 Hz, C_3–H), 6.1–6.7 (m, 2H, Ar–CH=CH–), 7.0–7.5 (m, 9H, aromatic H's). (Found: C, 82.40; H, 7.27; N, 4.92. Calc. for $C_{20}H_{21}ON$: C, 82.44; H, 7.26; N, 4.81%).

1,2,4,5 - *Tetrahydro* - 1 - *propargyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2l**). IR (Nujol) 1655, 3260 cm^{-1}; ^1H NMR δ 1.96 (t, 1H, J = 2 Hz, acetylenic H). 2.6–4.2 (m, 7H), 2.91 (s, 3H, N–Me), 4.45 (t, 3H, J = 8 Hz, C_3–H), 7.0–7.4 (m, 4 H, aromatic H's). (Found: C, 78.98; H, 7.16; N, 6.44. Calc for $C_{14}H_{15}ON$: C, 78.84; H, 7.09; N, 6.57%).

1,2,4,5 - *Tetrahydro* - 1 - *benzyl* - 3 - *methyl* - 3H - 3 - benzazepin - 2 - one (**2m**). IR (Nujol) 1658 cm^{-1}; ^1H NMR δ 2.86 (s, 3H, N–Me), 3.0–4.1 (m, 6H, 3 × CH_2), 4.43 (dd, 1H, J = 6.8 Hz, C_3–H), 7.0–7.3 (m, 9H, aromatic H's). (Found: C, 81.35; H, 7.31; N, 5.25. Calc. for $C_{18}H_{19}ON$: C, 81.47; H, 7.22; N, 5.28%).

1,2,4,5 - *Tetrahydro* - 1 - (3,4 - *methylenedioxybenzyl*) - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2n**). IR (Nujol) 1660 cm^{-1}; ^1H NMR δ 2.92 (s, 3H, N–Me), 2.8–4.2 (m, 6H, 3 × CH_2), 4.42 (dd, 1H, J = 6, 8 Hz, C_3–H), 5.91 (s, 2H, O–CH_2–O), 6.6–6.9 (m, 3H, aromatic H's on benzyl group), 7.1–7.3 (m, 4H, aromatic H's). (Found: C, 73.69; H, 6.23; N, 4.54. Calc. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19; N, 4.53%).

1,2,4,5 - *Tetrahydro* - 1 - (2,3, - *dimethoxybenzyl*) - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**2o**). IR (Nujol) 1655 cm^{-1}; ^1H NMR δ 2.90 (s, 3H, N–Me), 3.0–4.2 (m, 6H, 3 × CH_2), 3.81 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.63 (t, 1H, J = 7.5 Hz, C_3–H), 6.7–7.3 (m, 7H, aromatic H's). (Found: C, 73.96; H, 7.16; N, 4.23. Calc. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30%).

Methyl 3 - (1,2,4,5 - *tetrahydro* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *on* - 1 - *yl*) *propionate* (**2p**). IR (Neat) 1650, 1732 cm^{-1}; ^1H NMR δ 2.0–2.9 (m, 4H, MeOOC–CH_2CH_2–), 2.94 (s, 3H, N–Me), 2.9–4.4 (m, 5H), 3.68 (s, 3H, O–Me), 7.1–7.3 (m, 4H, aromatic H's). (Found: C, 68.66; H, 7.35; N, 5.27. Calc. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36%).

†This chloroacetamide has appeared without experimental and physical details in the literature,[12] and was observed to exist as two rotamers (1 : 1) at ambient temp due to tertiary amide group in its ^1H NMR spectrum.

When a stirred mixture of **1a** (175 mg, 1 mmol), NaH (24 mg, 1 mmol) and methyl β-bromopropionate (167 mg, 1 mmol) in 2 ml of the same solvent system was heated in the same manner for 1 hr, the work-up as usual afforded a crystalline solid (160 mg), m.p. 114–116°, of the starting material **1a**.

Ethyl 3 - (1,2,4,5 - *tetrahydro* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *on* - 1 - *yl*) *propionate* (**2q**). IR (Neat) 1652, 1730 cm^{-1}; ^1H NMR δ 1.23 (t, 3H, J = 7 Hz, CH_3CH_2O), 2.0–2.9 (m, 4H, $EtOOC-CH_2CH_2-$), 2.94 (s, 3H, N–Me), 2.9–4.4 (m, 5H), 4.15 (q, 2H, J = 7 Hz, CH_3CH_2O), 7.1–7.3 (m, 4H, aromatic H's). (Found: C, 69.86; H, 7.77; N, 5.27. Calc. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09%).

Reaction of 1,2,4,5 - *tetrahydro* - 3H - 3 - *benzazepin* - 2 - *one* (**1b**) *with methyl iodide and* NaH. (A) A mixture of **1b**[8] (m.p. 158–160°, 332 mg, 2 mmol), MeI (1.136 mg, 8.0 mmol) and NaH (120 mg, 5.0 mmol) in dry THF–DMF (10:1 volume %, 4 ml) was heated in 50° oil bath for 2.5 hr and worked up in the same manner as the above. Crystallization of the residue from ether led to white crystals 158 mg (84%), m.p. 75–77°, which were identical in all respects with **2a**. (B) **1b** (161 mg, 1 mmol), MeI (142 mg, 1 mmol) and NaH (24 mg, 1 mmol) were treated in dry THF–DMF (10:1 volume %, 2 ml) at 50° for 2.5 hr. ^1H NMR spectrum of the oily residue (194 mg) obtained displayed peaks at 3.86 (s) and 1.56 (d, J = 7 Hz) due to the C_1-protons of **1a** and secondary methyl group, respectively. Judging from their intensities (6.3 and 4.3), a ratio of N- to C-methylation reaction was estimated at 11:5.

Reaction of **1a** *with ω,ω'-dibromoalkanes.* A mixture of **1a** (350 mg, 2 mmol), appropriate dibromide (2.2 mmol) and NaH (144 mg, 6 mmol) in dry THF–DMF (10:1 volume %, 4 mmol) was heated under the conditions specified in Table 5. Usual workup gave oily residues, which were chromatographed on silica gel plates in the above manner. Each fraction was distilled *in vacuo* or crystallized. (A) With 1,2-dibromoethane: 275 mg of **1a**, m.p. 115–116°, was recovered. (B) With 1,3-dibromopropane: A band with R_f 0.7 yielded an oil (344 mg), b.p. 190–191°/0.5 mm, which was identical in all respects with the aforementioned allylated benzazepinone **2j**. (C) With 1,4-dibromobutane: A R_f 0.7 band gave a crystalline substance (290 mg, m.p. 60–62°) from ether-petroleum ether. Recrystallization from the same solvents afforded a pure **4d**, m.p. 61–62°. IR (Nujol) 1681 cm^{-1}; ^1H NMR δ 1.55–1.95 (m, 4H, 2 × CH_2), 1.95–2.4 (m, 2H), 2.6–3.0 (m, 2H), 2.93 (s, 3H, N–Me), 3.1–3.4 (m, 2H, $ArCH_2CH_2N$), 3.5–3.8 (m, 2H, $ArCH_2CH_2N$), 7.0–7.5 (m, 4H, aromatic H's). (Found: C, 78.30; H, 8.18; N, 5.82. Calc. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.11%). An R_f 0.3 solid (131 mg, m.p. 183–189°) consisted of **4d**, whose recrystallization from benzene gave an analytical sample, m.p. 188–190°. IR (Nujol) 1660 cm^{-1}; ^1H NMR δ 1.3–1.7 (m, 4H, 2 × CH_2), 1.6–2.5 (m, 4H, 2 × CH_2), 2.96 (s, 6H, 2 × N–Me), 3.0–4.1 (m, 8H, 2 × $ArCH_2CH_2N$), 4.08 (dd, 2H, J = 6, 8 Hz, 2 × C_1–H). (Found: C, 78.10; H, 7.98; N, 7.06. Calc. for $C_{26}H_{32}O_2N_2$: C, 77.19; H, 7.97; N, 6.39%). (D) With 1,5-dibromopentane: A mobile fraction with R_f 0.7 was crystallized from ether to yield **4e** (203 mg), m.p. 103–104°. IR (Nujol) 1624 cm^{-1}; ^1H NMR δ 1.1–2.1 (m, 8H), 2.5–2.8 (m, 2H), 3.01 (s, 3H, N–Me), 3.26 (br t, 2H, J = 6.5 Hz, $ArCH_2CH_2N$), 3.73 (br t, 2H, J = 6.5 Hz, $ArCH_2CH_2N$), 7.0–7.6 (m, 4H, aromatic H's). (Found: C, 79.24; H, 8.45; N, 5.74. Calc. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.76%). A less mobile fraction with R_f 0.3 gave **5d** (109 mg), which did not crystallize so far. IR (Neat) 1650 cm^{-1}; ^1H NMR δ 1.2–1.7 (m, 6H, 3 × CH_2), 1.5–2.5 (m, 4H, 2 × CH_2), 2.96 (s, 6H, 2 × N–Me), 3.0–4.1 (m, 8H, 2 × $ArCH_2CH_2N$), 4.08 (dd, 2H, J = 6, 8 Hz, 2 × C_1–H); *m/e* 418.2660 (Calc. for $C_{27}H_{34}O_2N_2$: 418.2620).

The same series of the reactions were also achieved in dioxane, in place of DMF–THF, in 120° oil bath, and worked up as above. The results obtained are summerized in Table 5.

1,2,4,5 - *Tetrahydro* - 1,1 - *dibutyl* - 3 - *methyl* - 3H - 3 - *benzazepin* - 2 - *one* (**3d**), b.p. 137–139°/0.1 mm was prepared from the reaction of **1a** or **2d** with excess n-BuBr and NaH in dry boiling dioxane, and purified by preparative silica gel tlc. IR (Neat) 1615 cm^{-1}; ^1H NMR δ 0.79 (br t, 6H, 2 × Me), 0.8–1.5 (m, 8H, 4 × CH_2), 1.5–2.6 (m, 4H, 2 × CH_2), 2.9–3.1 (m, 2H, $ArCH_2CH_2N$), 3.45–3.65 (m, 2H, $ArCH_2CH_2N$), 6.9–7.6 (m, 4H, aromatic H's). (Found: C, 79.53; H, 10.01; N, 4.76. Calc. for $C_{19}H_{29}ON$: C, 79.39; H, 10.17; N, 4.87%).

Reaction of **1a** *with methyl and ethyl acrylate.* To a stirred suspension of **1a** (350 mg, 2 mmol), NaH (48 mg, 2 mmol) and a mixture (2 ml) of dry THF and DMF (10:1 volume %) on 80° oil bath, methyl acrylate (190 mg, 2.2 mmol) in the same solvents (2 ml) was added. After heating under a stream of N_2 in 80° oil bath for 1 hr, the mixture was worked up as described. Distillation of the crude product gave an analytically pure substance (425 mg, 81%), b.p. 170–171°/0.4 mm, which was identical in all respects with **2p**.

In the same way, 220 mg (2.2 mmol) of ethyl acrylate gave **2q** (413 mg, 75%), b.p. 172–173°/0.3 mm.

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