Chem. Pharm. Bull.
36(7)2386—2400(1988)

Agents Acting on the Central Nervous System. Synthesis of 3-Phenyl-2-piperazinyl-1-benzazocines, 3-Substituted-2-piperazinyl-1-benzazepines and Related Compounds

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(Received October 6, 1987)

Three series of compounds, 3-phenyl-5,6-dihydro-1-benzazocines (**7**—**9**), 3-methyl-5*H*-1-benzazepines (**15**—**20**) and 3-phenyl-4,5-dihydro-3*H*-1-benzazepines (**24**—**35**), having a 2-(1-piperazinyl) group, were synthesized, and their pharmacological effects on the central nervous system were evaluated in mice. Among them, 3-methyl- (**15**—**18**) and 3-phenyl-4,5-dihydro-2-piperazinylbenzazepines (**26** and **33**—**35**) showed mild anti-reserpine activity. However, no significant anti-exploratory, anti-maximal electroshock seizure or anti-tremorine activity was generally found.

Novel ring transformations of α-chlorolactams are also described. The reaction of the 3-chloro-3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-ones (**37a**, **b**) and benzazocinone analogs (**46a**, **b**) with piperidine or various piperazines resulted in ring contraction to give the 2-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxamides (**38**—**41**) and the analogous benzazepine-2-carboxamides (**47** and **48**), respectively. The reaction of analogous 3-chloro-3-methylbenzazepinone (**14a**) with potassium carbonate in methanol also resulted in similar ring transformation to give methyl tetrahydroquinoline-2-carboxylate (**50**). These rearrangements were supposed to proceed *via* the azirinone intermediate.

Keywords——3-phenyl-2-piperazinylbenzazocine; 3-methyl-2-piperazinylbenzazepine; α-chlorolactam; ring contraction; 2-phenyl-tetrahydroquinoline-2-carboxamide; 2-phenyl-tetrahydrobenzazepine-2-carboxamide; methyl 2-phenyl-tetrahydroquinoline-2-carboxylate; central nervous system activity; anti-reserpine activity

A number of tricyclic dibenzepines (I), which possess two benzo structures fused with a central seven-membered ring with a basic side chain, act on the central nervous system (CNS) and exhibit neuroleptic effects.[1] Among them, clozapine (I; X=NH, R^1=Cl, R^2=H)[2] and fluperlapine (I; X=CH_2, R^1=F, R^2=H)[3] are regarded as nonclassical (atypical) antipsychotics, because of their novel activity pattern, producing minimal extrapyramidal side effects in man (Chart 1). In the course of our search for new neuroleptics, some 3-(substituted)phenyl-2-(1-piperazinyl)-5*H*-1-benzazepine derivatives (II) were found to show potent neuroleptic activities in experimental animals.[4] Structural comparison with the parent dibenzepines suggests that the moiety consisting of the 3-phenyl group and the conjugated 3,4-double bond in II plays essentially the same role as the fused phenyl ring of dibenzepines as regards the CNS activity. This finding has prompted us to synthesize three series of compounds possessing the same partial structure as II, derived from II by structural modification, and to evaluate their pharmacological actions on the CNS. In the first series, the seven-membered azepine skeleton of II is enlarged to the eight-membered azocine one. The second modification is to replace the 3-phenyl group of II with a methyl group and the third is the saturation of the 3,4-double bond of II. These modifications provide the following compounds: 3-phenyl-2-(1-piperazinyl)-5,6-dihydro-1-benzazocines (III), 3-methyl-2-(1-piperazinyl)-5*H*-1-benzazepines (IV), 3-phenyl-2-(1-piperazinyl)-4,5-dihydro-3*H*-1-benz-

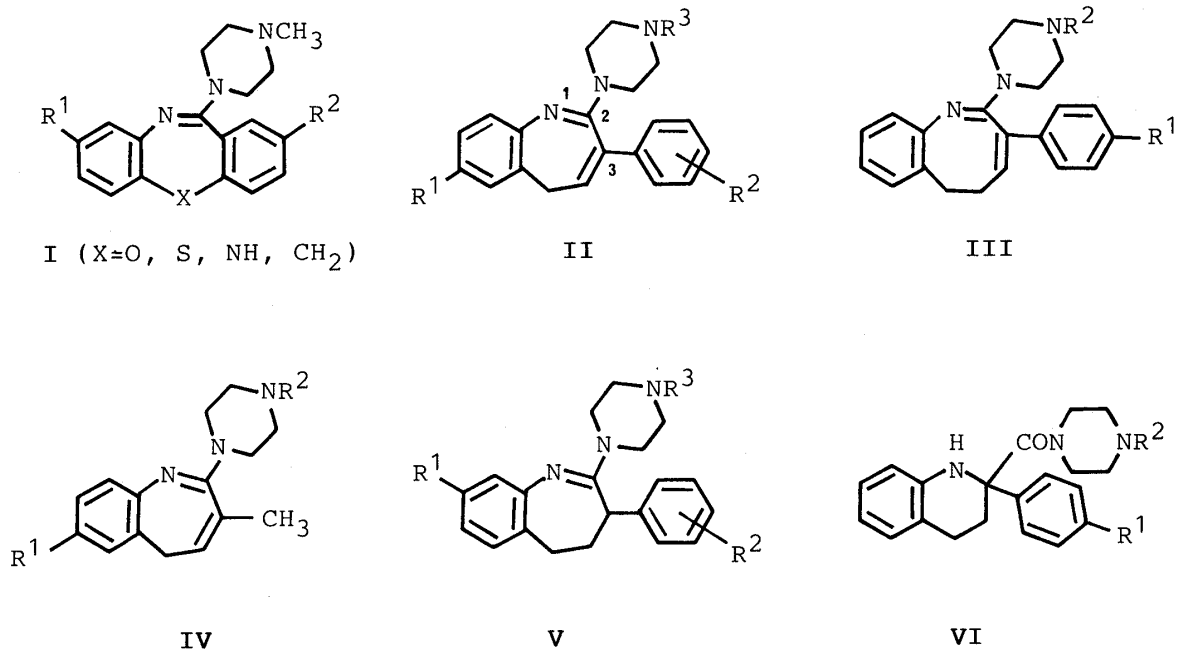


Chart 1

azepines (V). Pharmacological evaluation of these compounds might cast light on the role of the 3-phenyl group or the 3,4-double bond of II in the CNS activity, especially the neuroleptic activity.

In this paper, we describe the synthesis of III, IV, V and related compounds including the 2-phenyl-tetrahydroquinoline-2-carboxamides (VI), and the results of primary evaluation of their pharmacological activity on the CNS. We also describe some novel reactions found in these studies, *i.e.*, the ring contraction of α-chlorolactams under basic conditions (3-chloro-3-phenyl-tetrahydrobenzazepin-2-ones, 3-chloro-3-phenyl-hexahydrobenzazocin-2-ones and 3-chloro-3-methyl-tetrahydrobenzazepin-2-one to VI, 2-phenyl-tetrahydrobenzazepine-2-carboxamides and methyl 2-methyl-tetrahydroquinoline-2-carboxylate, respectively), as the first examples of ring transformations of fused α-chlorolactams.

The synthetic route to 3-phenyl-2-(1-piperazinyl)-5,6-dihydro-1*H*-1-benzazocines (**7**—**9**), shown in Chart 2, was similar to that in the case of the benzazepine analogs (II).[4] Thus, the nitriles (**1a**, **b**) were hydrolyzed to the 2,4-diphenylvaleric acids (**2a**, **b**), which were converted into the 2-phenylbenzosuberones (**3a**, **b**) *via* the Friedel–Crafts cyclization. The oximes (**4a**, **b**) derived from **3** were subjected to the Beckmann reaction to give 3-phenyl-1,2,3,4,5,6-hexahydro-1-benzazocin-2-ones (**5a**, **b**). The reactions from **2** to **5** were incomplete and the crude materials (**3**, **4**) were used for the next reaction, so the yields of **5** (20—22%) from **2** were never satisfactory in contrast to the higher yields in the case of the analogous benzazepinones (**21**).[4] Compounds **5a** and **5b** exhibited signals assignable to 3-H at δ 3.50 and 3.44, respectively, in their proton nuclear magnetic resonance (^{1}H-NMR) spectra, and lactam carbonyl absorptions at 1660—1655 cm^{-1} in their infrared (IR) spectra, indicating a benzamide-type lactam structure such as **21**. It is known that **21a**, **b** react with 2 mol of phosphorus pentachloride (PCl_5) to give the 2,3-dichlorides (**36a**, **b**).[4] In the same reaction, **5a**, **b** gave the expected 2,3-dichlorides (**6a**, **b**). The M^+ peak at *m*/*z* 303 in the mass spectrum (MS) and the $\nu_{C=N}$ absorption (1675 cm^{-1}) in the IR spectrum of **6a**, as well as those of **6b**, were consistent with the proposed structure **6**. Heating of **6a**, **b** with an excess of piperazines gave the desired 3-phenyl-2-(1-piperazinyl)-5,6-dihydro-1-benzazocines (**7**—**9**) in 56—22% yields (Table I). The ^{1}H-NMR spectrum of **8** (as the maleate) revealed signals assignable to

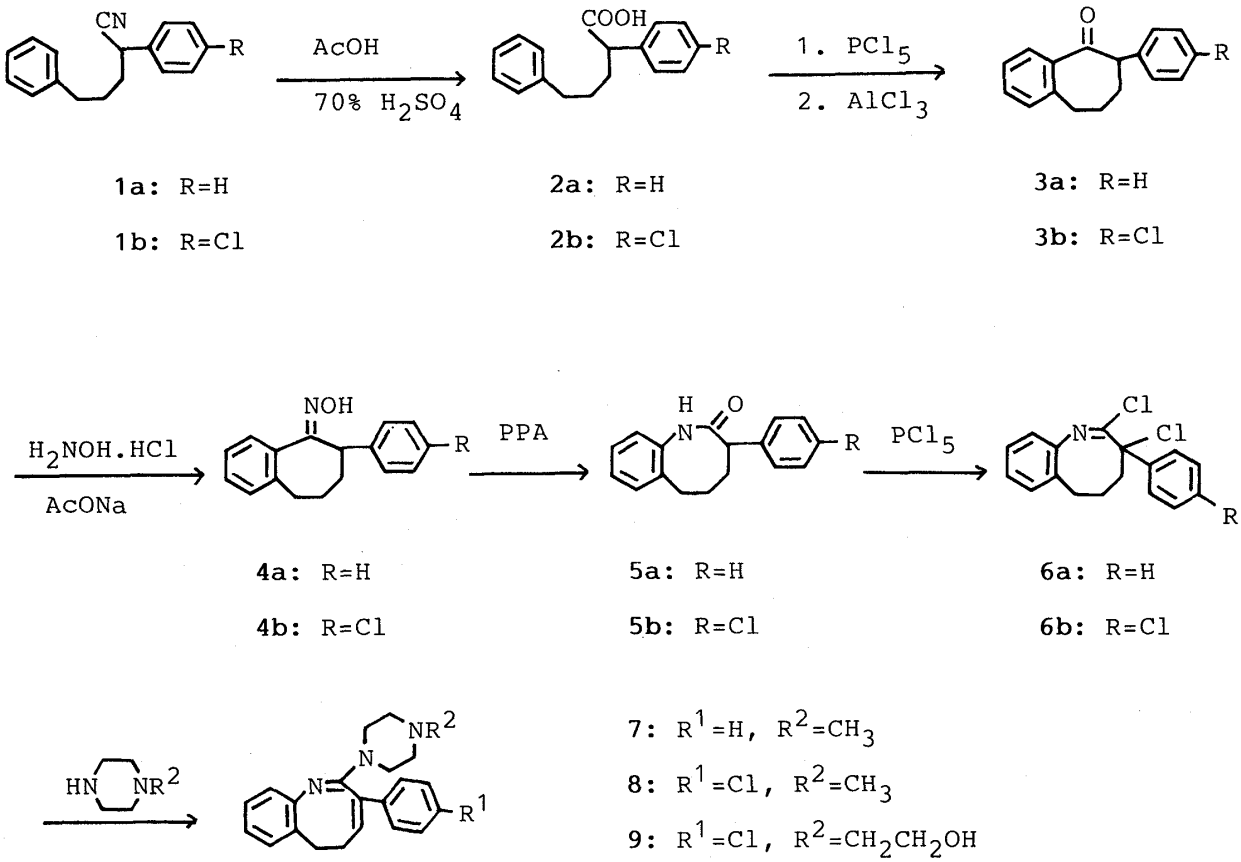


Chart 2

olefinic 4-H (δ 6.25, dd, $J=12$, 7 Hz), and the MS of **8** showed the M^+ peak at *m/z* 365. These results indicate that the reaction of **6** with the appropriate piperazine resulted in substitution at the 2-position and the concurrent formation of the 3,4-double bond due to dehydrochlorination, as found in the same reaction of **36** to II.[4]

The oxime (**11**) of 2-methyltetralone (**10**)[5] was subjected to the Beckmann reaction to give 3-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**12a**) in an excellent yield (93%) (Chart 3). Bromination of **12a** readily afforded the 7-bromide (**12b**), whose ^{1}H-NMR spectrum showed three aromatic proton signals at δ 6.91 (d, $J=9$ Hz, 9-H), 7.42 (dd, $J=9$, 2 Hz, 8-H) and 7.49 (d, $J=2$ Hz, 6-H). This brominated position *para* to the lactam nitrogen of **12a** was in accordance with those of the 3-phenyl isomers[4] and the 3-phenyl- and 3-methyl-3,4-dihydrocarbostyrils.[6] When treated with 2 mol of PCl_5, however, **12a**, **b** did not afford the expected 2,3-dichlorides (**13a**, **b**) but gave the 3-chlorobenzazepinones (**14a**, **b**), which were characterized on the basis of the following spectral data. Compound **14a** exhibited a lactam carbonyl absorption at 1655 cm^{-1} in its IR spectrum, the M^+ peak at *m/z* 209 in its MS and a singlet methyl signal assignable to 3-CH_3 (δ 1.77) in its ^{1}H-NMR spectrum. Taking into consideration the 2,3-dichlorination in the same reaction of the benzazocinones (**5**) and benzazepinones (**21**), along with a reduction of the yield of **14a** upon employing 1 mol of the reagent (namely, this reaction requires 2 mol of the reagent), it is reasonable to suppose that **14** was produced from the initially formed **13**, as a consequence of hydrolysis of the susceptible iminochloride moiety during work-up. A similar easy hydrolysis of a reactive iminochloride to an amide has been observed in 2,3-dichloro-5*H*-1-benzazepin-5-one.[7] The target 2-piperazinyl-5*H*-1-benzazepines (**15**—**20**) (Table I) were prepared by the reaction of **14a**, **b**, without isolation, with various piperazines. In this reaction, the amination was also found to be accompanied with a loss of hydrogen chloride forming the 3,4-unsaturation as in

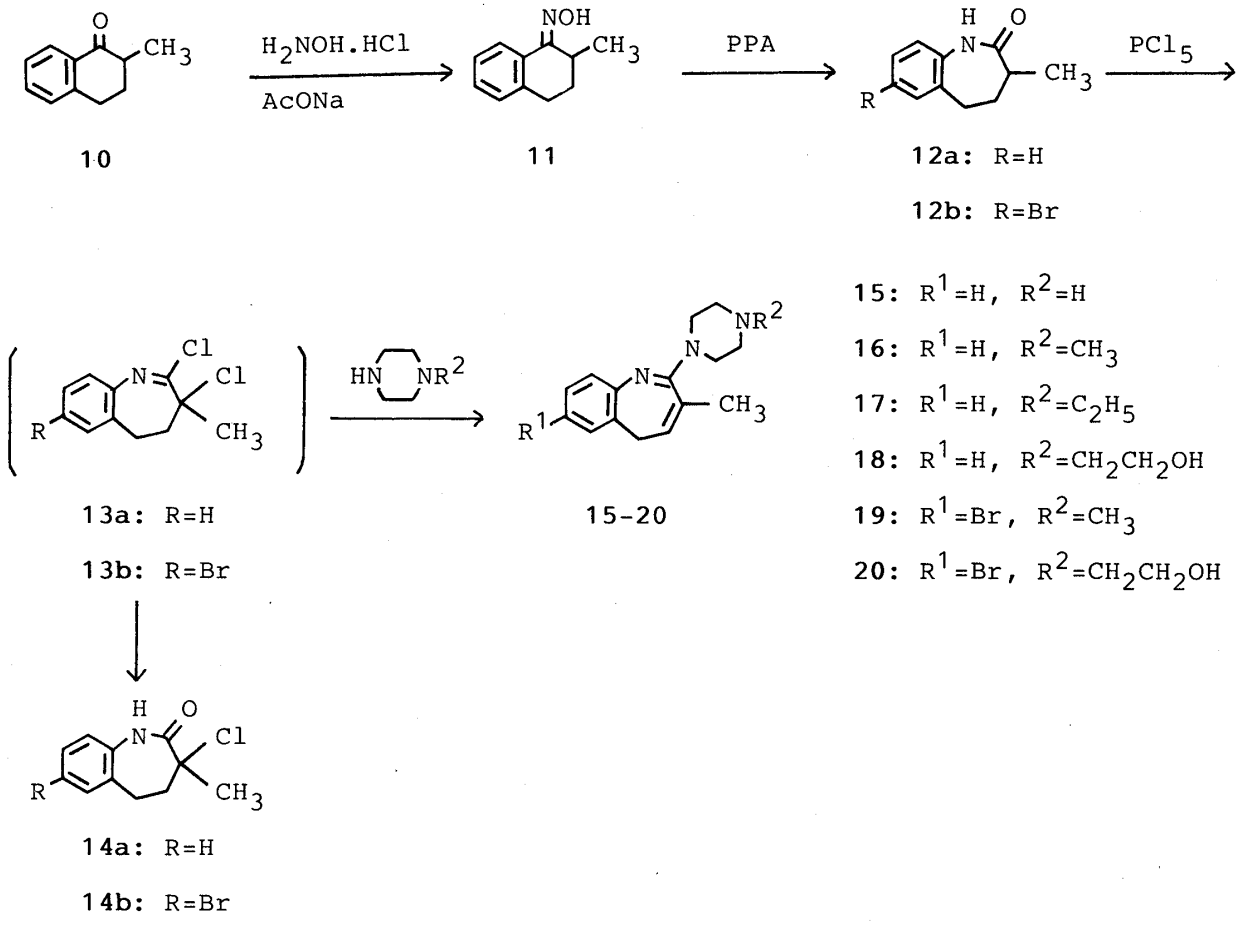


Chart 3

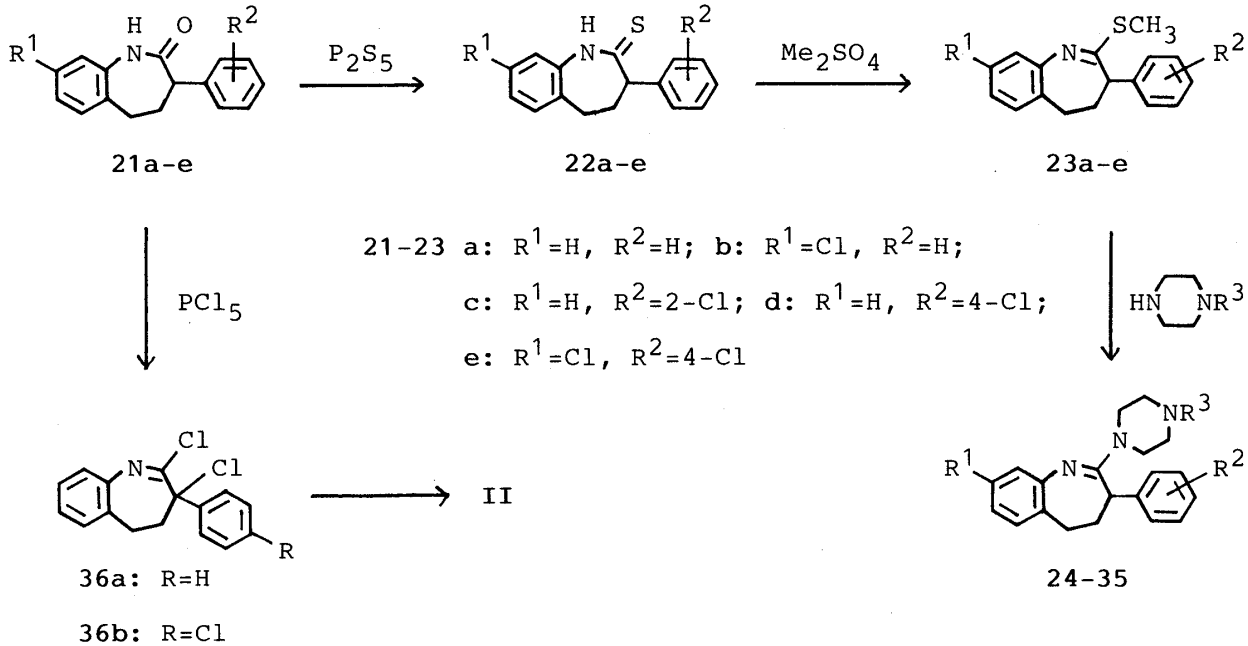
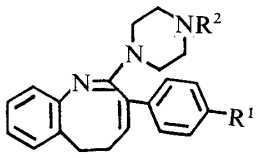


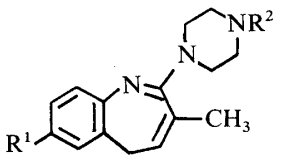
Chart 4

the 3-phenyl (**36**)[4] and the above mentioned benzazocine (**6**) analogs, as evidenced by the olefinic 4-H signal (δ 6.90, diffused t, $J=7.8$ Hz) and singlet 3-CH_3 signal (δ 1.98) in the ^{1}H-NMR spectrum of **16**, along with the M^+ peak at m/z 255 in the MS of **16**.

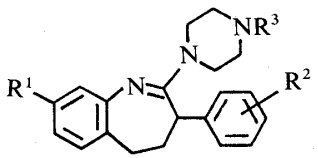
TABLE I. Physicochemical and Pharmacological Data for **7**—**9**, **15**—**20**, **24**—**35** and **29**—**41**



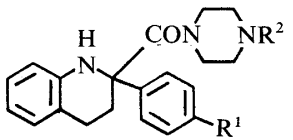
7—**9**



15—**20**



24—**35**



39—**41**

Compd. No.	R^1	R^2	R^3	mp (°C) Recryst. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found)					CNS activity[b]	
							C	H	Br	Cl	N	RES[c]	Others
7	H	CH_3	—	179—181	56[d]	$C_{22}H_{25}N_3$	63.82	6.07			7.44	−[f]	
				A		$\cdot 2(C_4H_4O_4)$[e]	(64.04	6.15			7.57)		
8	Cl	CH_3	—	169—171	37[d]	$C_{22}H_{24}ClN_3$	60.25	5.39		5.93	7.03	−[f]	+[f,g]
				A		$\cdot 2(C_4H_4O_4)$[e]	(60.22	5.47		5.92	7.16)		
9	Cl	CH_2CH_2OH	—	135—137	22[d]	$C_{23}H_{26}ClN_3O$	59.28	5.46		5.65	6.69	−[f]	
				A		$\cdot 2(C_4H_4O_4)$[e]	(59.06	5.42		5.69	6.63)		
15	H	H	—	159—160	55[d]	$C_{15}H_{19}N_3$	58.35	5.75			8.87	++	
				A–AE		$\cdot 2(C_4H_4O_4)$[e]	(58.30	5.73			8.78)		
16	H	CH_3	—	250—254	51[d]	$C_{16}H_{21}N_3$	55.49	7.28		20.48	12.13	+	+++[h]
				M–Ac		$\cdot 2HCl \cdot H_2O$	(55.29	7.49		20.48	12.11)		
17	H	C_2H_5	—	250—255	41[d]	$C_{17}H_{23}N_3$	59.65	7.36		20.72	12.28	+	
				A–AE		$\cdot 2HCl$	(59.64	7.22		20.84	12.27)		
18	H	CH_2CH_2OH	—	233—238	43[d]	$C_{17}H_{23}N_3O$	56.99	7.03		19.79	11.73	+	
				A–AE		$\cdot 2HCl$	(56.83	7.07		19.94	11.52)		
19	Br	CH_3	—	215—225	57[d]	$C_{16}H_{20}BrN_3$	46.17	5.59	19.20	17.04	10.10	−	
				A–Ac		$\cdot 2HCl \cdot 1/2\,H_2O$	(46.47	5.45	18.91	16.82	10.09)		
20	Br	CH_2CH_2OH	—	239—242	62[d]	$C_{17}H_{22}BrN_3O$	46.70	5.53	18.28	16.22	9.61	−	+[g]
				A		$\cdot 2HCl$	(46.90	5.63	18.19	16.14	9.55)		
24	H	H	CH_3	157—159	24	$C_{21}H_{25}N_3$	63.14	6.03			7.62	−	
				A–E		$\cdot 2(C_4H_4O_4)$[e]	(63.39	6.24			7.37)		

25	H	H	CH_2CH_2OH	87—88 AE–H	16	$C_{22}H_{27}N_3O$	75.61 (75.70	7.79 7.62		12.03 12.12)	−	
26	Cl	H	CH_3	157—159 A	37	$C_{21}H_{24}ClN_3$ $\cdot 2(C_4H_4O_4)$[e]	59.43 (59.35	5.50 5.59	6.05 6.06	7.17 6.97)	+	
27	Cl	H	CH_2CH_2OH	252—255 A–Ac	19	$C_{22}H_{26}ClN_3O$ $\cdot 2HCl$	57.84 (57.72	6.18 5.96	23.28 23.11	9.20 8.91)	−	
28	H	2-Cl	CH_3	263—266 A	20	$C_{21}H_{24}ClN_3$ $\cdot 2HCl \cdot 1/2\,H_2O$	57.87 (57.85	6.25 6.30	24.41 24.67	9.64 9.58)	−	
29	H	2-Cl	CH_2CH_2OH	258—262 A	36	$C_{22}H_{26}ClN_3O$ $\cdot 2HCl$	57.84 (57.74	6.18 6.30	23.28 22.44	9.20 8.96)	−	
30	H	2-Cl	C_6H_5	221—226 A	53	$C_{26}H_{26}ClN_3$ $\cdot 2HCl$	63.88 (63.89	5.79 5.55	21.76 21.43	8.59 8.56)	−	
31	H	4-Cl	CH_3	178—180 A–E	38	$C_{21}H_{24}ClN_3$ $\cdot 2(C_4H_4O_4)$[e]	59.43 (59.44	5.50 5.30	6.05 6.17	7.17 7.20)	−	+[h]
32	H	4-Cl	CH_2CH_2OH	237—240 A	19	$C_{22}H_{26}ClN_3O$ $\cdot 2HCl$	57.84 (57.63	6.18 5.89	23.28 23.00	9.20 9.13)	−	
33	H	4-Cl	C_6H_5	181 A–AE	27	$C_{26}H_{26}ClN_3$ $\cdot C_4H_4O_4$[e]	67.72 (67.55	5.68 5.77	7.90 7.75	6.67 6.63)	++	
34	Cl	4-Cl	CH_3	247—250 A	31	$C_{21}H_{23}Cl_2N_3$ $\cdot 2HCl$	54.68 (54.55	5.46 5.39	30.75 30.74	9.11 9.05)	++	+[g]
35	Cl	4-Cl	CH_2CH_2OH	227—232 A	38	$C_{22}H_{25}Cl_2N_3O$ $\cdot 2HCl \cdot 1/2\,H_2O$	53.10 (53.35	5.53 5.50	28.50 28.57	8.44 8.22)	+	
39	H	CH_3	—	130—132 E–H	81	$C_{16}H_{21}N_3O$	75.19 (75.48	7.51 7.80		12.53 12.54)	−	
40	H	CH_2CH_2OH	—	146 E	77	$C_{22}H_{27}N_3O_2$	72.30 (72.08	7.45 7.49		11.50 11.23)	−	
41	Cl	CH_3	—	162 C–E	86	$C_{21}H_{24}ClN_3O$	68.19 (67.91	6.54 6.67	9.59 9.82	11.36 11.25)	−	

a) Recrystallization solvents used are as follows: A, ethanol; AE, ethyl acetate; Ac, acetone; E, diethyl ether; H, hexane. *b*) Test compounds were administered *p.o.* (100 mg/kg). The symbols have the following meanings: −, no inhibition; +, slight inhibition (31—50%); ++, moderate inhibition (51—70%); +++, potent inhibition (>71%). *c*) Anti-reserpine activity in mice. *d*) Yield from the lactam (**5** or **12**). *e*) Maleate. *f*) Administered at 50 mg/kg, *p.o.* *g*) Anti-exploratory activity in mice. *h*) Anti-tremorine activity in mice.

Treatment of the 3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepinones (**21a—e**)[4] with phosphorus pentasulfide (P_2S_5) in pyridine readily afforded the thiolactams (**22a—e**), which were converted into the methyl thioethers (**23a—e**) in good yeilds. The aminolysis of **23a—e** was carried out with appropriate piperazines to give **24—35** in 16—53% yield (Chart 4, Table I).

To examine the reactivity of α-chlorolactams, such as **14a**, we attempted to prepare other α-chlorolactams (Chart 5). Though not more so than the 3-methyl isomers (**13a, b**), 2,3-dichloro-3-phenylbenzazepines (**36**) were generally unstable,[4] and readily hydrolyzed to the desired 3-chloro-3-phenylbenzazepinones (**37a, b**) in 90—91% yields by hydrochloric acid (HCl) in acetone at room temperature. Compounds **37a** and **37b** exhibited M^+ peaks at *m/z* 271 and 305 in their MS, respectively, in addition to lactam carbonyl absorptions at 1695 cm^{-1} in their IR spectra at a higher region due to α-substitution by chlorine. The structures of **37a, b** were characterized from the spectral and analytical data. Treatment of **37a** with 1 mol of PCl_5 at room temperature readily afforded **36a**, suggesting that the α-chloro substitution in this benzazepinone may result in enhanced reactivity of the amide group for iminochlorination, as compared with the parent benzazepinone. Under similar hydrolysis conditions, **6a, b** afforded the 3-chlorobenzazocinones (**46a, b**) (62—69% yield), in which the carbonyl absorptions of α-chlorolactam were observed in a normal region (1645—1655 cm^{-1}), as in **14a, b**.

On treatment with piperidine or various piperazines, **37a, b** smoothly afforded the ring-contracted 2-carboxy-2-phenyl-tetrahydroquinoline derivatives (**38—41**) in excellent yields (77—98%). The structure of **38** was well characterized on the basis of its metastable ion MS [*m/z* 320 (M^+) and 208 ($M^+ - CON$⟨⟩)] and a characteristic ν_{NH} absorption band at 3390 cm^{-1} in its IR spectrum as well as formation of its hydrochloride salt. These results and those for **39—41** were consistent with the proposed tetrahydroquinoline structure and ruled out another possible one. The amide carbonyl absorption (1615—1620 cm^{-1}) at unusually low wave number in **38—41** might be due to hydrogen bonding between the carbonyl oxygen and the 1-NH hydrogen.

When treated with potassium carbonate (K_2CO_3) in dioxane, **37a, b** afforded the dehydrochlorinated **42a, b**. Compounds **42a** showed signals assignable to an olefinic 4-H (δ 6.78, t, J=7.3 Hz) and 5-H_2 (δ 3.35, d, J=7.3 Hz) in its ^{1}H-NMR spectrum and an M^+ peak at *m/z* 235 in its MS, along with a lactam carbonyl absorption at 1650 cm^{-1} in its IR spectrum. These spectral and analytical data as well as those of **42b** supported the 3,4-unsaturated structure (**42**) as formulated. On the other hand, the similar reaction of **37a, b** in methanol (MeOH) yielded a mixture of **42a, b**, **43a, b** and **44a, b**. Compounds **43a** showed signals assignable to two olefinic protons of 4-H (δ 6.06, dd, J=10, 5.9 Hz) and 5-H (δ 6.90, dd, J=10, 1.9 Hz) in addition to 3-H (δ 3.78, dd, J=5.9, 1.9 Hz) in its ^{1}H-NMR spectrum, and the M^+ peak at *m/z* 235 in its MS, besides a lactam carbonyl absorption at 1675 cm^{-1} in its IR spectrum. These spectral and analytical data as well as those of **43b** revealed that **43a, b** possessed the proposed 4,5-unsaturated structures. Compounds **44a** and **44b** showed M^+ peaks at *m/z* 267 and 301 in their MS, respectively, in addition to a lactam carbonyl absorption at 1670 cm^{-1} in their IR spectra. Their ^{1}H-NMR spectra revealed methyl signals (δ 3.02 for **44a** and δ 3.00 for **44b**) and no signal assignable to a proton on a carbon bearing a methoxy group, suggesting the substitution at the 3-position by the methoxy group. On reduction with lithium aluminum hydride ($LiAlH_4$), **44a, b** afforded the amines (**45a, b**), which exhibited M^+ peaks at *m/z* 253 and 287 in their MS, respectively, and a characteristic ν_{NH} absorption at 3360 cm^{-1} in their IR spectra. These spectral and analytical data support the proposed structures of **44a, b** and **45a, b**. Treatment of benzazocine isomers (**46a, b**) with piperidine also caused a similar ring transformation, affording the 2-carboxy-2-phenylbenzazepine derivatives (**47, 48**) in excellent yields (95%). Compounds **47** and **48** were

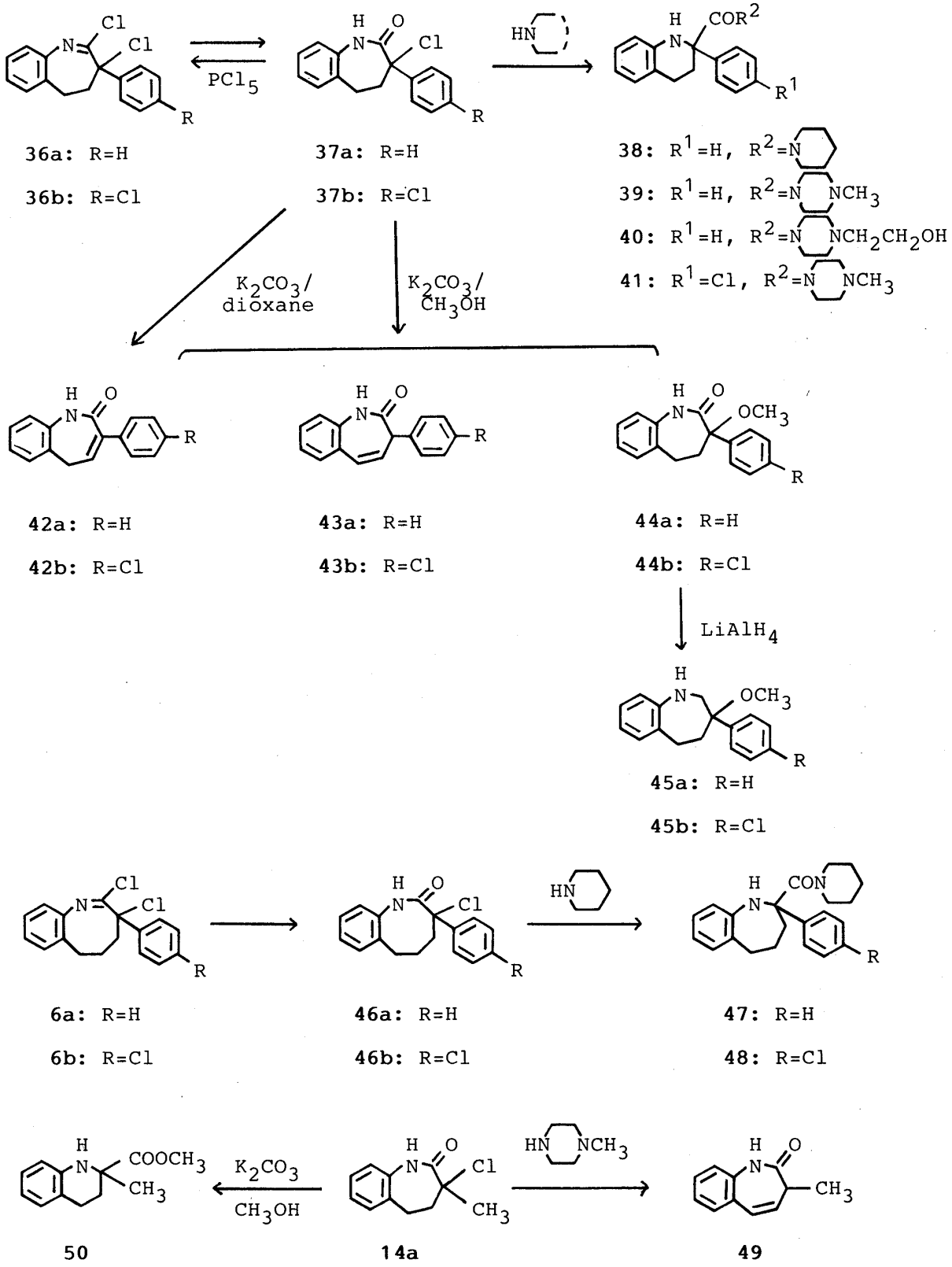
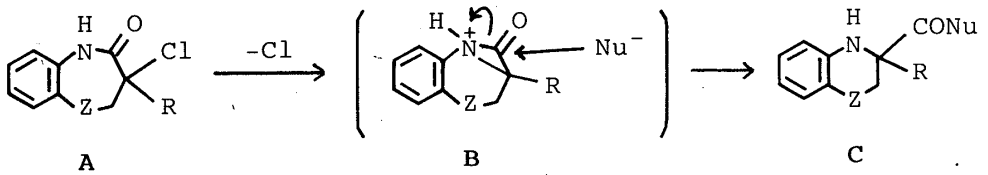


Chart 5

identified from the metastable ion MS [*m/z* 334 (M^+) and 222 ($M^+ - CON\langle\rangle$)] and secondary ion MS [*m/z* 369 (MH^+) and 256 ($M^+ - CON\langle\rangle$)], respectively. Further verification of the assigned structure was provided by formation of the hydrochloride salts.



A B C

Z: $-CH_2-$ or $-CH_2CH_2-$

Chart 6

The amide carbonyl absorptions in the IR spectra also appeared in a rather lower region (1615—1620 cm^{-1}) presumably due to hydrogen bonding as observed in **38**—**41**.

Treatment of the 3-methyl analog (**14a**) with *N*-methylpiperazine afforded the 4,5-unsaturated derivative (**49**), which exhibited two olefinic proton signals at δ 5.64 (dd, $J=10$, 5 Hz, 4-H) and 6.71 (dd, $J=10$, 2 Hz, 5-H), and a doublet methyl signal at δ 1.42 ($J=7$ Hz, 3-CH_3) in its ^{1}H-NMR spectrum, in addition to the M^+ peak at *m/z* 173 in its MS and a lactam carbonyl absorption at 1650 cm^{-1} in its IR spectrum. On the other hand, the reaction of **14a** with K_2CO_3 in MeOH gave the ester (**50**) alone, which exhibited amino (3380 cm^{-1}) and ester (1730 cm^{-1}) absorptions in its IR spectrum and two singlet methyl signals ascribable to 2-CH_3 (δ 1.44) and 2-$COOCH_3$ (δ 3.70). Based on these results, the product was characterized as the methyl ester of the tetrahydroquinoline derivative (**50**) produced *via* similar ring contraction as found above in **37** and **46**. Further support for this structure was provided by formation of the hydrochloride salt.

Sheehan and Lengyel have reported the reaction of acyclic α-haloamides with nucleophilic potassium *tert*-butoxide to give glycine butyl ester and α-butoxyamide *via* the intermediate α-lactam (azirinone).[8a] The ammonolysis of cyclic α-chlorocaprolactam has been reported to result in the formation of both 2-piperidinecarboxamide and α-aminocaprolactam.[9] The mechanism of the rearrangement of **37a, b**, **46a, b**, and **14a** to **38**—**41**, **47**, **48** and **50**, respectively, may follow the same course as described by the above authors. Thus, as formulated in Chart 6, removal of a chlorine anion and simultaneous transannelation taking place between nitrogen and C(3) (A) give rise to the azirinonium intermediate (B). Nucleophiles (amine or methoxy anion) attack the carbonyl carbon to result in the fission of the amide linkage, giving ring-contracted C. The rearrangement of **42**—**44** and **49** from **37** and **14a**, respectively, also seemed to proceed *via* the same intermediate (B), followed by the fission of the N–C(3) bond, with elimination of hydrogen (for **42**) and isomerization of the produced double bond (for **43**), or substitution by a methoxy group (for **44**). Similar α,β-unsaturated amides and α-alkoxyamides have been obtained from azirinones.[8] Formation of **49** as a sole product can be explained in terms of its relative stability with respect to the 3,4-unsaturated isomer due to the conjugation of the 4,5-double bond with the aromatic ring. The reason for the difference of reactivity between **37** and **14a** for the two nucleophiles is not clear.

Though there have been some reports about ring transformations of 1-benzazepines,[10] little work has been done on fission of the amide linkage to give 2-carboxyquinoline derivatives. There have been reports on the rearrangements of 2,3-dihydro-2,3-dioxo-1*H*-1-benzazepine[11] and 2,5-dihydro-2,5-dioxo-1*H*-1-benzazepines[7] to 2-carboxyquinoline and kynurenic acids, respectively, under warm alkaline conditions. These rearrangements seemed to proceed *via* intermediate azirinones. The rearrangements of **37a, b**, **14a** and **46a, b** to **38**—**41**, **50** and **47**, **48**, respectively, are the first examples of ring transformations of fused α-chlorolactams, and should be useful as a synthetic route to α-substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid and analogous tetrahydrobenzazepine-2-carboxylic acid derivatives.

Pharmacology

All the compounds (**7**—**9**, **15**—**20**, **24**—**35** and **39**—**41**) having a piperazine substituent were examined at 100 (or 50) mg/kg, *p.o.* in mice as a primary screening test for CNS activity [anti-exploratory activity, anti-reserpine activity, anti-maximal electroshock seizure (MES) activity and anti-tremorine activity]. The results of the anti-reserpine test and the other items (anti-exploratory or anti-tremorine tests) where positive effects were found, are summarized in Table I. As is clear from the data, no significant suppression of exploratory activity, protection against MES or antagonism of tremor induced by tremorine was found. Exceptionally, **16** showed potent anti-tremorine activity. Anti-exploratory activities were found in some compounds (**8**, **20** and **34**) but were weak. Most 3-methyl-5*H*-1-benzazepines (**15**—**18**) and some 4,5-dihydro-3*H*-1-benzazepines (**26** and **33**—**35**) exhibited slight to moderate anti-reserpine activity. On the basis of the results, a seven-membered azepine skeleton and a moiety consisting of the 3-phenyl group and the conjugated 3,4-double bond, are essential in this class of compounds for a potent neuroleptic effect.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer in KBr disks unless otherwise noted, and mass spectra were taken on a JEOL JMS-D300 or Hitachi M-80B spectrometer. ^{1}H-NMR spectra were taken on a Varian A-60, FT-80A or XL-300 spectrometer using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. The chemical shifts are given as δ (ppm). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Organic extracts were dried over anhydrous magnesium sulfate. The following abbreviations are used: ether, diethy ether; AcOEt, ethyl acetate; $CHCl_3$, chloroform; MeOH, methanol; EtOH, ethanol; PPA, polyphosphoric acid; NaOH, sodium hydroxide.

2,5-Diphenylvaleronitrile (1a)——Benzyl cyanide (35.1 g, 0.3 mol) was added dropwise to a suspension of 60% sodium hydride (13.2 g, 0.33 mol) in dimethylformamide (130 ml) during 1 h at room temperature, and the reaction mixture was stirred for an additional 30 min. A solution of 3-bromopropylbenzene (59.7 g, 0.3 ml) in toluene (130 ml) was added dropwise during 2 h. The reaction mixture was stirred for 4 h, then diluted with ice-water and acidified with dilute HCl. The organic layer was separated and washed with water, dried and concentrated. Distillation of the residue gave **1a** (45 g, 64%) as a light yellow oil. bp 190—200 °C (2 mmHg). IR (neat): 2240 (C≡N) cm^{-1}.

2-(4-Chlorophenyl)-5-phenylvaleronitrile (1b)——4-Chlorobenzylcyanide was treated in the same manner as described for **1a** to give **1b** (62%). bp 220—227 °C (7 mmHg). IR (neat): 2240 (C≡N) cm^{-1}.

2,5-Diphenylvaleric Acid (2a)——A solution of **1a** (45 g), acetic acid (200 ml) and 70% sulfuric acid (50 ml) was refluxed for 7 h. The reaction mixture was diluted with ice-water and extracted with ether. The organic layer was extracted with dilute NaOH, and the extract was acidified with dilute HCl and extracted with ether. The organic layer was washed with water, dried and concentrated. The residue was crystallized from hexane to give **2a** (44.4 g, 91%), mp 77 °C. IR: 1700 (C=O) cm^{-1}. MS *m/z*: 254 (M^+). *Anal.* Calcd for $C_{17}H_{18}O_2$: C, 80.29; H, 7.13. Found: C, 80.05; H, 7.24.

2-(4-Chlorophenyl)-5-phenylvaleric Acid (2b)——Compound **1b** was treated in the same manner as described for **2a** to give **2b** (86%), mp 111—112 °C (ether–hexane). IR: 1700 (C=O) cm^{-1}. MS *m/z*: 288 (M^+). *Anal.* Calcd for $C_{17}H_{17}ClO_2$: C, 70.71; H, 5.94; Cl, 12.28. Found: C, 70.98; H, 5.89; Cl, 12.14.

3-Phenyl-1,2,3,4,5,6-hexahydro-1-benzazocin-2-one (5a)——A mixture of **2a** (13.4 g, 0.053 mol) and PCl_5 (11 g, 0.053 mol) was stirred for 20 min at room temperature and the volatile materials were evaporated *in vacuo*. The residue was dissolved in methylene chloride (100 ml), and $AlCl_3$ (7 g, 0.053 mol) was added portionwise under ice-cooling during 2 h. After stirring for an additional 1 h, the reaction mixture was poured into ice-water containing HCl, and extracted with AcOEt. The organic layer was washed with water, dried and concentrated, affording crude **3a** (13 g) as a light yellow oil. IR (neat): 1680 (C=O) cm^{-1}. A mixture of the above **3a**, hydroxylamine hydrochloride (14.8 g), sodium acetate (17.4 g), dioxane (70 ml) and water (35 ml) was stirred at 80 °C for 4 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water, dried and concentrated to give crude **4a** (13 g) as a residual oil. A mixture of the above **4a** (13 g) and PPA (170 g), preheated to 120 °C, was stirred for 20 min. After being cooled, the reaction mixture was poured into ice-water, and the resulting solid was collected, chromatographed on silica gel with $CHCl_3$–hexane (1 : 1) and recrystallized from ether to give **5a** (2.6 g, 20% from **2a**), mp 166—167 °C. IR: 1660 (C=O) cm^{-1}. MS *m/z*: 251 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.5—3.0 (6H, m, $-(CH_2)_3-$), 3.50 (1H, dd, J=10, 2 Hz, 3-H), 7.0—7.5 (9H, m, Ar-H), 7.60 (1H, NH). *Anal.* Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.13; H, 6.86; N, 5.36.

3-(4-Chlorophenyl)-1,2,3,4,5,6-hexahydro-1-benzazocin-2-one (5b)——Compound **2b** was treated in the same manner as described for **5a** to give **5b** (22% from **2b**), mp 203 °C ($CHCl_3$–ether). IR: 1655 (C=O) cm^{-1}. MS *m/z*: 285 (M^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.61 (1H, m, H_a), 1.94 (1H, m, H_b), 2.25 (2H, m, H_c and H_d), 2.67 (1H, t, J= 12 Hz, 6-H_a), 2.89 (1H, dd, J=14, 7 Hz, 6-H_b), 3.44 (1H, d, J=10.6 Hz, 3-H), 7.1—7.4 (8H, m, Ar-H), 7.52 (1H, NH). Signals H_a, H_b, H_c and H_d were ascribable to the protons of 4-H_2 and 5-H_2. *Anal.* Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; Cl, 12.41; N, 4.90. Found: C, 71.78; H, 5.61; Cl, 12.67; N, 4.71.

3-(4-Chlorophenyl)-2-(4-methyl-1-piperazinyl)-5,6-dihydro-1-benzazocine (8) (Typical Procedure)——A mixture of **5b** (1.43 g, 0.005 mol) and PCl_5 (2.6 g, 0.0125 mol) was stirred at 110 °C for 1 h. The volatile materials were removed *in vacuo* and the residue was partitioned between ice-water and ether. The organic layer was washed with water, dried and concentrated, affording crude **6b**. IR (liquid): 1680 (C=N) cm^{-1}. MS *m/z*: 337 (M^+). A mixture of the above **6b** and *N*-methylpiperazine (1.5 g, 0.015 mol) was then heated at 130 °C for 1 h. The reaction mixture was dissolved in a mixture of water and ether. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (100:1), subsequently converted into the maleate and recrystallized to give **8** (1.1 g, 37% from **5b**). MS *m/z*: 365 (M^+). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.81 (3H, s, NCH_3), 2.4—3.7 (12H, m, $-CH_2CH_2-$ and piperazine-8H), 6.14 [4H, s, $(=CHCOO)_4$], 6.25 (1H, dd, J=12, 7 Hz, 4-H), 6.83 (1H, diffused d, J=13 Hz, 7- or 10-H), 6.85 (1H, dt, J=13, 2.5 Hz, 8- or 9-H), 7.05 (1H, dt, J=13, 2.5 Hz, 9- or 8-H), 7.13 (1H, dd, J=13, 2.5 Hz, 10- or 7-H), 7.25 and 7.38 (4H, ABq, J=13 Hz, $-C_6H_4Cl$), 12—14 [4H, br, $(COOH)_4$]. Signals at the δ 2.4—3.7 region changed at 100 °C as follows: 2.40—2.65 [2H, m, 5- (or 6-)H_2], 2.70—2.80 [1H, m, 6-(or 5-)H_a], 2.70 (3H, s, NCH_3), 2.83—3.07 [5H, m, $W_{h/2}$=40 Hz, 6-(or 5-)H_b and piperazine-4H], 3.60 (4H, m, $W_{h/2}$=20 Hz, piperazine-4H). In the same manner, compounds **7** and **9** were prepared from **5a** and **5b**, respectively. The results are shown in Table I. The intermediate **6a** exhibited $\nu_{C=N}$ (1680 cm^{-1}) and *m/z* 303 (M^+) in its IR spectrum (neat) and MS, respectively.

2-Methyl-1-tetralone Oxime (11)——A mixture of 2-methyl-1-tetralone (**10**)[5] (53 g, 0.33 mol), hydroxylamine hydrochloride (93 g, 1.33 mol), sodium acetate (108 g, 1.32 mol), MeOH (300 ml) and water (100 ml) was stirred at 60 °C for 5 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with water, dried and concentrated. The residue was crystallized from ether–hexane to give **11** (41.9 g, 73%), mp 95—96 °C. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.10; H, 7.26; N, 7.98.

3-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (12a)——A mixture of PPA (300 g), preheated to 120 °C, and **11** (30 g) was stirred for 20 min. The reaction mixture was poured into ice-water and the resulting solid was collected and recrystallized from $CHCl_3$–ether to give **12a** (28 g, 93%), mp 172—173 °C. IR: 1660 (C=O) cm^{-1}. MS *m/z*: 175 (M^+). ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 0.92 (3H, d, J=6 Hz, CH_3), 1.6—2.8 (5H, m, $-CH_2CH_2CH-$), 6.8—7.3 (4H, m, Ar-H), 9.95 (1H, NH). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.49; H, 7.70; N, 8.05.

7-Bromo-3-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (12b)——A solution of bromine (5.75 g, 0.036 mol) in $CHCl_3$ (10 ml) was added dropwise to a refluxing solution of **12a** (5.25 g, 0.03 mol) in $CHCl_3$ (10 ml). After refluxing for a further 4 h, the reaction mixture was cooled, washed with water, dried and concentrated. The crystalline residue was recrystallized from $CHCl_3$–ether to give **12b** (7.05 g, 93%), mp 183—184 °C. IR: 1665 (C=O) cm^{-1}. MS *m/z*: 253 (M^+). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 0.94 (3H, d, J=6 Hz, CH_3), 1.7—1.9 (5H, m, $-CH_2CH_2CH-$), 6.91 (1H, d, J=9 Hz, 9-H), 7.42 (1H, dd, J=9, 2 Hz, 8-H), 7.49 (1H, d, J=2 Hz, 6-H), 9.60 (1H, NH).

3-Chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14a)——A mixture of **12a** (8.8 g, 0.05 mol), PCl_5 (22.9 g, 0.11 mol) and benzene (10 ml) was stirred at 100 °C for 1 h. The volatile materials were removed *in vacuo* and the residue was partitioned between ice-water and AcOEt. The organic layer was washed with water, dried and concentrated. The residue was recrystallized from $CHCl_3$–AcOEt to give **14a** (6.9 g, 66%), mp 180—181 °C. IR: 1655 (C=O) cm^{-1}. MS *m/z*: 209 (M^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.77 (3H, s, CH_3), 2.54 (1H, ddd, J=15.2, 6.6, 3.7 Hz, 4-H_a), 2.66 (1H, ddd, J=15.2, 11.9, 5.6 Hz, 4-H_b), 2.78 (1H, ddd, J=14.4, 5.6, 3.7 Hz, 5-H_a), 3.05 (1H, ddd, J=14.4, 11.9, 6.6 Hz, 5-H_b), 6.94 (1H, diffused d, J=7.5 Hz, 9-H), 7.12 (1H, m, 7-H), 7.20 (1H, m, 6-H), 7.25 (1H, m, 8-H), 7.74 (1H, NH). *Anal.* Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; Cl, 16.91; N, 6.68. Found: C, 62.83; H, 5.90; Cl, 17.12; N, 6.70. The same reaction, not with 2 mol but with 1 mol of PCl_5, resulted in the formation of **14a** (15%) and recovery of **12a** (52%).

7-Bromo-3-chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14b)——Compound **12b** was treated in the same manner as described for **14a** to give **14b** (55%), mp 197—199 °C ($CHCl_3$–AcOEt). IR: 1665 (C=O) cm^{-1}. MS *m/z*: 287 (M^+). *Anal.* Calcd for $C_{11}H_{11}BrClNO$: C, 45.78; H, 3.84; Br, 27.69; Cl, 12.29; N, 4.85. Found: C, 46.00; H, 3.63; Br, 27.99; Cl, 12.42; N, 4.87.

3-Methyl-2-(4-methyl-1-piperazinyl)-5*H*-1-benzazepine (16) (Typical Procedure)——A mixture of **12a** (1.75 g, 0.01 mol), PCl_5 (4.4 g, 0.021 mol) and benzene (2 ml) was stirred at 100 °C for 1 h and the volatile materials were removed *in vacuo*. *N*-Methylpiperazine (10 ml) was added to the residue, and the resulting mixture was stirred at 130 °C for 1 h. The reaction mixture was dissolved in a mixture of water and ether. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$, subsequently converted into the hydrochloride and recrystallized to give **16** (1.78 g, 51%) as a hydrate. MS *m/z*: 255 (M^+). ^{1}H-NMR

TABLE II. Physicochemical and Analytical Data for **22a**—**e** and **23a**—**c**

Compd. No.	R^1	R^2	mp (°C) Recryst. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found)				
						C	H	Cl	N	S
22a	H	H	219—222[b] A	99	$C_{16}H_{15}NS$	75.84 (76.04	5.97 6.09		5.53 5.47	12.66 12.74)
22b	Cl	H	247—249 C–A	90	$C_{16}H_{14}ClNS$	66.77 (66.99	4.90 4.78	12.32 12.56	4.87 4.86	11.14 11.24)
22c	H	2-Cl	243—244 C–A	97	$C_{16}H_{14}ClNS$	66.77 (66.87	4.90 4.99	12.32 12.53	4.87 4.78	11.14 11.13)
22d	H	4-Cl	260—262 C–A	98	$C_{16}H_{14}ClNS$	66.77 (66.76	4.90 5.20	12.32 12.59	4.87 4.76	11.14 11.19)
22e	Cl	4-Cl	220—221[c] C–A	91	$C_{16}H_{13}Cl_2NS$	59.63 (59.68	4.06 3.95	22.00 22.26	4.35 4.32	9.95 9.77)
23a	H	H	78[d] A	99	$C_{17}H_{17}NS$	76.36 (76.24	6.41 6.49		5.24 5.13	11.99 11.84)
23b	Cl	H	125—126 AE	71	$C_{17}H_{16}ClNS$	67.64 (67.37	5.34 5.23	11.75 12.01	4.64 4.61	10.62 10.70)
23c	H	2-Cl	100—101 E–M	73	$C_{17}H_{16}ClNS$	67.64 (67.36	5.34 5.10	11.75 11.78	4.64 4.57	10.62 10.92)

a) Recrystallization solvents used are as follows: A, ethanol; C, $CHCl_3$; AE, ethyl acetate; E, diethyl ether; M, methanol. *b*) Lit. mp 224—225 °C.[12] *c*) Lit. mp 267—270 °C.[12] *d*) Lit. oil.[12]

(300 MHz, D_2O) δ: 1.98 (3H, diffused s, 3-CH_3), 3.06 (3H, s, NCH_3), 3.0—4.6 (8H, m, piperazine-8H), 3.24 (1H, m, 5-H_a), 3.43 (1H, m, 5-H_b), 6.90 (1H, diffused t, J=7.8 Hz, 4-H), 7.35—7.6 (4H, m, Ar-H). Compounds **15** and **17**—**20** were prepared in a similar manner and the results are shown in Table I.

3-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-thiones (22a—e)——Compounds **21a**—**e** were treated with P_2S_5 in pyridine according to the method of Barsky and Bencze[12] to give **22a**—**e**. The results are shown in Table II.

2-Methylthio-3-phenyl-4,5-dihydro-3*H*-1-benzazepines (23a—e)——Compounds **22a**—**e** were treated with dimethyl sulfate in aqueous NaOH according to the method described[12] to give **23a**—**e**. Compounds **23a**—**c**, obtained in a crystalline form, are listed in Table II. Compounds **23d** (lit. oil[11]) and **23e** were each obtained as an oil in 80% yield.

3-(4-Chlorophenyl)-2-(4-methyl-1-piperazinyl)-4,5-dihydro-3*H*-1-benzazepine (31) (Typical Procedure)——A mixture of **23d** (9 g) and *N*-methylpiperazine (20 ml) was refluxed for 2 d. The reaction mixture was dissolved in a mixture of ether and dilute HCl. The aqueous layer was basified with dilute NaOH and extracted with ether. The organic layer was washed with water, dried and concentrated. The residue was converted into the maleate, which was recrystallized to give **31** (6.6 g, 38%). MS *m/z*: 353 (M^+). Compounds **24**—**30** and **32**—**35** were prepared in substantially the same manner and the results are shown in Table I.

2,3-Dichloro-3-phenyl-4,5-dihydro-3*H*-1-benzazepine (36a)——Procedure A[4]: A mixture of **21a** (7.12 g, 0.03 mol) and PCl_5 (13.7 g, 0.066 mol) was heated to 110 °C for 1 h. The volatile materials were removed *in vacuo*, and the residue was partitioned between ice-water and ether. The organic layer was repeatedly washed with water quickly and thoroughly, then dried and evaporated to give a crystalline residue, which was recrystallized from $CHCl_3$–ether to give **36a** (7.9 g, 97%), mp 123—124 °C. IR: 1660 (C=N) cm^{-1}. MS *m/z*: 289 (M^+). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.43 (1H, dd, J=15.4, 10.7 Hz, 4-H_a), 2.68 (1H, dd, J=15.4, 7.8 Hz, 4-H_b), 2.87 (1H, dd, J=15.6, 7.8 Hz, 5-H_a), 3.22 (1H, dd, J=15.6, 10.7 Hz, 5-H_b), 7.0—7.6 (9H, m, Ar-H). *Anal.* Calcd for $C_{16}H_{13}Cl_2N$: C, 66.22; H, 4.52; Cl, 24.44; N, 4.83. Found: C, 66.21; H, 5.59; Cl, 24.60; N, 4.71.

Procedure B: A mixture of **37a** (1.36 g, 5 mmol), PCl_5 (1.25 g, 6 mmol) and benzene (2 ml) was stirred at room temperature for 1 h. Work-up as described in procedure A gave **36a** (1.2 g, 83%), which was identical with the compound obtained in procedure A.

2,3-Dichloro-3-(4-chlorophenyl)-4,5-dihydro-3*H*-1-benzazepine (36b)[4]——Compound **21d** was treated in the same manner as described in procedure A for **39a**, except for the use of AcOEt instead of ether as the extracting solvent, to give **36b** (89%). mp 113—115 °C ($CHCl_3$–ether). IR: 1660 (C=N) cm^{-1}. MS *m/z*: 323 (M^+). *Anal.* Calcd for $C_{16}H_{12}Cl_3N$: C, 59.21; H, 3.73; Cl, 32.77; N, 4.32. Found: C, 58.82; H, 3.72; Cl, 33.02; N, 4.53.

3-Chloro-3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (37a)——A mixture of **36a** (6.8 g), acetone (100 ml) and concentrated HCl (20 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with ice-water and the resulting crystalline solid was collected. Recrystallization from $CHCl_3$–ether gave **37a** (6.1 g, 90%), mp 143—144 °C. IR: 1695 (C=O) cm^{-1}. MS *m/z*: 271 (M^+), 236 (M^+ – Cl), 208 (*m/z* 236 – CO). ^{1}H-NMR (300 MHz,

$CDCl_3$) δ: 2.84 (1H, m, H_a), 2.96 (1H, m, H_b), 3.18—3.40 (2H, m, H_c and H_d), 6.52 (1H, m, Ar-H), 6.94 (2H, m, Ar-H), 7.10 (4H, m, Ar-H), 7.24 (2H, m, Ar-H), 7.74 (1H, NH). Signals H_a, H_b, H_c and H_d were ascribable to the protons of 4-H_2 and 5-H_2. *Anal.* Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; Cl, 13.05; N, 5.16. Found: C, 70.44; H, 5.06; Cl, 13.24; N, 4.96.

3-Chloro-3-(4-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (37b)——Compound **36b** was treated in the same manner as described for **37a** to give **40b** (91%), mp 195—196 °C ($CHCl_3$–EtOH). IR: 1695 (C=O) cm^{-1}. MS *m/z*: 305 (M^+), 270 ($M^+ - Cl$), 242 (*m/z* 270 − CO). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.83 (2H, m, H_a and H_b), 3.03 (1H, m, H_c), 3.45 (1H, m, H_d), 6.53 (1H, m, Ar-H), 6.91 (2H, m, Ar-H), 7.11 (1H, m, Ar-H), 7.18 (4H, m, Ar-H), 10.02 (1H, NH). Signals H_a, H_b, H_c and H_d were ascribable to the protons of 4-H_2 and 5-H_2. *Anal.* Calcd for $C_{16}H_{13}Cl_2NO$: C, 62.76; H, 4.28; Cl, 23.16; N, 4.40. Found: C, 62.63; H, 4.30; Cl, 23.12; N, 4.58.

2-Phenyl-2-(1-piperidinylcarbonyl)-1,2,3,4-tetrahydroquinoline (38) (Typical Procedure)——A mixture of **37a** (1.3 g, 4.8 mmol) and piperidine (2.12 g, 25 mmol) was refluxed for 2 h and concentrated. The residue was dissolved in a mixture of AcOEt and water. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$ and recrystallized from $CHCl_3$–hexane to give **38** (1.5 g, 98%), mp 157—158 °C. IR: 3390 (NH), 1615 (C=O) cm^{-1}. MS (metastable ion MS) *m/z*: 320 (M^+), 208 ($M^+ - CON$⟨⟩). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.0—1.6 (6H, m, piperidine-H), 2.25 (1H, m, H_a), 2.44 (2H, m, H_b and H_c), 2.75 (1H, m, H_d), 3.2—3.4 (4H, m, piperidine-H), 4.29 (1H, NH), 6.67 (2H, m, Ar-H), 6.96 (1H, diffused d, J=8 Hz, Ar-H), 7.04 (1H, dt, J=8, 1 Hz, Ar-H), 7.2—7.4 (5H, m, Ar-H). *Anal.* Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.48; H, 7.65; N, 8.77. This was converted into the hydrochloride in a usual manner, mp 175—178 °C (MeOH–AcOEt). *Anal.* Calcd for $C_{21}H_{24}N_2O \cdot HCl \cdot 1/4H_2O$: C, 69.79; H, 7.11; Cl, 9.81; N, 7.55. Found: C, 69.76; H, 7.27; Cl, 9.65; N, 7.55. Compounds **39**—**41** were prepared in a similar manner.

39: [IR: 3390 (NH), 1615 (C=O) cm^{-1}. MS *m/z*: 335 (M^+), 208 ($M^+ - CON$⟨⟩NCH_3). A metastable ion (M^+ to *m/z* 208) was observed in the ion kinetic energy MS. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.86 (1H, m, H_a), 1.8—2.2 (4H, m, piperazine-H), 2.20 (3H, s, NCH_3), 2.30 (2H, m, H_b and H_c), 2.70 (1H, m, H_d), 3.20 (2H, br, piperazine-H), 3.3—3.7 (2H, m, piperazine-H), 6.10 (1H, s, NH), 6.51 (1H, dt, J=8, 1 Hz, Ar-H), 6.83 (2H, m, Ar-H), 6.93 (1H, dt, J=8, 1 Hz, Ar-H), 7.25—7.42 (5H, m, Ar-H). Signals H_a, H_b, H_c and H_d were ascribable to the protons of 3-H_2 and 4-H_2].

40: [IR: 3530 (OH), 3390 (NH), 1620 (C=O) cm^{-1}. MS *m/z*: 365 (M^+), 208 ($M^+ - CON$⟨⟩NCH_2CH_2OH)].

41: [IR: 3390 (NH), 1620 (C=O) cm^{-1}. MS *m/z*: 369 (M^+), 242 ($M^+ - CON$⟨⟩NCH_3)]. Other results are shown in Table I.

3-Phenyl-2,5-dihydro-1*H*-1-benzazepin-2-one (42a)——A mixture of **37a** (1.3 g, 4.8 mmol), K_2CO_3 (0.73 g, 5.3 mmol) and dioxane (20 ml) was refluxed for 3 h. The reaction mixture was diluted with water, and the resulting solid was collected (1.13 g, 96%) and recrystallized from $CHCl_3$–ether to give **42a** (0.93 g, 79%), mp 231 °C. IR: 1650 (C=O) cm^{-1}. MS *m/z*: 235 (M^+). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.35 (2H, d, J=7.3 Hz, 5-H_2), 6.78 (1H, t, J=7.3 Hz, 4-H), 7.0—7.5 (9H, m, Ar-H), 10.05 (1H, NH). *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.56; H, 5.71; N, 5.96. The ^{1}H-NMR spectrum of the crude product before recrystallization proved that **42a** was a sole product in this reaction.

3-(4-Chlorophenyl)-2,5-dihydro-1*H*-1-benzazepin-2-one (42b)——Compound **37b** was treated in the same manner as described for **42a** to give **42b** (77%), mp 220—221 °C ($CHCl_3$–ether). IR: 1650 (C=O) cm^{-1}. MS *m/z*: 269 (M^+). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.35 (2H, d, J=7.3 Hz, 5-H_2), 6.78 (1H, t, J=7.3 Hz, 4-H), 7.0—7.5 (8H, m, Ar-H), 10.05 (1H, NH). *Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49; Cl, 13.15; N, 5.19. Found: C, 70.99; H, 4.34; Cl, 12.92; N, 5.05.

Reaction of 37a with Potassium Carbonate in Methanol——A mixture of **37a** (2.72 g, 0.01 mol), K_2CO_3 (1.45 g, 0.01 mol) and MeOH (50 ml) was refluxed for 3 h and concentrated. The residue was dissolved in a mixture of $CHCl_3$ and water. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel, and elution with $CHCl_3$–hexane (1 : 1) gave firstly a solid (1.2 g) after recrystallization from $CHCl_3$–ether. The ^{1}H-NMR spectrum showed that this solid was a mixture of **42a** and **43a** in a ratio of approximately 35 : 65. A portion of this was subjected to preparative thin layer chromatography (TLC) with AcOEt–hexane (1 : 3) to afford **42a** and **43a**. Compound **42a** was identical with the compound obtained by the reaction of **37a** with K_2CO_3 in dioxane. **43a**: [mp 174—175 °C ($CHCl_3$–ether). IR: 1675 (C=O) cm^{-1}. MS *m/z*: 235 (M^+). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.78 (1H, dd, J=5.9, 1.9 Hz, 3-H), 6.06 (1H, dd, J=10, 5.9 Hz, 4-H), 6.90 (1H, dd, J=10, 1.9 Hz, 5-H), 7.0—7.5 (9H, m, Ar-H), 10.40 (1H, NH). *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.59; H, 5.63; N, 5.83]. The next fraction was recrystallized from $CHCl_3$–ether to give **44a** (1.0 g, 37%), mp 173—174 °C. IR: 1670 (C=O) cm^{-1}. MS *m/z*: 267 (M^+), 208 ($M^+ - OCH_3 - CO$). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.55 (1H, m, H_a), 2.86 (1H, m, H_b), 2.98 (2H, m, H_c and H_d), 3.02 (3H, s, OCH_3), 6.50 (1H, m, Ar-H), 7.02 (2H, m, Ar-H), 7.17 (4H, m, Ar-H), 7.27 (2H, m, Ar-H), 7.55 (1H, NH). Signals H_a, H_b, H_c and H_d were ascribable to the protons of 4-H_2 and 5-H_2. *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.41; N, 5.24. Found: C, 76.31; H, 6.47; N, 5.23.

Reaction of 37b with Potassium Carbonate in Methanol——Compound **37b** was treated in the same manner as described for the reaction of **37a**. After work-up, the crude product was chromatographed on silica gel. Elution with $CHCl_3$–hexane (1 : 1) furnished firstly **43b** (0.40 g, 19%), mp 188—189 °C ($CHCl_3$–ether). IR: 1670 (C=O) cm^{-1}. MS

m/z: 269 (M^+), 234 ($M^+ - Cl$). ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 3.77 (1H, dd, J=6, 2 Hz, 3-H), 6.00 (1H, dd, J=10, 6 Hz, 4-H), 6.89 (1H, dd, J=10, 2 Hz, 5-H), 7.0—8.5 (8H, m, Ar-H), 10.35 (1H, NH). *Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; Cl, 13.14; N, 5.19. Found: C, 71.09; H, 4.39; Cl, 13.43; N, 5.14. The second fraction gave **42b** (0.62 g, 29%) after recrystallization from $CHCl_3$–ether. This was identical with the compound obtained by the reaction of **37b** with K_2CO_3 in dioxane. The third fraction afforded **44b** (0.32 g, 13%), mp 197—199 °C ($CHCl_3$–ether). IR: 1670 (C=O) cm^{-1}. MS *m/z*: 301 (M^+), 242 ($M^+ - OCH_3 - CO$). ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 2.0—3.2 (4H, m, $-CH_2CH_2-$), 3.00 (3H, s, OCH_3), 6.8—7.4 (8H, m, Ar-H), 7.80 (1H, NH). *Anal.* Calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; Cl, 11.75; N, 4.64. Found: C, 67.77; H, 5.39; Cl, 11.90; N, 4.57.

3-Methoxy-3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (45a)——Compound **44a** (535 mg, 4 mmol) was added dropwise to a suspension of $LiAlH_4$ (152 mg, 4 mmol) in ether (40 ml) and the mixture was stirred under reflux for 8 h. Excess of the reagent was decomposed by adding AcOEt followed by tetrahydrofuran (THF) containing water and the insoluble materials were removed by filtration. The filtrate was concentrated to give a residue, which was chromatographed on silica gel with $CHCl_3$–hexane (1 : 1). The first eluate afforded **45a** (150 mg, 30%) after recrystallization from hexane. mp 76—77 °C. IR: 3360 (NH) cm^{-1}. MS *m/z*: 253 (M^+), 238 ($M^+ - CH_3$), 222 (*m/z* 238 − O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.25 (2H, m, 4-H_2), 2.74 (1H, ddd, J=15, 7, 2 Hz, 5-H_a), 3.14 (3H, s, OCH_3), 3.21 (1H, d, J=14 Hz, 2-H_a), 3.25 (1H, ddd, J=12, 11, 2 Hz, 5-H_b), 3.4 (1H, br, NH), 3.50 (1H, dd, J=14, 1 Hz, 2-H_b), 6.70 (1H, dd, J=7.5, 1 Hz, Ar-H), 6.82 (1H, dt, J=8, 1 Hz, Ar-H), 7.03 (1H, dt, J=8, 2 Hz, Ar-H), 7.10 (1H, diffused d, J=8 Hz, Ar-H), 7.28 (1H, m, Ar-H), 7.36 (2H, m, Ar-H), 7.45 (2H, m, Ar-H). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.58; H, 7.80; N, 5.46. Elution with $CHCl_3$ gave the unchanged starting material (300 mg, 56%).

3-(4-Chlorophenyl)-3-methoxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (45b)——Compound **44b** was treated in the same manner as described for **45a**, except for the use of THF instead of ether as the solvent, to give **45b** as an oil. Yield 50%. IR (neat): 3360 (NH) cm^{-1}. MS *m/z*: 287 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.1—3.7 (6H, m, $-CH_2CH_2-$ and NCH_2-), 3.02 (3H, s, OCH_3), 3.50 (1H, NH), 6.5—7.6 (8H, m, Ar-H).

3-Chloro-3-phenyl-1,2,3,4,5,6-hexahydro-1-benzazocin-2-one (46a)——A mixture of **5a** (7.54 g, 0.03 mol) and PCl_5 (13.7 g, 0.066 mol) was treated as described in the preparation of **8**, and the crude **6a** obtained was dissolved in a mixture of acetone (180 ml) and concentrated HCl (30 ml). After being kept for 2 d at room temperature, the reaction mixture was diluted with ice-water. The resulting solid was collected, washed with ether and recrystallized from $CHCl_3$–ether to give **46a** (5.3 g, 62%). mp 192—194 °C. IR: 1645 (C=O) cm^{-1}. MS *m/z*: 285 (M^+), 250 ($M^+ - Cl$). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.57 (1H, m, 5-H_a), 1.89 (1H, m, 6-H_a), 2.02 (1H, m, 6-H_b), 2.37 (1H, m, 5-H_b), 2.64 (1H, m, 4-H_a), 2.82 (1H, m, 4-H_b), 7.04 (1H, m, Ar-H), 7.1—7.6 (8H, m, Ar-H), 9.84 (1H, NH). *Anal.* Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.46; Cl, 12.41; N, 4.90. Found: C, 71.18; H, 5.67; Cl, 12.64; N, 4.82.

3-Chloro-3-(4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1-benzazocin-2-one (46b)——Compound **5b** was treated in the same manner as described for **46a** to give **46b** (69%), mp 157—158 °C ($CHCl_3$–ether). IR: 1655 (C=O) cm^{-1}. MS *m/z*: 319 (M^+), 284 ($M^+ - Cl$). ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 1.4—3.0 (6H, m, $-CH_2CH_2CH_2-$), 6.9—7.7 (8H, m, Ar-H), 9.82 (1H, NH). *Anal.* Calcd for $C_{17}H_{15}Cl_2NO$: C, 63.76; H, 4.72; Cl, 22.14; N, 4.37. Found: C, 63.68; H, 4.71; Cl, 22.03; N, 4.17.

2-Phenyl-2-(1-piperidinylcarbonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (47) (Typical Procedure)——A mixture of **46a** (0.85 g) and piperidine (2 ml) was refluxed for 2 h, and dissolved in a mixture of AcOEt and water. The organic layer was washed with water, dried and concentrated. The crystalline residue was crystallized from AcOEt–ether to give **47** (0.95 g, 95%), mp 128—129 °C. IR: 3325 (NH), 1615 (C=O) cm^{-1}. MS (metastable ion MS) *m/z*: 334 (M^+), 222 ($M^+ - CON$⟨⟩). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (4H, m, piperidine-H), 1.50 (2H, m, piperidine-H), 1.60 (1H, m, 4-H_a), 1.90 (1H, m, 4-H_b), 2.04 (1H, m, 3-H_a), 2.33 (1H, m, 3-H_b), 2.68 (1H, m, 5-H_a), 2.88 (1H, m, 5-H_b), 3.22 (2H, m, piperidine-H), 3.45 (4H, m, piperidine-H), 4.08 (1H, NH), 6.71 (1H, m, Ar-H), 6.90 (1H, m, Ar-H), 7.04 (2H, m, Ar-H), 7.30 (1H, m, Ar-H), 7.37 (2H, m, Ar-H), 7.55 (2H, m, Ar-H). The assignment of six proton signals at δ 1.60—2.88 was made on the basis of the spin decoupling results. *Anal.* Calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.83; H, 8.05; N, 8.52. This was converted into the hydrochloride in a usual manner. mp 152—154 °C (MeOH–AcOEt). IR: 1645 (C=O) cm^{-1}. *Anal.* Calcd for $C_{22}H_{26}N_2O \cdot HCl \cdot 1/4H_2O$: C, 70.38; H, 7.38; Cl, 9.44; N, 7.46. Found: C, 70.58; H, 7.58; Cl, 9.36; N, 7.34.

Compound **48** was prepared in a similar manner. Yield 95%, mp 164—165 °C ($CHCl_3$–ether). IR: 3350 (NH), 1620 (C=O) cm^{-1}. MS (secondary ion MS) *m/z*: 369 (MH^+), 256 ($M^+ - CON$⟨⟩). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.1—3.7 (16H, m, $-CH_2CH_2CH_2-$ and piperidine-H), 4.03 (1H, NH), 6.6—7.6 (8H, m, Ar-H). *Anal.* Calcd for $C_{22}H_{25}ClN_2O$: C, 71.63; H, 6.83; Cl, 9.61; N, 7.59. Found: C, 71.49; H, 6.91; Cl, 9.53; N, 7.49. This was converted into the hydrochloride in a usual manner. mp 163 °C (MeOH–AcOEt). IR: 1615 (C=O) cm^{-1}. *Anal.* Calcd for $C_{22}H_{25}ClN_2O \cdot HCl \cdot 3/4H_2O$: C, 63.08; H, 6.62; Cl, 16.93; N, 6.69. Found: C, 62.84; H, 6.57; Cl, 17.14; N, 6.57.

3-Methyl-2,3-dihydro-1*H*-1-benzazepin-2-one (49)——A mixture of **14a** (0.42 g) and *N*-methylpiperazine (2 ml) was stirred at 120 °C for 3 h. The reaction mixture was dissolved in a mixture of water and ether. The organic layer was washed with water, dried and concentrated. The residue, showing a single spot on TLC, was recrystallized from AcOEt–hexane, affording **49** (0.25 g, 72%), mp 144—146 °C. IR: 1650 (C=O) cm^{-1}. MS *m/z*: 173 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.42 (3H, d, J=7 Hz, CH_3), 2.56 (1H, m, 3-H), 5.64 (1H, dd, J=10, 5 Hz, 4-H), 6.71 (1H, dd, J=

10, 2 Hz, 5-H), 7.0—7.5 (4H, m, Ar-H), 9.26 (1H, NH). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.21; H, 6.47; N, 7.95.

Methyl 2-Methyl-1,2,3,4-tetrahydro-2-quinolinecarboxylate (50)——A mixture of **14a** (1.05 g, 5 mmol), K_2CO_3 (0.73 g, 5.3 mmol) and MeOH (25 ml) was refluxed for 4 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried and concentrated to give **50** (0.70 g, 68%) as an oil, which showed a single spot on TLC. IR (neat): 3380 (NH), 1730 (C=O) cm^{-1}. MS *m/z*: 205 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.44 (3H, s, CH_3), 1.5—2.9 (4H, m, $-CH_2CH_2-$), 3.70 (3H, s, $COOCH_3$), 4.3 (1H, NH), 6.5—7.1 (4H, m, Ar-H). This was converted into the hydrochloride in a usual manner. mp 148—151 °C (EtOH–AcOEt). IR: 1745 (C=O) cm^{-1}. *Anal.* Calcd for $C_{12}H_{15}NO_2 \cdot HCl$: C, 59.62; H, 6.67; Cl, 14.67; N, 5.80. Found: C, 59.58; H, 6.88; Cl, 14.78; N, 5.74.

Pharmacological Methods——Male Std-ddY strain mice (Shizuoka Lab. Animal Center, Shizuoka, Japan), weighing 20—25 g, were employed in the experiments. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and orally administered to groups of five mice. Detailed experimental methods for evaluating antagonistic effects on exploratory activity, hypothermia induced by reserpine, maximal electroshock seizure and tremor induced by tremorine were described earlier.[4]

Acknowledgements We wish to thank Dr. M. Hashimoto, the director of this laboratory, and Drs. J. Matsumoto and S. Naruto for their encouragement throughout this work. Thanks are also due to Dr. T. Karasawa for the biological evaluation, Mr. A. Itokawa for nuclear magnetic resonance spectral measurements and the staff of the analytical section of this laboratory for elemental analyses and spectral measurements.

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