Cyclic Guanidines. Part 2.[1] Rearrangement of *N*-Substituted 2-Arylamino-4,5,6,7-tetrahydro-1*H*-1,3-diazepines. *X*-Ray Molecular Structure of 1-(2,6-Dichlorophenyl)-2-(2-methylallylimino)hexahydro-1,3-diazepine

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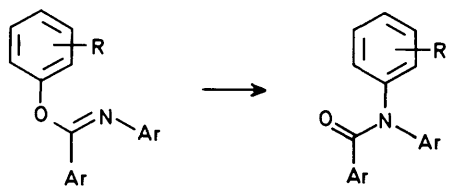
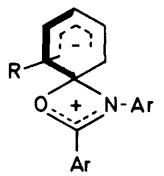
1,3-Aryl migrations of title compounds (**2**) are shown to be triggered by base catalysis under mild conditions. Alternative rearrangement conditions, limiting factors, as well as the occurrence of by-products, and competing products are investigated. A crossover experiment reveals the purely intramolecular nature of the Chapman-type rearrangement. The structure of the rearrangement product 1-(2,6-dichlorophenyl)-2-(2-methylallylimino)hexahydro-1,3-diazepine (**3a**) is confirmed by *X*-ray analysis. An explanation for the directionality of the reaction is furnished by an MNDO calculation on the reaction enthalpy.

1,3-Aryl migrations which proceed *via* 4-membered-ring transition states are well known from the literature.[2–4] A thoroughly investigated example is the Chapman rearrangement [equation (1)], which repeatedly has been shown to constitute



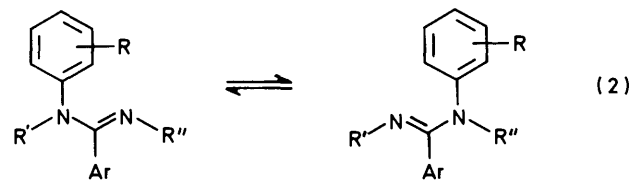
(1)

an intramolecular process;[5] a zwitterionic spiro transition state (**1**) can be postulated.



(1)

This migration requires drastic conditions and usually does not occur at temperatures below 160 °C. The same holds true for the analogous amidine rearrangement [equation (2)], which also was originally described by Chapman.[6]

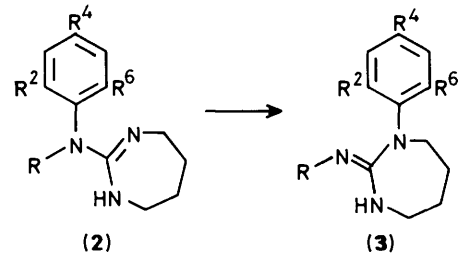


(2)

This aryl shift can be facilitated by attaching several electron-attracting substituents onto the migrating phenyl group.[7] To our knowledge this rearrangement has not been used preparatively, since it is reversible and yields equilibrium mixtures.

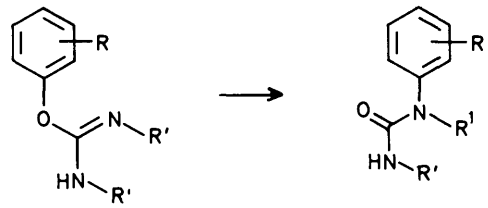
Results and Discussion

The present paper reports a rearrangement (3), which can be considered a special case of the amidine rearrangement. The reaction could be carried out under basic or neutral conditions.



(3)

The base-catalysed migration [KOBu^t–dimethyl sulphoxide (DMSO)] proceeded smoothly at room temperature and constitutes the typical procedure, by which all the examples in Table 1 have been prepared. This reaction is closely related to the Chapman-type isourea rearrangement [equation (4)], which



(4)

is also catalysed by base at ambient temperature and therefore can be called an anionic rearrangement.[8] All base-catalysed migrations—as judged by t.l.c.—proceeded to completion.

Neutral reaction conditions [dimethylformamide (DMF); 100—120 °C] were less generally applicable, but seemed to work if the aromatic ring was sufficiently electron deficient. In this fashion (**3j**) and (**3l**) (R = CH_2CH_2Ph, $R^2 = R^6 = Me$, $R^4 = NO_2$) could be prepared in reasonable yields. In the latter case an equilibrium of educt/product ratio ~1:4 was observed.

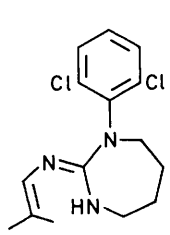
In a number of cases (Table 1) side products could be detected: product (**3a**) was accompanied by 5% of its isomer (**4a**), which in addition to the aryl migration, had suffered a double-bond migration within the alkenyl chain.

The low yield of compound (**3f**) is well explained by the formation of two by-products (**5f**) and (**6f**). Amine (**5f**) constitutes the rearranged molecule which has lost the allyl group. The cyclization products (**6f**), (**6g**), and (**6i**) could mostly be observed when the phenyl group was substituted by three halogens.

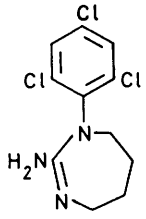
Table 1. Rearrangement products (**3**)[a] obtained from reactants (**2**) by the typical procedure (see Experimental section for details)

Compound	R^2	R^4	R^6	R	Yield (%)	M.p. (°C)	δ_H[b]	By-products
(**3a**)	Cl	H	Cl	$CH_2C(Me)=CH_2$	65	46—49	3.58 (s, 2 H)	(**4a**)
(**3b**)	Cl	H	Cl	$CH_2CH=CHMe$	34	Oil	3.54 (br m, 2 H)	
(**3c**)	Cl	H	Cl	CH_2Ph	83	104—107[c]	4.29 (s, 2 H)	
(**3d**)	Cl	H	Cl	$CH_2C_6H_4Me$-*m*	73	214—215[c]	4.28 (s, 2 H)	
(**3e**)	Cl	H	Cl	$CH_2C=CH(CH_2)_3CH_2$	81	96—98[c]	3.56 (s, 2 H)	
(**3f**)	Cl	Cl	Cl	$CH_2CH=CH_2$	24	205—207[c]	3.68 (m, 2 H)	(**5f**) + (**6f**)
(**3g**)	Cl	Cl	Cl	$CH_2C(Me)=CH_2$	54	77—79	3.60 (s, 2 H)	(**6g**)
(**3h**)	Cl	Cl	Cl	CH_2Ph	53	137—138[c]	4.31 (s, 2 H)	
(**3i**)	Cl	Cl	Cl	$CH_2C_6H_4Me$-*m*	63	204—207[c]	4.28 (s, 2 H)	(**6i**)
(**3j**)	Me	NO_2	Me	$CH_2C(Me)=CH_2$	61	108—110	3.58 (s, 2 H)	
(**3k**)	Me	NO_2	Me	CH_2Ph	46	230—233[c]	4.30 (s, 2 H)	

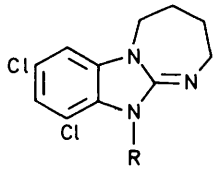
[a] Satisfactory analytical data (±0.4% for C, H, Cl, and N, except (**3g**): C, −0.41%; Cl, −0.53%; (**3h**): Cl, −0.94%; and (**3i**): C, −0.48%; Cl, −0.63%; N, 0.41%). [b] Free bases; signal of $NCH_2C\geqslant$; solvent $CDCl_3$. [c] Hydrochloride.



(**4a**)

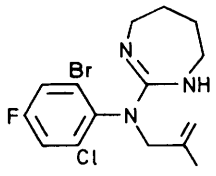


(**5f**) (3.8%)

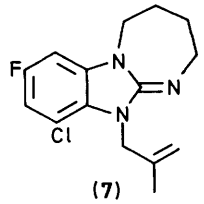


(**6f**) (18%)
(**6g**) (12%)
(**6i**) (9%)

If one of the *ortho* substituents was bromine instead of chlorine, the ring closure became the dominant event and the rearrangement product was not observed [equation (5)].

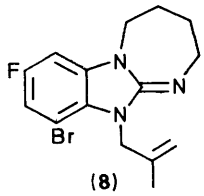


(**2m**)



(**7**)

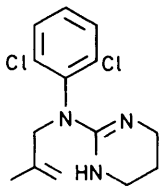
+ (5)



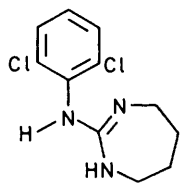
(**8**)

According to g.c.–m.s. the two cyclization products (**7**) and (**8**) were formed in 95:5 ratio. The favoured cyclization is closely paralleled by the observations of Reineke[9] concerning side reactions of the rearrangement of thiocarbamates.

The aryl migration could not be achieved if, as in educt (**9**), the diazepine ring was replaced by a pyrimidine ring, nor when the side chain R was absent as in structure (**2n**).

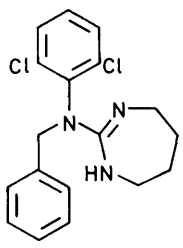


(**9**)

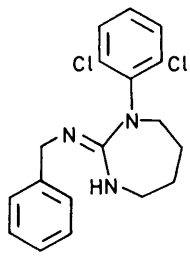


(**2n**)

As far as the reaction mechanism is concerned, we were able to establish an intramolecular process. For this purpose a crossover experiment [equation (6)] with a 1:1 mixture of

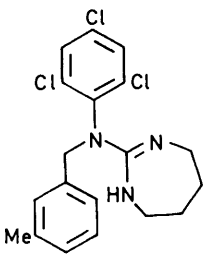


(**2c**)

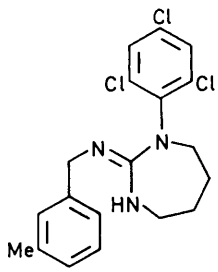


(**3c**)

$KOBu^t$ / DMSO (6)



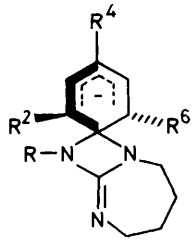
(**2i**)



(**3i**)

compounds (**2c**) and (**2i**) as starting material was conducted. The crossover products (**3d**) and (**3h**), which would be expected if the reaction proceeded intermolecularly, were prepared by a separate synthesis (see Table 1). H.p.l.c. analysis of the crossover reaction products revealed that [apart from cyclization

products of type (**6**)] (**3c**) and (**3i**)) were the main products and no trace of the crossover products (**3d**) and (**3h**) was detected. This finding gives clear evidence for the intramolecular nature of the transformation and, in analogy to related rearrangements, the spiro transition state (**10**) is postulated.



(**10**)

The principal arguments for the ease of the base-catalysed migration are the high nucleophilicity of the negatively charged guanidino group, which triggers the internal S_NAr reaction, and the more favourable anionic intermediate structure (**10**) as compared with the zwitterionic transition state (**1**). This interpretation is in accord with the finding concerning the anionic low-temperature rearrangement of *O*-arylisoureas.[8]

The relatively mild conditions for the thermal rearrangement may be explained by the more advantageous charge distribution within the guanidinium moiety in a transition state of type (**1**). Whether or not the two *ortho* substituents in the aryl group facilitate the migration by 'steric acceleration due to hindered rotation,' as suggested for the Chapman[10] and the thiocarbamate rearrangements,[11] will be subject to further investigations.

Molecular structure of compounds (**3**) was initially analysed by the ^1H n.m.r. spectra which yielded a completely analogous but substantially shifted set of resonances in comparison with those of compounds (**2**). The NCH_2 signals of the side chains in the rearranged isomers are characteristically shifted upfield by an average 0.6 p.p.m. (Table 1). Definite proof of the structure of the rearrangement product was furnished by the *X*-ray analysis of compound (**3a**), which was crystallized as the hydrochloride dihydrate. A representation of the protonated molecule is given in the Figure. Final non-H atomic positional parameters are presented in Table 2.

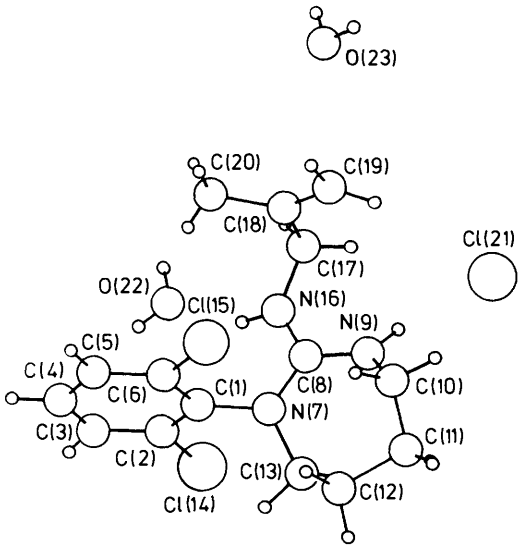


Figure. Computer drawing of the calculated conformation of (**3a**)

Table 2. Fractional co-ordinates (× 10^4) for compound (**3a**) with e.s.d.s in parentheses

Atom	*x*	*y*	*z*
C(1)	−1 545(4)	1 318(2)	−883(4)
C(2)	−2 508(5)	929(2)	−1 609(4)
C(3)	−3 358(5)	1 039(2)	−2 965(5)
C(4)	−3 205(5)	1 540(2)	−3 578(4)
C(5)	−2 257(5)	1 940(2)	−2 917(5)
C(6)	−1 444(4)	1 824(2)	−1 547(4)
N(7)	−726(3)	1 209(1)	529(3)
C(8)	826(4)	1 109(2)	662(4)
N(9)	1 681(4)	1 190(2)	1 933(3)
C(10)	1 364(6)	1 616(2)	2 999(5)
C(11)	102(6)	1 473(3)	3 905(5)
C(12)	−1 506(7)	1 503(3)	2 935(6)
C(13)	−1 636(5)	1 101(2)	1 765(5)
Cl(14)	−2 625(2)	287(1)	−871(2)
Cl(15)	−290(2)	2 329(0)	−668(1)
N(16)	1 440(3)	924(1)	−495(3)
C(17)	3 108(4)	956(2)	−637(5)
C(18)	3 569(5)	1 519(2)	−1 050(5)
C(19)	4 516(6)	1 813(2)	−142(7)
C(20)	2 910(7)	1 704(3)	−2 581(6)
Cl(21)	4 859(1)	757(1)	3 375(1)
O(22)	278(4)	403(2)	−3 181(3)
O(23)	7 555(4)	4 935(2)	124(4)

The protonation occurs on the exocyclic nitrogen N(16). The short C(8)–N distances are indicative of double-bond character. The geometry around C(8) is planar and almost trigonal although the C(8)–N(7) distance is 0.038 Å longer than the mean value of C(8)–N(9) and C(8)–N(16) (1.324 Å). The sum of the bond angles at C(8) is 360°. This planar geometry for the guanidinium cation and these differences in the C–N bond lengths have been observed in several imidazolidines and dihydroimidazoles.[12] One can also note a difference between C(11)–C(10) = 1.494(7) Å and C(12)–C(13) = 1.449(8) Å. The shortening of the latter distance is balanced by a lengthening of C(11)–C(12) = 1.562(8) Å. No explanation is proposed for this observation. Other bond lengths and angles are as expected.

In order to obtain insight into the thermodynamics of the rearrangement reaction, MNDO calculations were performed on both educt (**2a**) and product (**3a**). The semiempirical MNDO method has been parameterized with particular emphasis on the calculation of heat of formation values[13] and is the method of choice for these molecules. For (**2a**) and (**3a**) the calculated heats of formation were 54.2 and 49.9 kcal mol^{-1}, respectively, showing the product to be stabilized by 4.3. kcal mol^{-1} relative to the starting compound. This result gives an explanation for the directionality of the reaction.

The tautomeric shift from the exo- to the endo-cyclic double bond in structure (**3a**) yields an additional energy gain of *ca.* 0.5 kcal mol^{-1}. However, this value is only approximate, due to the limited accuracy of the MNDO method.

First results obtained with the AMPAC program[14] and the new AM1 Hamiltonian[15] confirm the energy stabilization of structure (**3a**) with respect to structure (**2a**) found with MNDO.

Experimental

M.p.s were determined on a Büchi 510 melting point apparatus and are uncorrected. ^1H N.m.r. spectra of the free bases were measured, unless stated otherwise, on a Bruker WH-90 MHz spectrometer. G.c.–m.s. analysis was performed on a Nermag 10-10 C instrument in electron-impact mode. A 10 m CP-SIL 19 CB fused silica column was employed.

Preparation of 2-[N-*Benzyl*-N-(2,6-*dichlorophenyl*)*amino*]-4,5,6,7-*tetrahydro*-1H-1,3-*diazepine* (**2c**).—*Typical procedure.* 2-(2,6-Dichlorophenylamino)-4,5,6,7-tetrahydro-1H-1,3-diazepine (12.91 g, 50 mmol) was dissolved in acetonitrile (130 ml), benzyl bromide (9.41 g, 55 mmol) was added, and the mixture refluxed for 1 h. After cooling, the precipitated white crystals were separated by suction, washed successively with acetonitrile and ether, and dried to give the salt (**2c**)·HBr (18.3 g, 85%), m.p. 261—262 °C; R_F (silica gel) 0.26 [mobile phase toluene–dioxane–ethanol–ammonia (10:8:3:1)] (Found: C, 50.1; H, 4.7; Br, 18.5; Cl, 15.9; N, 10.1. $C_{18}H_{19}Cl_3N_2$·HBr requires C, 50.37; H, 4.70; Br, 18.62; Cl, 16.52; N, 9.79%); $\delta_H(CDCl_3)$ 1.61 (s, 4 H), 2.86 (br, 2 H), 3.41 (br, 2 H), 3.60 (br, 1 H), 4.85 (s, 2 H), and 7.05—7.33 (m, 8 H).

Rearrangement of Compound (**2c**).—*Typical procedure.* 2-*Benzylimino*-1(2,6-*dichlorophenyl*)*hexahydro*-1,3-*diazepine* (**3c**). Compound (**2c**)·HBr was transformed into the corresponding base as follows: a suspension of the salt (15.9 g) in water (100 ml) was made strongly alkaline by addition of 5M-NaOH and the precipitated crystals were separated by suction, washed with water, and dried to yield free base (**2c**) (12.8 g).

Free base (**2c**) (11.8 g, 33.9 mmol) was suspended in dry DMSO (43 ml) and potassium t-butoxide (0.48 g, 4.24 mmol) was added. The resulting yellow solution was stirred at room temperature for 2.3 h; after that time t.l.c. showed the reaction to be complete. The reaction mixture was poured into ice-cold water (400 ml), and the mixture was made alkaline by addition of 5M-NaOH, then extracted twice with ether, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield a yellow oil (11.7 g), which was taken up in ether. Addition of water (200 ml) and 2M-HCl (18 ml) caused a precipitate to form, which was washed with ether and dried to give the salt (**3c**)·HCl (6.78 g) as white crystals, m.p. 104—107 °C. The aqueous phase of the mother liquor was neutralized by addition of 2M-NaOH (pH 7), and extracted with ether. The aqueous layer was made alkaline by stepwise addition of a 2M-NaOH (5 × 1.5 ml) and each time extracted with ether. After t.l.c. analysis the ether extracts 2—5 were combined, and concentrated under reduced pressure and the residue taken up in ether (40 ml); the solution was mixed with water (20 ml) and adjusted to pH 2 by addition of 2M-HCl. The precipitated crystals were washed successively with little water and ether, and dried to yield another crop of *compound* (**3c**)·HCl (4.05 g) as white crystals, m.p. 104—107 °C. Total yield 10.83 g (83%); R_F (silica gel) 0.36 [mobile phase toluene–dioxane–ethanol–ammonia (10:8:3:1)] (Found: C, 55.85; H, 5.2; Cl, 27.4; N, 10.6. $C_{18}H_{19}Cl_2N_3$·HCl requires C, 56.19; H, 5.24; Cl, 27.64; N, 10.92%); $\delta_H(CDCl_3)$ 1.59—1.87 (m, 4 H), 3.10—3.63 (m, 5 H), 4.29 (s, 2 H), and 7.05—7.41 (m, 8 H).

Rearrangement of 2-[N-(2,6-*Dichlorophenyl*)-N-(2-*methylallyl*)*amino*]-4,5,6,7-*tetrahydro*-1H-1,3-*diazepine* (**2a**) *to* 1-(2,6-*Dichlorophenyl*)-2-(2-*methylallylimino*)*hexahydro*-1,3-*diazepine* (**3a**) *and* 1-(2,6-*Dichlorophenyl*)-2-(2-*methylprop*-1-*enylimino*)*hexahydro*-1,3-*diazepine* (**4a**).—Compound (**2a**) (free base; 22.2 g, 71.1 mmol) was treated with KOBu^t in DMSO as described in the typical procedure and the mixture was stirred for 19 h, poured into ice-cold water (1 l), and extracted with ether (3 × 200 ml) and the combined extracts were extracted with 0.3M-HCl (286 ml). After extraction of the acidic aqueous layer with ether, 2M-NaOH (6 × 3 ml) was added portionwise to the aqueous phase, followed each time by an extraction step with ether (total 6 × 100 ml). Finally the aqueous phase was made strongly alkaline by addition of 5M-NaOH and extracted with ether (2 × 100 ml). After t.l.c. analysis the last two ether extracts were combined with extracts 5 and 6 of the stepwise extraction, dried, and concentrated under reduced pressure to yield *compound* (**3a**) as a cream-coloured oil (14.5 g, 65%), which solidified after one month, m.p. 46—49 °C (Found: C, 57.55; H, 6.0; Cl, 23.0; N, 13.2. $C_{15}H_{19}Cl_2N_3$ requires C, 57.70; H, 6.13; Cl, 22.71; N, 13.46%); $\delta_H(CDCl_3)$ 1.48—1.97 (m, 7 H), 3.28—3.76 (m, 7 H), 4.48—4.86 (m, 2 H), and 7.04—7.48 (m, 3 H).

The free base (**3a**) (2.2 g) was transformed to the corresponding hydrochloride by treatment of an ether solution of (**3a**) with 2M-HCl. The white crystals obtained were recrystallized from ethanol to give compound (**3a**) (1.4 g) as its *hydrochloride dihydrate*, which was used for the *X*-ray analysis; m.p. 201—203 °C (Found: C, 46.9; H, 6.0; Cl, 27.3; N, 11.1. $C_{15}H_{19}Cl_2N_3$·HCl·$2H_2O$ requires C, 46.83; H, 6.29; Cl, 27.64; N, 10.92%).

Ether extract 2 of the aforementioned stepwise extraction contained, according to t.l.c., a second product. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to leave an oily residue, which crystallized after a short time. The white crystals were treated with cyclohexane, separated by suction, washed with cyclohexane and light petroleum (b.p. 40—80 °C), and dried to yield *compound* (**4a**) (1.04 g, 5%), m.p. 114—116 °C (Found: C, 57.7; H, 6.1; Cl, 22.8; N, 13.4. $C_{15}H_{19}Cl_2N_3$ requires C, 57.70; H, 6.13; Cl, 22.71; N, 13.46%); $\delta_H(CDCl_3)$ 1.51 (s, 3 H), 1.60 (s, 3 H), 1.65—1.88 (m, 4 H), 3.26—3.65 (m, 5 H), 6.07 (s, 1 H), and 7.10—7.46 (m, 3 H).

Rearrangement of 2-[N-*Allyl*-N-(2,4,6-*trichlorophenyl*)-*amino*]-4,5,6,7-*tetrahydro*-1H-1,3-*diazepine* (**2f**) *to* 2-*Allylimino*-1-(2,4,6-*trichlorophenyl*)*hexahydro*-1,3-*diazepine* (**3f**), 2-*Amino*-1-(2,4,6-*trichlorophenyl*)-4,5,6,7-*tetrahydro*-1H-1,3-*diazepine* (**5f**) *and* 11-*Allyl*-8,10-*dichloro*-2,4,5,11-*tetrahydro*-3H-[1,3]-*diazepino*[1,2-a]*benzimidazole* (**6f**).—Compound (**2f**) (free base; 19.96 g, 60 mmol) was dissolved in DMSO (79 ml), treated with KOBu^t (2.84 g, 25.3 mmol), and the solution was stirred at room temperature 21 h. Because t.l.c. showed the reaction to be incomplete, more KOBu^t (2 g, 17.8 mmol) was added and the mixture was agitated for another 3 h. After addition of ether (200 ml) and 1M-NaOH (700 ml) the mixture was shaken and the organic layer was separated. The aqueous phase was once more extracted with ether and the combined organic phases were evaporated to dryness to yield a sherry-coloured oil (19 g). The residue was subjected to column chromatography on silica gel with tetrahydrofuran (THF)–MeOH (4:1) as eluant which resulted in the collection of fractions 1—6. Final elution of the column with THF–MeOH–ammonia (18:4:3) gave fraction 7.

After t.l.c. analysis, fractions 5 and 6 were combined and the single product was transformed into its hydrochloride by addition of ethereal HCl, to give the *salt* (**3f**)·HCl (5.4 g, 24%), m.p. 205—207 °C (Found: C, 45.5; H, 4.7; Cl, 38.35; N, 11.3. $C_{14}H_{16}Cl_3N_3$·HCl requires C, 45.56; H, 4.64; Cl, 38.42; N, 11.38%); $\delta_H(CDCl_3)$ 1.57—1.95 (m, 4 H), 3.29—3.66 (m, 4 H), 3.66—3.85 (m, 2 H), 4.79—5.20 (m, 2 H), 5.56—6.06 (m, 1 H), and 7.35 (s, 2 H).

Fraction 7 was concentrated under reduced pressure and the residue was mixed with ether, to cause precipitation of white crystals which were washed with ether and dried to give *compound* (**5f**) (0.67 g, 3.8%), m.p. 180—181 °C (Found: C, 44.9; H, 4.1; Cl, 35.7; N, 14.1. $C_{11}H_{12}Cl_3N_3$ requires C, 45.15; H, 4.13; Cl, 36.35; N, 14.36%); $\delta_H(CDCl_3)$ 1.75 (br s, 4 H), 3.12—3.76 (m, 4 H), 4.36 (br s, 2 H), and 7.43 (s, 2 H).

Fractions 2 and 3 were combined, evaporated to dryness, and, by addition of ethereal HCl, transformed to the hydrochloride, to give the *salt* (**6f**)·HCl (3.65 g), m.p. 250—251 °C (Found: C, 50.3; H, 4.8; Cl, 31.7; N, 12.55. $C_{14}H_{15}Cl_2N_3$·HCl requires C, 50.55; H, 4.85; Cl, 31.97; N, 12.63%); $\delta_H(CDCl_3)$ 1.79—2.28 (m, 4 H), 3.50—3.91 (m, 4 H), 4.66—5.34 (m, 4 H), 5.73—6.21 (m, 1 H), 6.65 (d, 1 H), and 6.88 (d, 1 H).

Rearrangement of 2-[N-(2,6-*Dimethyl*-4-*nitrophenyl*)-N-*phenethylamino*]-4,5,6,7-*tetrahydro*-1H-1,3-*diazepine* (**2l**) *under Neutral Conditions.* 1-(2,6-*Dimethyl*-4-*nitrophenyl*)-2-*phenethyliminohexahydro*-1,3-*diazepine* (**3l**).—Compound (**2l**) (free base; 0.62 g, 1.69 mmol) was combined with DMF (13 ml) and heated for 4.25 h at 120 °C. T.l.c. revealed a conversion rate of ~80%. The solution was concentrated under reduced pressure and the resulting oil was taken up in 2M-HCl (~5 ml) which caused crystals to precipitate. These were separated by suction, washed successively with water and ether, and dried, to give the guanidine (**3l**) (0.34 g, 50%) as its hydrochloride hemihydrate, m.p. 220—226 °C (Found: C, 61.0; H, 7.0; Cl, 8.6; N, 14.0. $C_{21}H_{26}N_4O_2$·HCl·0.5H_2O requires C, 61.23; H, 6.85; Cl, 8.61; N, 13.60%); δ_H($CDCl_3$; Bruker 250 MHz) 1.45—2.0 (m, 4 H), 2.20 (s, 6 H), 2.62 (t, *J* 6.5 Hz, 2 H), 2.98—3.48 (m, 6 H, 3 NCH_2), 3.58 (br s, 1 H), 6.71—7.35 (m, 5 H), and 7.87 (s, 2 H).

When a sample of (**3l**) (free base) was heated in DMF for 3 h at 120 °C, t.l.c. showed an equilibrium mixture of estimated ratio (**2l**):(**3l**) = 1:4.

Cyclization of 2-[N-(2-*Bromo*-6-*chloro*-4-*fluorophenyl*)-N-(2-*methylallyl*)*amino*]-4,5,6,7-*tetrahydro*-1H-1,3-*diazepine* (**2m**) *to* 10-*Chloro*-8-*fluoro*-11-(2-*methylallyl*)-2,4,5,11-*tetrahydro*-3H-[1,3]*diazepino*[1,2-a]*benzimidazole* (**7**) *and* 10-*Bromo*-8-*fluoro*-11(2-*methylallyl*)-2,4,5,11-*tetrahydro*-3H-[1,3]*diazepino*[1,2-a]*benzimidazole* (**8**).—Compound (**2m**) (free base; 3.1 g. 8.27 mmol) was dissolved in DMSO (10.5 ml), treated with KOBu^t (0.12 g, 1 mmol), and the solution was kept for 65 h at room temperature. T.l.c. showed no rearrangement product, mostly starting material, and one new substance to be present. Therefore additional KOBu^t (0.82 g, 7.3 mmol) was added and after 21 h at ambient temperature t.l.c. indicated the reaction to be complete. The reaction mixture was poured into water, adjusted to pH 10 by addition of 10M-NaOH, and extracted with ether. and the extract was dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was chromatographed on a short column of silica gel with ethyl acetate–MeOH (1:1) as eluant. The eluted compounds were crystallized from ether to give a mixture of products (**7**) and (**8**) (1.1 g) as a slightly yellow coloured substance. T.l.c. showed one spot, R_F 0.7 [silica gel; toluene–dioxane–ethanol–ammonia (10:8:3:1)]. G.c.–m.s. showed 2 fractions, peak area ratio 95:5. The major, earlier eluting fraction had M^+, 293/295 [(**7**)], the minor, later eluting fraction M^+, 337/339 [(**8**)].

Crossover Experiment.—Compound (**2c**) (1.04 g, 3 mmol) and 2-[*N*-(*m*-methylbenzyl)-*N*-(2,4,6-trichlorophenyl)amino]-4,5,6,7-tetrahydro-1H-1,3-diazepine (**2i**) (1.19 g, 3 mmol) were dissolved in DMSO (7.6 ml), KOBu^t (0.17 g, 1.5 mmol) was added, and the reaction mixture was stirred for 24 h at room temperature. T.l.c. revealed, apart from a trace of unchanged (**2c**), that the reaction was complete. The reaction mixture was diluted with ethyl acetate and shaken with 1M-NaOH, and the organic layer was filtered, and concentrated under reduced pressure. After the residue had been dissolved in ether, the solution was shaken with 1M-NaOH, and the ether phase was filtered, and concentrated under reduced pressure to yield a cream-coloured oil (2.11 g). H.p.l.c. on a stainless steel column (150 × 4.5 mm i.d.) with stationary phase Nucleosil 120—127 °C, 18; mobile phase acetonitrile–0.01M aqueous ammonium carbonate–diethylamine (850:150:5 v/v/v); flow rate 2 ml min^{-1}; and u.v. detection at 254 nm showed the principal products to be (**3c**), (**3i**), and (**6i**). Among 10 detectable side products no traces of the crossover products (**3d**) or (**3h**) could be found.

X-*Ray Analysis of Compound* (**3a**).—*Crystal data.* $C_{15}H_{19}Cl_2N_3$·HCl·2H_2O, *M* = 384.7. Monoclinic, *a* = 8.677(3), *b* = 24.402(10), *c* = 9.173(3) Å, β = 97.02(2)°, *V* = 1 927.7 Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 1.541 78 Å), space group $P2_1/n$ (alt. $P2_1/c$, No. 14), *Z* = 4, D_x = 1.32 g cm^{-3}. Colourless blocks (from ethanol). Crystal dimensions 0.625 × 0.5 × 0.25 mm, μ(Cu-K_α) = 43.90 cm^{-1}; *F*(000) = 808.

Data collection and processing. CAD4 Diffractometer, ω/2θ mode with ω scan width = 1.0 + 0.14 tanθ, ω-scan speed 0.4—3.8 deg min^{-1}, graphite-monochromated Cu-K_α radiation; 3 280 unique reflections measured ($1 \leqslant \theta \leqslant 65°$, $\pm h,k,l$), no absorption correction, 2 181 with $I \geqslant 3\sigma(I)$ considered as observed after correction for Lorentz-polarization effects. No deviation of two standard reflections (020; 0$\bar{2}$0), intensities checked every 5 400s, was observed during the data collection.

Structure analysis and refinement. This was by direct methods[16] and electron density synthesis. Besides the protonated molecule and the Cl^- anion appeared two water molecules originating from the crystallization process. Block-diagonal-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens isotropic in calculated positions or found in Fourier-difference synthesis. The weighting scheme $w = 1$ if $|F_o| < P$, $P = [F_o^2(\text{max.})/10]^{\frac{1}{2}}$, $w = (P/F_o)^2$ if $|F_o| > P$ gave satisfactory agreement analyses. Final *R* and R_w values were 0.056 and 0.072. Programs and computer used and sources of scattering factor data are given in ref. 17.*

Comparative MNDO Calculation of Structures (**2a**) *and* (**3a**).—The MOPAC program[18] was slightly modified to allow data exchange with SYBYL.[19] The modification procedure was supplied by TRIPOS.[19]

The input for all calculations was generated using the SYBYL program. The *X*-ray structure was modified to give the crude starting structures (**2a**) and (**3a**). This first step was followed by a force field optimization using the MINIM optimizer in SYBYL to remove unfavourable steric strain. While the conformation of the 7-membered ring was kept fixed, the side chain torsion angles were varied systematically to find the lowest-energy conformations of the molecules. The resulting structures were used as input for MOPAC.

In addition to the structures described above, the corresponding conformations of compound (**3a**) with endocyclic double bonds were generated in the same way.

MOPAC optimizations were performed on all structures until Herbert's test of convergence[18] was satisfied. All internal degrees of freedom were varied independently.

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* *Supplementary data* (see section 5.6.3 of Instructions for Authors, January issue). H-Atom co-ordinates, atomic thermal parameters, and bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

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