for 15 min. The solution was extracted with ice–water (2 × 66 mL) and dried (Na_2SO_4). The CH_2Cl_2 was flash-evaporated and the residue was triturated in cold Et_2O. The white solid (**2**) was recrystallized from EtOH: NMR ($CDCl_3$) δ 5.83 (d, H-1, J_{HH} = 9 Hz), 4.0 (s, $ClCH_2$), 2.1–2.03 (overlapping q, $4CH_3CO$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(chloroacetamido)-β-D-galactose [GalNCl(Ac)$_5$] (**8**) was prepared from tetra-*O*-acetyl-2-amino-2-deoxy-β-D-galactose as described for **2**: NMR ($CDCl_3$) δ 5.95 (d, H-1, J_{HH} = 9 Hz), 4.05 (s, $ClCH_2$), 2.2–2.05 (d of d, $4CH_3CO$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(bromoacetamido)-β-D-glucose [GlcNBr(Ac)$_5$] (**3**) **and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(bromoacetamido)-β-D-galactose [GalNBr(Ac)$_5$]** (**9**) were prepared as detailed for the chloroacetamido derivatives from the appropriate tetra-*O*-acetyl-2-amino-2-deoxy-β-D-hexose and bromoaceticanhydride: NMR ($CDCl_3$) for GlcNBr(Ac)$_5$ δ 5.85 (d, 1 H-1, J_{HH} = 8.5 Hz), 3.8 (s, 2 H, $BrCH_2$), 2.18–2.10 (br d, 12 H, $4CH_3CO$), and for GalNBr(Ac)$_5$ δ 5.95 (d, 1 H-1, J_{HF} = 8.5 Hz), 3.8 (s, 2 H, $BrCH_2$), 2.18–2.05 (d of d, 12 H, $4CH_3CO$).

2-Deoxy-2-(fluoroacetamido)-D-glucose (GlcNFAc) (**4**). Compound **1** (1.9 g, 4.7 mmol) was added to a solution of 80 mL of MeOH–Et_3N–H_2O (2:1:1 v/v) at 4 °C. After 40 h, the cold solution was flash evaporated to one-half of its original volume. Water (40 mL) was added to the residue and the solution was brought to pH 6 with Amberlite IR-120 (H^+). The resin was removed by filtration and the aqueous solution was flash-evaporated. The viscous residue was dissolved in chromatography solvent (BuOH–EtOH–saturating H_2O, 4:1:5 v/v) and fractionated on a microcrystalline cellulose column (2.5 × 64 cm). Fractions of approximately 15 mL were collected and those fractions containing the product were located by the R_f value (0.45) on cellulose sheets and flash-evaporated to dryness. The residue was crystallized from ethanol.

2-Deoxy-2-(fluoroacetamido)-D-galactose (GalNFAc) (**10**) was prepared by de-O-acetylation of **7**, as described for compound **4** above.

2-Deoxy-2-(chloroacetamido)-D-glucose (GlcNClAc) (**5**) was prepared by de-O-acetylation of **2**.

2-Deoxy-2-(chloroacetamido)-D-galactose (GalNClAc) (**11**) was prepared by de-O-acetylation of compound **8**.

2-Deoxy-2-(bromoacetamido)-D-glucose (GlcNBrAc) (**6**). Compound **3** (3.0 g, 6.4 mmol) was added to a solution of 80 mL of MeOH–Et_3N–H_2O (2:1:1 v/v) at −6 °C. The reaction mixture was stirred vigorously for 5 h. The resulting material was processed and crystallized as described for compound **4**.

2-Deoxy-2-(bromoacetamido)-D-galactose (GalNBrAc) (**12**) was prepared by de-O-acetylation of **9**, as described for compound **6**.

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References and Notes

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Neuroleptics Related to Butaclamol. An Investigation of the Effects of Chlorine Substituents on the Aromatic Rings

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The synthesis of analogues of the antipsychotic drug butaclamol bearing chloro substituents on the benzene rings is described. On the basis of a perceived topographical similarity of a putative chlorophenylethylamine pharmacophore present in these analogues and in VUFB-10032 and doclothepin, agents related to octoclothepin which do not induce catalepsy, they have been tested for "noncataleptic" neuroleptic activity. None of the butaclamol analogues exhibit this type of activity. Depending on the position of the chlorine, the analogues either retained butaclamol-like activity or were inactive.

The demonstration that clozapine (I) is a clinically effective antipsychotic agent which does not cause extrapyramidal side effects[1] has stimulated a search for similar types of drugs. The observation that clozapine causes agranulocytosis[2] has intensified the search for "clozapine-like" agents which would be devoid of this toxic manifestation.

Clozapine differs strikingly in its biochemical and psychopharmacological profile[3] from the classical neuroleptics such as fluphenazine and haloperidol. Clozapine's

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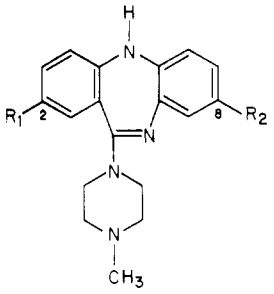
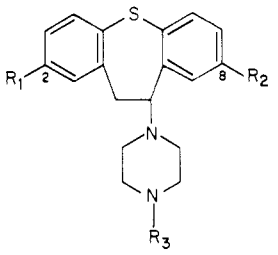
spectrum of psychotropic activities is also entirely different from that of its isomer, II (HF-2046), in which the 8-chloro



I (clozapine), R_1 = H; R_2 = Cl
II (HF-2046), R_1 = Cl; R_2 = H



III (octoclothepin), R_1 = H; R_2 = Cl; R_3 = CH_3
IV (perathiapine), R_1 = R_2 = H; R_3 = CH_3
V (doclothepin), R_1 = Cl; R_2 = H; R_3 = CH_3
VI (VUFB-10032), R_1 = Cl; R_2 = H; R_3 = $(CH_2)_2OH$

substituent of clozapine is transposed to the 2 position. Indeed, the pharmacological effects elicited in animals by II are similar to those of the typical, potent, low-dose neuroleptics.[3]

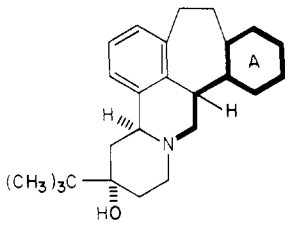
There are other instances where the position, or presence, of a chlorine atom on the skeleton of a neuroleptic molecule results in profound quantitative or significant qualitative changes in its psychopharmacological effects. For example, promazine, which differs from chlorpromazine in lacking the 2-chloro substituent, is 33 and 14 times less potent than chlorpromazine in the anti-apomorphine and conditioned avoidance response tests in dogs, respectively.[4] Promazine is regarded as being "devoid of truly antipsychotic potential"[5] and is not used clinically for this indication. The mechanism whereby the chlorine atom of chlorpromazine exerts its potency-enhancing effect has been the subject of much recent speculation, ranging from the induction of a favorable conformational change in the side chain[6] to a direct effect on the receptor.[7]

Octoclothepin (III) is a typical antipsychotic agent, being similar to fluphenazine and haloperidol both in its pharmacological and clinical effects. The compound possesses an 8-chloro substituent. In this case, however, the presence of the 8-chloro substituent is not required for neuroleptic activity as the dechloro analogue, perathiapine (IV), is about equipotent to octoclothepin both in animals and man.[8,9] Interestingly, while the removal of octoclothepin's chlorine atom does not substantially affect its biological profile, the transposition of the chlorine from position 8 to position 2, to afford doclothepin (V) (VUFB 10030), results in a profound change; like clozapine, doclothepin does not induce catalepsy.[10,11] In animal studies doclothepin, the closely related analogue VI (VUFB-10032), and clozapine are qualitatively very similar.[10-13] Clearly, while the 8-chloro substituent is not required for the typical neuroleptic activities displayed by octoclothepin, its presence at position 2 is essential for the clozapine-like profile of doclothepin and VI.

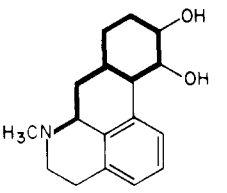
The purpose of the present study is to investigate if the transposition of octochlothepin's chlorine from position 8 to position 2 results in the generation of a unique chlorophenylethylamine pharmacophore which is responsible for clozapine-like activity and whether this type of activity will be seen if the pharmacophore is incorporated into a molecular framework other than that of octoclothepin.

The uniqueness of this putative pharmacophore derives from its incorporation into a semirigid framework, and the precise nature of the topography of the pharmacophore is known since the crystal and molecular structures of (±)-octoclothepin and of its neuroleptically active[14,15] S-(+) enantiomer have recently been described.[14,16]

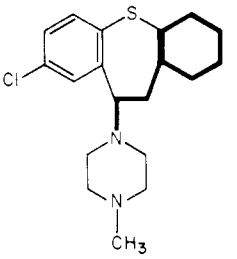
The drug (±)-butaclamol (VII) shares several remarkable



VII [(+)-butaclamol]



VIII [(−)-apomorphine]



IX [(+)-octoclothepin]

features with (±)-octoclothepin. It is a clinically active antipsychotic agent[17-20] whose neuroleptic activity is due solely to the (+) enantiomer.[21,22] The crystal and molecular structures have been determined and the absolute configuration of the (+) enantiomer is known.[23]

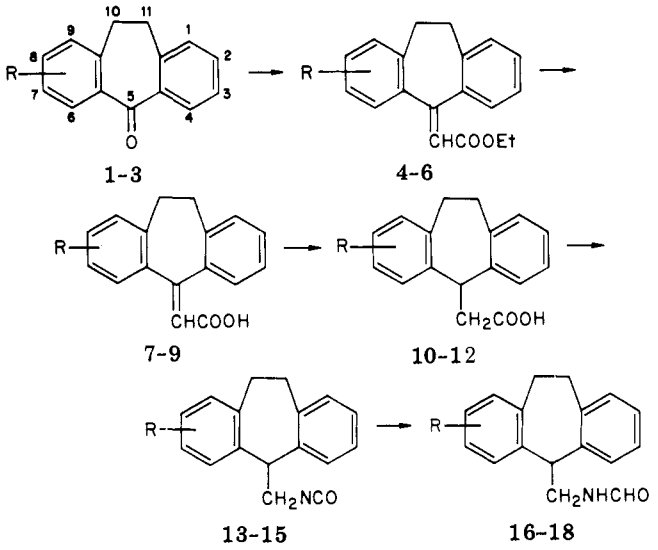
We have shown previously[22] that the extended phenylethylamine moieties of (+)-butaclamol and (−)-apomorphine (VIII) have similar topographical features in that, when the molecules are superimposed, the phenyl rings are concentric and coplanar and the nitrogen atoms are coincident.

A comparison of the molecular structures of (+)-butaclamol and (+)-octoclothepin (IX) has been carried out by inspection of Dreiding models and also by direct superimposition of molecular structures generated from crystallographic coordinates and standard bond lengths and angles using a molecular graphics display system.[24] This comparison reveals that in the phenylethylamine moieties of both (+)-butaclamol and (+)-octoclothepin the phenyl rings are concentric and coplanar and the nitrogen atoms are coincident.

Because of these similarities we have chosen to incorporate chlorine atoms into ring A of the butaclamol ring system to generate a chlorophenylethylamine pharmacophore topographically similar to that in doclothepin and VI and to evaluate the resulting compounds for some psychopharmacological activities.

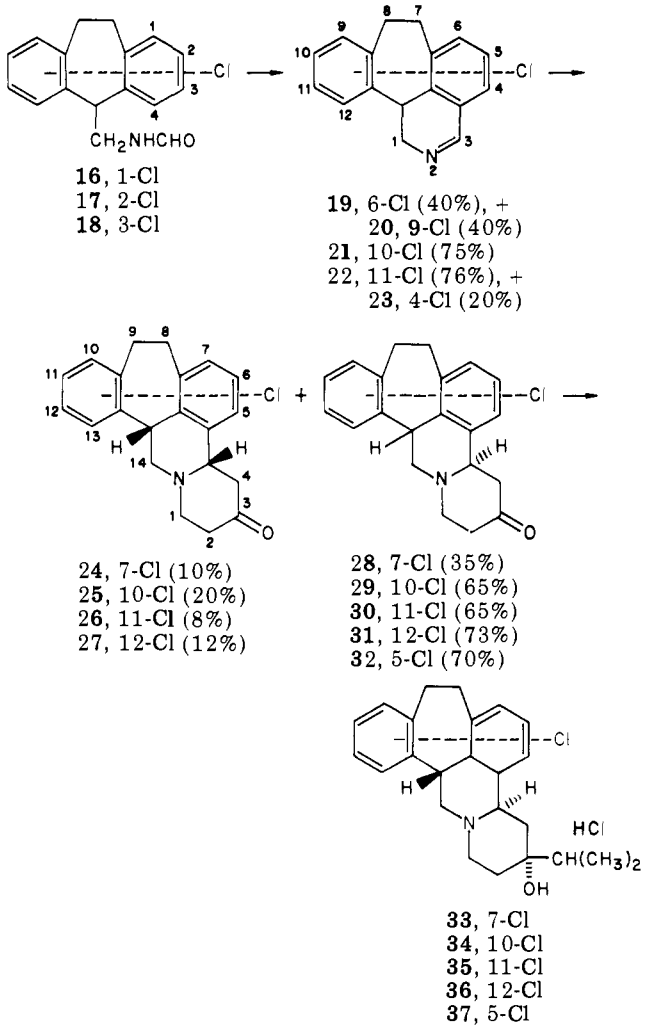
Chemistry. The synthetic pathway used was similar to that developed for butaclamol[25] and is shown in Schemes I and II. The known 1-chloro,[26] 2-chloro,[26,27] and 3-chloro[27] derivatives of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-one (**1**–**3**) were condensed with triethyl phosphonoacetate in the presence of sodium hydride to afford the 5-ylideneacetic esters **4**–**6** which were hydrolyzed directly to the 5-ylideneacetic acids **7**–**9**. Sodium amalgam reduction of these unsaturated acids gave the 5-ylacetic acids **10**–**12**. They were converted to their mixed anhydrides with triethylamine and ethyl chloroformate and treated with sodium azide, and the intermediate acyl azides were rearranged thermally to the isocyanates **13**–**15**. The formamides **16**–**18** were conveniently prepared, in one step from the isocyanates, by reduction with sodium borohydride.

Scheme I



1, **4**, **7**, **10**, **13**, **16**, R = 1-Cl
2, **5**, **8**, **11**, **14**, **17**, R = 2-Cl
3, **6**, **9**, 12, **15**, **18**, R = 3-Cl

Scheme II



16, 1-Cl
17, 2-Cl
18, 3-Cl

19, 6-Cl (40%), +
20, 9-Cl (40%)
21, 10-Cl (75%)
22, 11-Cl (76%), +
23, 4-Cl (20%)

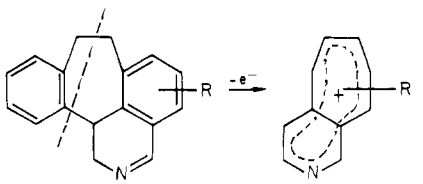
24, 7-Cl (10%)
25, 10-Cl (20%)
26, 11-Cl (8%)
27, 12-Cl (12%)

28, 7-Cl (35%)
29, 10-Cl (65%)
30, 11-Cl (65%)
31, 12-Cl (73%)
32, 5-Cl (70%)

33, 7-Cl
34, 10-Cl
35, 11-Cl
36, 12-Cl
37, 5-Cl

Cyclizations of the formamides to Schiff bases were conducted by heating with polyphosphoric acid at 150 °C for 2 h. The results are shown in Scheme II. The 1-chloroformamide **16** gave an 80% yield of a 1:1 mixture of the 6- and 9-chloro-1,7,8,12b-tetrahydrobenzo[1,2]-

Scheme III



R = H; *m/e* 142
R = Cl; *m/e* 176, **178**

cyclohept[3,4,5-*de*]isoquinolines (**19** and **20**). The 2-chloroformamide **17** afforded only a single Schiff base, the 10-chloro derivative **21**, in 75% yield, while the 3-chloroformamide **18** afforded 76 and 20%, respectively, of the 11-chloro and 4-chloro Schiff bases **22** and **23**.

Analysis of the splitting pattern of the aromatic region in the 220-MHz NMR spectra of the pairs of compounds obtained from the cyclizations of the 1- and 3-chloroformamides **16** and **18** permitted the assignment of the positions of the chlorine atoms in **19**, **20**, **22**, and **23**. Thus, one of the isomers obtained from **16** exhibits a one-proton doublet at δ 6.95 with a characteristic ortho coupling constant of 9 Hz and a second one-proton doublet is located at δ 7.19, also with J = 9 Hz. This isomer is assigned the 6-chloro structure **19** since of all the protons in **19** and **20** only those at positions 4 and 5 in **19** can produce such a pattern. One of the spectra of the isomers derived from **18** shows a one-proton doublet, completely separated from the other aromatic protons in the expanded spectrum, at δ 7.29 with a small coupling constant of 2 Hz, characteristic of meta coupling. This doublet is assigned to the C_{12} proton of **22**. Its C_{10} proton was observed at δ 7.07 as a doublet of doublets (J = 2 and 8.5 Hz) due to its coupling with the ortho and meta protons, while the C_9 proton appeared as a doublet at δ 6.95 (J = 8.5 Hz).

These assignments based on NMR spectroscopy, as well as the assignment of the structure of **21** based on the expected low reactivity of the position meta to the chlorine in **17**, were fully confirmed by mass spectroscopy. Each of the chlorinated Schiff bases **19**–**23** undergoes a fragmentation (Scheme III) to produce a resonance-stabilized pyridotropylium ion. In accordance with this fragmentation, the 4- and 6-chloro derivatives **23** and **19** gave the isotopic fragments with *m/e* 176 and 178 while the 9-, 10-, and 11-chloro analogues **20**–**22** gave a fragment with *m/e* 142.

The Schiff bases were reacted, as their hydrochloride salts, with methyl vinyl ketone to afford the pentacyclic amino ketones shown in Scheme II and Table I. The 6-, 9-, 10-, and 11-chloro Schiff bases **19**–**23** gave mixtures of the cis (**24**–**27**) and trans (**28**–**31**) amino ketones with a preponderance of the trans isomers being formed. No cis isomer could be isolated on reaction of the 4-chloro Schiff base **23** with methyl vinyl ketone. The 4a,13b relative configurations in amino ketones **24**–**31** were assigned in analogy with the dechloro analogues[28] such that the isomer of a pair which is obtained in higher yield and which has the lower R_f value and the lower melting point is assigned the 4a,13b-trans configuration. The 4a,13b relative configuration of the dechloro amino ketones related to **24**–**27** and to **28**–**32** has been confirmed indirectly by crystallographic studies,[23] and it had been noted[28] that the NMR signal of the C_{13b} hydrogen of the 4a,13b-trans isomer appears as a triplet while that of the 4a,13b-cis isomer is a doublet. Similar splitting patterns for the C_{13b} hydrogens of the amino ketones **24**–**32** (see Table I) lend support to the configurational assignments shown in Scheme II and Table I.

Table I. Chemical Data on Pentacyclic Amino Ketones

compd	R	4a,13b config	starting material	yield, %	eluting solvents	mp, °C	crystn solvent	formula (analyses)[a]	NMR signal of C_{13b}-H, δ ($CDCl_3$)[d]
24	7-Cl	cis	**19**	10	EtOAc–C_6H_6 (1:10)	220–224	Et_2O	*b*	4.62 (1, d, J = 4.5)
28	7-Cl	trans	**19**	35	EtOAc–C_6H_6 (1:5)	215–219	EtOAc	$C_{21}H_{20}ClNO$ (C, H, N)	4.80 (1, t, J = 5.0)
25	10-Cl	cis	**20**	20	EtOAc–C_6H_6 (1:10)	220	Et_2O	$C_{21}H_{20}ClNO$ (C, H, N)	4.70 (1, d, J = 3.0)
29	10-Cl	trans	**20**	65	EtOAc–C_6H_6 (1:5)	182–184	Et_2O	$C_{21}H_{20}ClNO$ (C, H, N)	4.72 (1, t, J = 3.5)
26	11-Cl	cis	**21**	8	$CHCl_3$–C_6H_6 (1:1)	200–205	Et_2O	*b*	4.50 (1, d, J = 4.5)
30	11-Cl	trans	**21**	65	$CHCl_3$–C_6H_6 (1:1)	178	Et_2O	$C_{21}H_{20}ClNO$ (C, H, N)	4.65 (1, t, J = 4.5)
27	12-Cl	cis	**22**	12	$CHCl_3$–C_6H_6 (1:5)	230–231	Et_2O	*b*	4.55 (1, d, J = 4)
31	12-Cl	trans	**22**	73	$CHCl_3$–C_6H_6 (1:1)	174–176	Me_2CO	$C_{21}H_{20}ClNO$ (C, H, N)	4.75 (1, t, J = 4)
32	5-Cl	trans	**23**	70	Me_2CO–C_6H_6 (1:20)	170–172	Et_2O	$C_{21}H_{20}ClNO \cdot HCl$ (C, H, N)[c]	4.60 (1, t, J = 3.0)

[a] Compounds were analyzed for the elements shown in parentheses. All results were within ±0.4% of the calculated values. [b] Analytical data were not obtained on these compounds. They were homogeneous by TLC and their mass spectra showed molecular ions with m/e 337 and 339. [c] Analyzed as the HCl salt: mp 195–200 °C (2-propanol–Et_2O); $C_{21}H_{20}ClNO \cdot HCl$. [d] J values in hertz.

The 4a,13b-trans amino ketones **28–32** were reacted with 2-propylmagnesium chloride to afford the tertiary carbinols **33–37**. Chemical data on these compounds are collected in Table II. Compound **37** was obtained in only 10% yield, and the quantity available was not sufficient for the preparation of an analytical sample or for pharmacological evaluation. The 3-(2-propyl) group was introduced instead of the *tert*-butyl group which is present in butaclamol, since higher yields are generally obtained when 2-propylmagnesium chloride is used in the Grignard reaction, and the replacement of butaclamol's *tert*-butyl by a 2-propyl group reduces its potency only slightly.[25]

The 3-OH,13b-H-trans configurations have been assigned for the tertiary carbinol centers in **33–37** on the basis of considerations which had allowed the prediction,[25] subsequently confirmed by X-ray crystallography,[23] of the configuration of the tertiary carbinol center in the dechloro analogue.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are corrected. All temperatures are stated in Celsius degrees. Mass spectra were recorded on an LKB-9000S at 70 eV and a source temperature of 250 °C. Nuclear magnetic resonance spectra were determined in $CDCl_3$ using a Model CFT-20 spectrometer at 80 MHz. Where stated, 220-MHz spectra were determined on a Varian HR-220 instrument at the Canadian 220-MHz NMR Center, Sheridan Park, Ontario. All chemical shifts are given in parts per million downfield from tetramethylsilane. Microanalyses were performed by the Ayerst Analytical Laboratory under the direction of Dr. G. Schilling. All results were within ±0.4% of the calculated values unless noted otherwise. All column chromatograms were done using silica gel 60 produced by E. Merck, Darmstadt, and thin-layer chromatograms were carried out on plates precoated with silica gel 60 F-254.

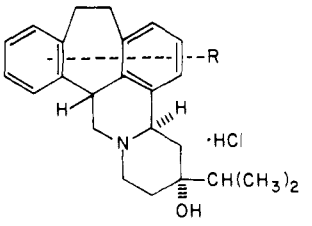
1-, 2-, and 3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptен-5-ylideneacetic Acids (7–9). To a suspension of NaH (7.4 g, 0.33 mol, 14.8 g of a 50% dispersion in oil) in THF (200 mL) was added triethyl phosphonoacetate (81.4 g, 0.36 mol), under N_2, at a rate such that the reaction temperature was maintained at 30–35 °C. The mixture was stirred at 22 °C for 1 h and a solution of 1-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptен-5-one[26] (1) (40 g, 0.165 mol) in THF (200 mL) was added during 30 min. The mixture was refluxed for 20 h and poured into ice–H_2O. The organic phase was separated, combined with the EtOAc extract of the aqueous phase, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel. Elution with C_6H_6–hexane (1:10) gave the ethyl ester **4** as an oil (50 g, 97%): NMR δ 1.1 (3, t, J = 7 Hz, CH_3), 3.2 (4, m, CH_2CH_2), 4.1 (2, q, J = 7 Hz, CH_2CH_3), 6.2 (1, s, =CH), and 7.2 (7, m, aromatic H's). The foregoing ester was hydrolyzed by refluxing for 3 h in a mixture of EtOH (500 mL) and 10% aqueous NaOH (500 mL). A conventional workup procedure gave product **7** (30 g, 66%): mp 200–202 °C (Et_2O–hexane); NMR δ 3.15 (4, s, CH_2CH_2), 6.2 (1, s, =CH), and 7.2 (7, m, aromatic H's).

By following the same procedure, but using the 2-chloro ketone **2**, there was obtained the 2-chloro-5-ylidene ethyl ester **5** as an oil in 99% yield, which was hydrolyzed directly to the 2-chloro-5-ylideneacetic acid **8** in quantitative yield: mp 155–175 °C (Et_2O–hexane); NMR δ 3.05 (4, s, CH_2CH_2), 6.18 (1, s, =CH), and 7.2 (7, m, aromatic H's).

Similarly, starting with the 3-chloro ketone **3** and using the above procedure, there was obtained the 3-chloro-5-ylidene ethyl ester **6**, mp 110–113 °C (hexane), in 98% yield which was hydrolyzed to the 3-chloro-5-ylideneacetic acid **9** in 95% yield: mp 195–205 °C (Et_2O–hexane).

1-, 2-, and 3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptен-5-ylacetic Acids (10–12). A solution of 1-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptен-5-ylideneacetic acid (**7**) (30 g, 0.11 mol) in hot EtOH (300 mL) was added to a flask containing 5% sodium amalgam (300 g). The mixture was stirred for 3 h at 60–70 °C, the EtOH layer was decanted, and the residue was washed with EtOH. The combined EtOH solutions were diluted with an equal volume of H_2O, acidified with

Table II. Chemical Data on Grignard Reaction Products



compd	R	starting material	yield, %	eluting solvent	mp, °C dec	crystn solvent	formula (analyses)[a]
33	7-Cl	**28**	50	EtOAc-C_6H_6 (1:50)	270	2-PrOH-Et_2O	$C_{24}H_{28}ClNO\cdot HCl$ (C, H, N)[b]
34	10-Cl	**29**	60	EtOAc-C_6H_6 (1:5)	260-270	*c*	$C_{24}H_{28}ClNO\cdot HCl$ (C, H, N)
35	11-Cl	**30**	70	MeOH-C_6H_6 (1:20)	270	*c*	$C_{24}H_{28}ClNO\cdot HCl$ (C, H, N)
36	12-Cl	**31**	50	EtOAc-C_6H_6 (1:5)	270	2-PrOH-Et_2O	$C_{24}H_{28}ClNO\cdot HCl$ (C, H, N)
37	5-Cl	**32**	10	Me_2CO-C_6H_6 (1:5)	270	2-PrOH-Et_2O	*d*

[a] Compounds were analyzed for the elements shown in parentheses. All results were within ±0.4% of the calculated values except where indicated. [b] Anal. N: calcd, 3.35; found, 3.79. [c] Triturated with acetone. [d] Analytical data were not obtained on this compound. The free base was homogeneous by TLC when developed with benzene-acetone (4:1), and the mass spectrum showed the expected molecular ion with *m/e* 381 and 383.

concentrated HCl, and extracted with $CHCl_3$. The extracts were dried and concentrated, and the residue was crystallized from Et_2O–hexane to afford the product: mp 170–171 °C (28 g, 95%); NMR δ 3.1 (2, d, J = 7.5 Hz, CH_2COOH), 3.2 (4, s, CH_2CH_2), and 4.9 (1, t, J = 7.5 Hz, C_3CH). Anal. ($C_{17}H_{15}ClO_2$) C, H.

Using the same procedure with **8** as the starting material there was obtained the 2-chloro-5-ylacetic acid **11**, mp 142–146 °C (Et_2O–hexane), in 80% yield: NMR δ 3.1 (2, t, J = 7.5 Hz, CH_2COOH), 3.18 (4, s, CH_2CH_2), and 4.7 (1, t, J = 7.5 Hz, C_3CH). Anal. ($C_{17}H_{15}ClO_2$) C, H.

Similarly, using **9** as the starting material, the 3-chloro-5-ylacetic acid **12** was obtained in 90% yield: mp 147 °C (Et_2O-hexane); NMR δ 3.08 (2, t, J = 7.5 Hz, CH_2COOH), 3.17 (4, s, CH_2CH_2), 4.75 (1, t, J = 7.5 Hz, C_3CH). Anal. ($C_{17}H_{15}ClO_2$) C, H.

1-, 2-, and 3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylmethylformamides (16-18). To a solution of the 1-chloro-5-ylacetic acid **10** (22.0 g, 0.08 mol) in THF (500 mL) was added Et_3N (15.4 g, 0.15 mol) and then ClCOOEt (12.5 g, 0.11 mol) at 0 °C under N_2. The mixture was kept at 0 °C for 1 h and then cooled to -10 °C, and a solution of NaN_3 (7.0 g, 0.11 mol) in H_2O (50 mL) was added during 15 min. After 1 h at -10 °C Et_2O (250 mL) was added, and the organic phase was separated, dried, and evaporated at 22 °C to give the acyl azide, γ max 2100 cm^{-1}, as an oil. It was dissolved in C_6H_6 and the solution was refluxed for 1 h. The C_6H_6 was evaporated to leave the isocyanate **13** as an oil, γ max 2250 cm^{-1}. It was dissolved in 1,2-dimethoxyethane (200 mL) and added during 15 min at 0 °C to a stirred suspension of $NaBH_4$ (11 0 g) in 1,2-dimethoxyethane (110 mL) under a N_2 atmosphere. The mixture was stirred at 0 °C for 2 h and then concentrated in vacuo. $CHCl_3$ was added to the residue and 1 N HCl was added while cooling to 0 °C. The organic phase was separated, dried, and evaporated. The residue was chromatographed on silica gel. Elution with Me_2CO–C_6H_6 (1:10) gave the formamide **16** (16.0 g, 70%): mp 107–109 °C (Et_2O–hexane); NMR δ 3.25 (4, m, CH_2CH_2), 4.0 (2, d, J = 6 Hz, CH_2N), 4.3 (1, m, C_3CH), and 8.06 (1, s, CHO). Anal. ($C_{17}H_{16}ClNO$) C, H, N.

Following the procedure described above but using the 2-chloro-5-ylacetic acid **11** as the starting material, there was obtained the formamide **17**, eluted with Me_2CO–C_6H_6 (1:1), in 50% yield: mp 122–124 °C (Et_2O-hexane). Anal. ($C_{17}H_{16}ClNO$) C, H, N.

In a similar manner, but using the 3-chloro-5-ylacetic acid **12** as the starting material, there was obtained the formamide **18**, eluted with Me_2CO–C_6H_6 (1:1), in 73% yield: mp 115–118 °C (Et_2O-hexane). Anal. ($C_{17}H_{16}ClNO$) C, H, N.

Cyclizations of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ylmethylformamides. The formamides **16-18** were cyclized by heating with 10 times their weight of polyphosphoric acid for 2 h at 150 °C. The mixture was then poured onto ice and the precipitated phosphate salts were isolated by filtration. They were partitioned between $CHCl_3$ and 10% aqueous NaOH solution, and the organic phase was dried and concentrated to give a residue which was treated as described below.

(a) **Products from the 1-Chloroformamide 16.** The residue from the cyclization consisted of two compounds with R_f values on TLC of 0.398 and 0.425 when developed with EtOAc. One-gram batches of the residue were chromatographed on 1 kg of silica gel. Elution with EtOAc gave, first, the isomer with R_f 0.425, **6-chloro-1,7,8,12b-tetrahydrobenzo[1,2]cyclohept[3,4,5-*de*]isoquinoline (19)**: 370 mg (40%); mp 160–162 °C (Et_2O); MS *m/e* 176, 178; NMR (220 MHz, $CDCl_3$)[29] δ 2.95 (1, m, H_{7a}), 3.3 (2, m, $H_{8a}H_{8b}$), 3.48 (1, m, H_{7b}), 3.91 (1, 4 d, H_{1a}, $J_{H_{1a}H_3}$ = 3.5, $J_{H_{1a}H_{12b}}$ = 8, $J_{H_{1a}H_{1b}}$ = 16 Hz), 4.65 (1, d, H_{12b}, $J_{H_{12b}H_{1a}}$ = 8 Hz), 4.75 (1, d, H_{1b}, $J_{H_{1b}H_{1a}}$ = 16 Hz), 6.95 (1, d, H_5, $J_{H_5H_4}$ = 9 Hz), 7.19 (1, d, H_4, $J_{H_4H_5}$ = 9 Hz), and 8.3 (1, d, H_3, $J_{H_3H_{1a}}$ = 3.5 Hz). Anal. ($C_{17}H_{14}ClN$) C, H, N.

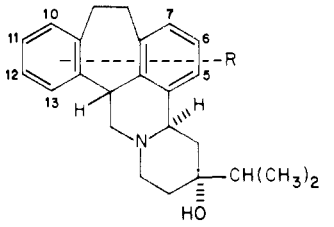
Continued elution with EtOAc gave the isomer with R_f 0.398, **9-chloro-1,7,8,12b-tetrahydrobenzo[1,2]cyclohept[3,4,5-*de*]isoquinoline (20)**: 370 mg (40%); mp 162–164 °C (Et_2O); MS *m/e* 142; NMR (220 MHz, $CDCl_3$) δ 2.94 (1, m, H_{7a}), 3.24 (2, m, $H_{8a}H_{8b}$), 3.58 (1, m, H_{7b}), 3.93 (1, 4 d, H_{1a}, $J_{H_{1a}H_3}$ = 3.5, $J_{H_{1a}H_{12b}}$ = 8, $J_{H_{1a}H_{1b}}$ = 16 Hz), 4.61 (1, d, H_{12b}, $J_{H_{12b}H_{1a}}$ = 8 Hz), 4.77 (1, d, H_{1b}, $J_{H_{1b}H_{1a}}$ = 16 Hz), 7.14 (7, m, aromatic H's), and 8.32 (1, d, H_3, $J_{H_3H_{1a}}$ = 3.5 Hz). Anal. ($C_{17}H_{14}ClN$) C, H, N.

(b) **Product from the 2-Chloroformamide 17.** The residue from the cyclization showed one major spot on TLC. Elution from a silica gel column with Me_2CO–C_6H_6 (1:5) afforded **10-chloro-1,7,8,12b-tetrahydrobenzo[1,2]cyclohept[3,4,5-*de*]isoquinoline (21)** in 75% yield: mp 106 °C (Et_2O); MS *m/e* 142; NMR ($CDCl_3$) δ 3.25 (4, m, CH_2CH_2), 7.4 (6, m, aromatic H's), and 9.1 (1, s, N=CH). The hydrochloride salt had mp 200–205 °C (Me_2CO). Anal. ($C_{17}H_{14}ClN\cdot HCl$) C, H, N.

(c) **Products from the 3-Chloroformamide 18.** The residue from the cyclization showed two spots on TLC with similar R_f values when developed with Me_2CO–C_6H_6 (1:5). The mixture (2.6 g) was chromatographed on 1.56 kg of silica gel. Elution with Me_2CO–C_6H_6 (1:5) gave, first, 520 mg (20%) of **4-chloro-1,7,8,12b-tetrahydrobenzo[1,2]cyclohept[3,4,5-*de*]isoquinoline (23)**: mp 150–154 °C (Et_2O); MS *m/e* 176, 178; NMR (220 MHz, $CDCl_3$) δ 2.92 (2, m, $H_{7a}H_{7b}$ or $H_{8a}H_{8b}$), 3.52 (2, m, $H_{8a}H_{8b}$ or $H_{7a}H_{7b}$), 3.91 (1, m, H_{1a}), 4.59 (1, d, H_{12b}, $J_{H_{12b}H_{1a}}$ = 8 Hz), 4.82 (1, m, H_{1b}), 7.01–7.45 (6, m, aromatic H's), and 8.73 (1, m, H_3). The hydrochloride salt had mp 192 °C dec (2-propanol-Et_2O). Anal. ($C_{17}H_{14}ClN\cdot HCl$) C, H, N.

Continued elution with the same solvent mixture afforded 2.0 g (76%) of **11-chloro-1,7,8,12b-tetrahydrobenzo[1,2]cyclohept[3,4,5-*de*]isoquinoline (22)**: mp 160-164 °C (Et_2O–C_6H_6); MS *m/e* 142; NMR (220 MHz, $CDCl_3$) δ 2.91 (2, m, $H_{7a}H_{7b}$ or $H_{8a}H_{8b}$), 3.47 (2, m, $H_{8a}H_{8b}$ or $H_{7a}H_{7b}$), 3.95 (1, 4 d, H_{1a} $J_{H_{1a}H_3}$ = 3.5, $J_{H_{1a}H_{12b}}$ = 8, $J_{H_{1a}H_{1b}}$ = 16 Hz), 4.55 (1, d, H_{12b} $J_{H_{12b}H_{1a}}$ = 8 Hz), 4.70 (1, d, H_{1b}, $J_{H_{1b}H_{1a}}$ = 16 Hz), 6.95 (1, d, H_9, $J_{H_9H_{10}}$ = 8.5 Hz), 7.07 (1, 2 d, H_{10}, $J_{H_{10}H_{12}}$ = 2, $J_{H_{10}H_9}$ = 8.5 Hz), 7.11 (1, m) and 7.19 (2, m) ($H_4H_5H_6$), 7.29 (1, d, H_{12}, $J_{H_{12}H_{10}}$ = 2 Hz), and 8.29 (1, d,

Table III. Results of Pharmacological Evaluation



compd	R	amphetamine stereotyped behavior,[a] mg/kg ip	conditioned avoidance response,[b] mg/kg ip	continuous (Sidman) avoidance response,[c] mg/kg ip	epinephrine mortality,[d] mg/kg ip	catalepsy,[e] mg/kg ip
X (AY-22814)	H	1.25	0.64 ± 0.1	0.5	15.0 ± 2.6	12.5
33	7-Cl	10	9.0 ± 6.0	2.5	50	50
34	10-Cl	20	>20	20	100	100
35	11-Cl	1.25	1.1 ± 0.3	0.62	13.9 ± 1.2	12.5
36	12-Cl	>20	*f*	>5	>60	*f*
VI (VUFB-10032)		20	4.5 ± 1.3	2.5	0.88 ± 0.3	>50
clozapine		50	6.8 ± 1.7	7.5	2.4 ± 1.1	>100

[a] Dose refers to the minimal effective dose which abolished the amphetamine-induced sniffing, licking, and gnawing. [b] Expressed as the ED_{50}, i.e., the dose which caused a 50% failure in the active avoidance response. [c] Dose which decreased the continuous (Sidman) lever-pressing response to <50%. Percent avoidance is >90% in untreated, control rats. [d] Expressed as the ED_{50}, i.e., the dose which protected 50% of the rats from the lethal effect of epinephrine. [e] Minimum dose which caused maximum catalepsy. [f] Not evaluated.

H_3, $J_{H_3H_{1a}}$ = 3.5 Hz). Anal. ($C_{17}H_{14}ClN$) C, H, N.

Preparation of 1,2,4,4a,8,9,13b,14-Octahydro-3*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ones 24-32. The appropriate Schiff base (0.005 mol) was dissolved in Et_2O and saturated with HCl. Evaporation left a residue to which was added toluene (21 mL), DMF (7 mL), and methyl vinyl ketone (0.017 mol). The mixture was stirred under N_2 at 100 °C for 1.5 h and then at 22 °C for 16 h. Et_2O was added, and the resulting precipitate was isolated and partitioned between EtOAc and 5% aqueous Na_2CO_3 solution. The organic phase was dried and evaporated to give a residue which was chromatographed on silica gel to afford the trans and cis isomers, listed in Table I along with relevant chemical data.

Grignard Reaction on Amino Ketones 28-32. To Mg turnings (0.074 g-atom) in Et_2O (10 mL) a few crystals of I_2 were added. 2-Propyl chloride (0.074 mol) in Et_2O (50 mL) was added at a rate such that gentle reflux was maintained. After stirring for 1 h at 22 °C Et_2O (50 mL) was added, the mixture was cooled to −40 °C, and a fine suspension of the trans amino ketone (0.0074 mol) was added under a N_2 atmosphere. The reaction mixture was allowed to warm and, after 3 h at 22 °C, THF (50 mL) was added, followed by H_2O (100 mL). The organic phase was separated, combined with the EtOAc extract of the aqueous phase, dried, and evaporated. The residue was chromatographed on silica gel to afford the tertiary carbinols which were converted to their HCl salts with ethereal HCl. Chemical data on these compounds are collected in Table II.

Pharmacological Methods. Animals. Experiments were performed on male Sprague-Dawley rats. The animals were housed in air-conditioned quarters and had free access to food and water until the start of the experiment.

Materials. The doses used were calculated as the free base. The compounds were dissolved in distilled water or suspended in distilled water with a few drops of Tween 80 (2-3 drops/10 mL). Fresh solutions were prepared on the day of the experiment. In addition to the test compounds, the following drugs were used: *d*-amphetamine sulfate (K & K Laboratories) and epinephrine bitartrate (Sigma Chemical Co.).

Statistics. The ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[30]

***d*-Amphetamine-Induced Stereotyped Behavior in Rats.** Details of the methodology and scoring system were recently described.[31] Rats (160-180 g) were injected ip with *d*-amphetamine, 10 mg/kg, followed 15 min later by an ip injection of graded doses of the test compounds or the vehicle. The highest dose evaluated was 20 mg/kg. Observations were made at 15-min intervals after the injection of amphetamine, and the behavior of the rats was scored from 0 to 2: "0" referring to normal, "1" to excited, and "2" to stereotyped behavior.

The results are expressed as the minimal effective dose (MED), arbitrarily defined as the dose which antagonized all the behavioral effects of amphetamine.

Conditioned Avoidance Behavior in Rats. The method of Morpurgo[32] was followed. Rats were trained to leave the starting chamber and move into one of two exit compartments which was lighted. Rats that failed to leave the starting chamber within 10 s were punished with shock. Details of our three-chambered discrimination box and training procedure are described in a previous paper.[33] On the day of the experiment rats (250-400 g) were tested in a control session of two trials prior to drug administration to ensure an accurate response. Graded doses of the test compounds were administered ip to groups of six rats, and drug effect was evaluated in 10 trials 30 min after injection. The "active avoidance failure", i.e., failure to leave the starting chamber prior to the onset of the shock, was recorded, and the mean number of failures per group was calculated as a percent of the total number of trials. The results are expressed as the ED_{50} values, defined as the dose of a compound that caused a 50% failure in the active avoidance response.

Epinephrine-Induced Mortality in Rats. The method of Janssen et al.[34] was followed. Groups of five rats (220-250 g) were injected ip with graded doses of the compounds, followed 1 h later by an iv injection of epinephrine bitartrate, 0.25 mg/kg. This dose of epinephrine is lethal to nontreated rats. Mortality was determined over a 24-h period. The results are expressed as protective ED_{50} values.

Catalepsy in Rats. The assessment of catalepsy in rats (160-180 g) was based upon the method of Morpurgo.[35] Graded doses of the compounds were injected ip to rats, and catalepsy was evaluated after 1, 2, 4, and 6 h according to stages III and IV of Wirth et al.[36] The rats were placed on a table with one front paw set on a cork (a) 3 cm high, the other remaining on the table (stage III), and (b) 9 cm high, the other permitted to hang freely (stage IV). The reaction was considered to be positive when the rat failed to correct the imposed posture within 10 s. Both stages were tested on the right and left forepaws, and half a point was given for each paw with a positive stage III reaction and one point for each paw with a positive stage IV reaction. Thus, three was the maximum score attainable. The results are expressed as the lowest dose which caused maximum catalepsy.

Continuous (Sidman) Avoidance Procedure. A standard Model 1111L two-lever rat chamber (Grason-Stadler, U.S.A.) was used. Details of the parameters used for the continuous avoidance schedule, the training procedure, and the experimental procedure

were recently described.[30] The compounds or the vehicle was injected following a 30-min control period, after which the rat was immediately returned to the box for the next 3 h. Shocks were recorded and summed at 0.5-h intervals and the mean percentage of avoided shocks was calculated.

Results and Discussion

The effects of the 7-, 10-, 11-, and 12-chloro analogues **33–36** were evaluated using the tests described above. The results are shown in Table III in comparison with those obtained with X (AY-22814),[25] the dechloro analogue. The latter compound is a butaclamol analogue in which the *tert*-butyl group has been replaced by a 2-propyl group. Comparative results obtained with clozapine and VI (VUFB 10032) are also included.

Clozapine and VI exert similar actions under the experimental conditions used. Both show high potency in preventing epinephrine mortality in the rat, having ED_{50} values of 2.4 and 0.88 mg/kg ip, respectively, these being the lowest values observed in the present studies with these compounds. Clozapine and VI are also moderately active in depressing both the conditioned avoidance and the continuous avoidance responses. However, they are weak blockers of amphetamine-induced stereotypy and they do not induce catalepsy.

The dechloro analogue X has the profile of a typical neuroleptic agent in these tests, viz., high potency in blocking stereotypy and depressing the conditioned and continuous avoidance responses, coupled with a relatively low potency in preventing epinephrine mortality, and a capacity to induce catalepsy.

From the results it is apparent that none of the chloro derivatives tested show clozapine-like activity. The 11-chloro analogue **35** retains activity in all five tests and is quantitatively similar to X. Chloro substitution in the 7 or 10 position (**33** and **34**, respectively) considerably decreases activity when compared to the dechloro analogue.

The 12-chloro derivative **36** was considered to be inactive as a typical neuroleptic since it did not antagonize amphetamine stereotypy. It was also devoid of clozapine-like activity as indicated by its lack of effect on epinephrine-induced mortality.

Compounds **33–36** have also been recently investigated in vitro by some biochemical–pharmacological methods, the results essentially supporting the in vivo behavioral studies reported herein.[37]

In conclusion, the study demonstrates that the structural requirements necessary for noncataleptic neuroleptics cannot be defined in terms of a chlorophenylethylamine pharmacophore as discussed in the introduction.

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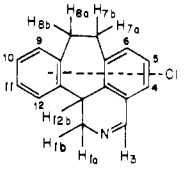
(29) The proton designations in the 220-MHz NMR spectra of compounds **19**, **20**, **22**, and **23** are as shown below.



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