Biological Methods. Blood Collection and Isolation of Plasma. Whole blood was obtained from voluntary, experienced donors before breakfast. Donors were instructed to take no drugs, specifically aspirin, for 5 days before giving blood. No plasma was used that was lipidemic or, in a preliminary aggregation experiment, showed no second-phase aggregation (aspirin-like effect). Blood was collected by the two-syringe technique. It was decalcified with 3.8% sodium citrate solution, one part to nine parts of blood. The citrated blood was centrifuged at 100g for 10 min and citrated platelet-rich plasma (PRP) was isolated. The residue was recentrifuged at 1500g for 15 min to give platelet-poor plasma (PPP).

Inhibition of ADP-Induced Platelet Aggregation. Compounds were tested for inhibition of ADP-induced aggregation in a Bryston platelet aggregometer by the procedure of Mustard et al.[5] Human PRP was diluted with autologous PPP to 400000 platelets/mm^3. Saline was added to another aliquot of the same plasma sample to serve as control. After incubation for 20 min at 37°, ADP (2 μg/ml final concentration) was added to induce aggregation. The increase in light transmittance (ΔT) through the plasma sample in the aggregometer, produced by platelet aggregating, was recorded. The maxima of the ΔT responses for control and test samples were then used to calculate percent inhibition of platelet aggregation by the test compound. More detail on the method and its variability is discussed elsewhere.[8]

Platelet Factor 3 Activation. Test compound solution was added to human citrated PRP and incubated at 37° for 20 min; a modified Stypven test was then performed. Plasma was diluted 1:10 for this modified test.[6]

In Vivo Effect on in Vitro ADP-Induced Aggregation.[8] Test compound was given to guinea pigs by a stomach tube at the indicated dose for 4 days. An untreated control group was maintained alongside. Blood was removed by heart pucture 2 h after the last dose and citrated PRP was isolated and adjusted for in vitro ADP-induced platelet aggregation. ADP was added at the concentration indicated in Table III. Max ΔT were obtained as described above. Total response was obtained by measuring the area between the aggregation curve and baseline transmittance for the 5-min period following ADP addition with a planimeter. Percent inhibition was calculated from the average total response of treated vs. control group.

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Central Nervous System Active 5-Oxo-1,4,5,6,7,8-hexahydrocinnolines[1]

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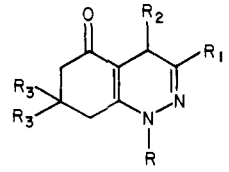
Among a series of 5-oxo-1,4,5,6,7,8-hexahydrocinnolines examined for their CNS activity, 1-(2-diethylaminoethyl)-3-(*p*-fluorophenyl)-5-oxo-7,7-dimethyl-1,4,5,6,7,8-hexahydrocinnoline (**23**) and 1-(2-dimethylaminoethyl)-3-phenyl-5-oxo-7,7-dimethyl-1,4,5,6,7,8-hexahydrocinnoline (**27**) had sedative and anticonvulsant properties and were also active in tests used to characterize antidepressants. But their narrow safety margin precluded further follow-up studies. Derivatives **35–38** of 2-(ω-phenacyl)-3-hydrazino-5,5-dimethyl-2-cyclohexenone were active in tests used to characterize antidepressants and were weakly sedative but not anticonvulsant.

The multifactorial etiology of the depressive syndrome calls for "wide-spectrum antidepressants", encompassing depression-relieving, drive-enhancing, and anxiolytic effects.[2a] The pharmacological profile of maprotiline demonstrates such bipolar activity with both antidepressant as well as sedative tranquillizing properties.[2b] In the course of our continuing work on CNS-active drugs,[3] we encountered moderately interesting wide-spectrum activity in the CNS profile in a series of novel 5-oxo-1,4,5,6,7,8-hexahydrocinnolines. We report briefly the results of our study of this series.

Chemistry. The title compounds **13–32** were synthesized in moderate to good yields from ketones **1–8** by reaction with appropriate hydrazines and are listed in Table I. The ketones became available from cyclohexane-1,3-diones by alkylation with phenacyl bromides

Table I. 5-Oxo-1,4,5,6,7,8-hexahydrocinnolines



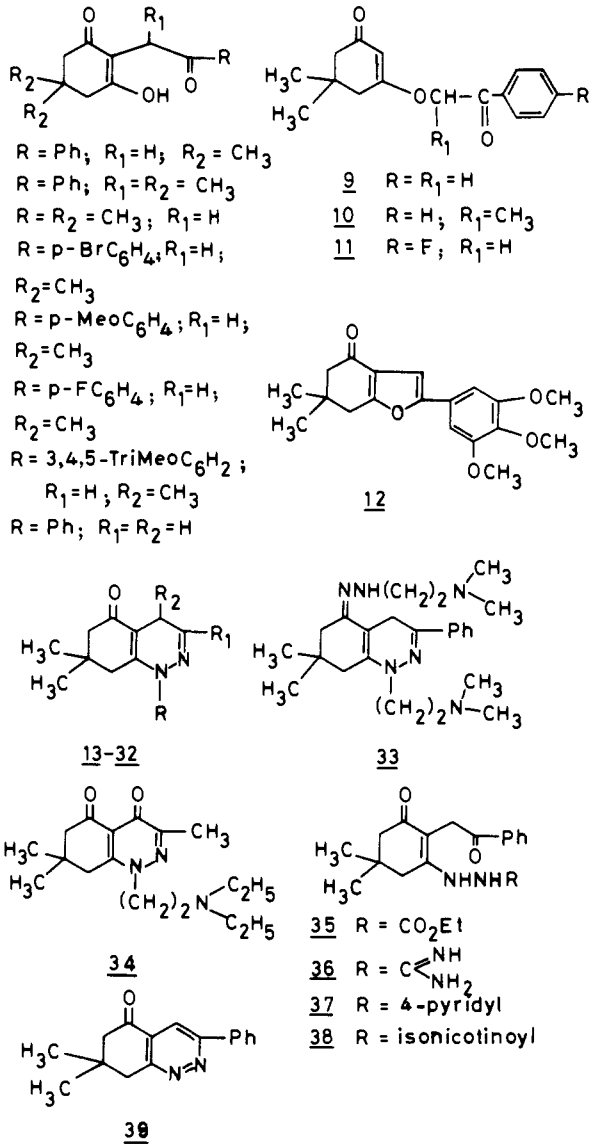
Compd no.	R	R_1	R_2	R_3	Yield, %	Solvent of crystn[a]	Mp, °C	Mol formula
13	H	CH_3	H	CH_3	79	A	157-159	$C_{11}H_{16}N_2O$
14	H	C_6H_5	H	CH_3	80	B	235-238	$C_{16}H_{18}N_2O$[k]
15	CH_3	C_6H_5	H	CH_3	33	C	105-108	$C_{17}H_{20}N_2O$
16	C_6H_5	C_6H_5	H	CH_3	80	C	141-142	$C_{22}H_{22}N_2O$
17	CH_2CH_2OH[b,c]	C_6H_5	H	CH_3	53	D	185-187	$C_{25}H_{20}N_2O_5S$
18	$CONH_2$	C_6H_5	H	CH_3	22	D	202-203	$C_{17}H_{19}N_3O_2$
19	$CH_2CH_2NEt_2$[d]	C_6H_5	H	CH_3	55	D	186-189	$C_{22}H_{22}ClN_3O_5$
20	$CH_2CH_2NEt_2$[e]	C_6H_5	CH_3	CH_3	63	E	228-230	$C_{23}H_{33}N_3O \cdot 1.5HClO_4$[l,m]
21	$CH_2CH_2NEt_2$[d]	p-MeO-C_6H_4	H	CH_3	69	D	162-163	$C_{23}H_{34}ClN_3O_6$
22	$CH_2CH_2NEt_2$	p-Br-C_6H_4	H	CH_3	60	F	124-125	$C_{22}H_{30}BrN_3O$
23	$CH_2CH_2NEt_2$	p-F-C_6H_4	H	CH_3	41	F	78-79	$C_{22}H_{30}FN_3O$
24	$CH_2CH_2NEt_2$[d]	3,4,5-$(MeO)_3$-C_6H_2	H	CH_3	5	D	205-207	$C_{25}H_{38}ClN_3O_8$
25	$CH_2CH_2NEt_2$[d]	C_6H_5	H	H	54	G	180-182	$C_{20}H_{28}ClN_3O_5$
26	$CH_2CH_2NEt_2$[f]	CH_3	H	CH_3	25	D	189-191	$C_{17}H_{31}Cl_2N_3O_9$[l]
27	$CH_2CH_2NMe_2$[d]	C_6H_5	H	CH_3	42	H	179-181	$C_{20}H_{28}ClN_3O_5$
28	$CH_2CH_2NMe_2$[d]	p-Br-C_6H_4	H	CH_3	46	H	202-204	$C_{20}N_{27}BrClN_3O_5$
29	$CH_2CH_2NMe_2$[g]	p-F-C_6H_4	H	CH_3	45	D	145-148	$C_{22}H_{28}FN_3O_5 \cdot 0.5H_2O$
30	$CH_2CH_2CH_2NMe_2$[h]	C_6H_5	H	CH_3	76	H	110-112	$C_{21}H_{30}ClN_3O_5 \cdot H_2O$
31	CH_2CH_2-c-$N(CH_2CH_2)_2NH$[i]	p-Br-C_6H_4	H	CH_3	45	D	185[m]	$C_{22}H_{31}BrCl_2N_4O \cdot 2H_2O$[l]
32	CH_2CH_2-c-$N(CH_2CH_2)_2NH$[j]	p-F-C_6H_4	H	CH_3	37	D	165-175	$C_{36}H_{45}FN_4O_7S_2 \cdot H_2O$

[a] The solvents are A, benzene; B, THF-EtOH; C, Et_2O-hexane; D, EtOH; E, MeOH; F, hexane; G, water; H, aqueous EtOH. [b] Tosylate salt. [c] Free base, mp 152-153° (from Et_2O-hexane). Anal. ($C_{18}H_{22}N_2O_2$) C, H, N. [d] Monoperchlorate. [e] Sesquiperchlorate. [f] Diperchlorate. [g] Oxalate hemihydrate. [h] Perchlorate monohydrate. [i] Dihydrochloride dihydrate. [j] Ditosylate monohydrate. [k] M^+ at m/e 254. [l] Correct chlorine. [m] M^+ at m/e 367. [n] $-H_2O$ at 130.

or chloroacetone. In occasional cases, O-alkylated products **9–11** and in one case, **7**, the ketotetrahydrobenzfuran **12** were isolated. The hexahydrocinnolines were characterized by analysis and NMR, ir, and uv spectra, the last one especially being typical of this series with a characteristic maximum at about 350–380 nm in addition to those at shorter wavelengths. In the reaction of **1** with 2-dimethylaminoethylhydrazine, the hydrazone **33** was obtained as a by-product. Dioxohexahydrocinnoline **34** (of tentative structure) was likewise formed as a minor product in the reaction of **3** with 2-diethylaminoethylhydrazine presumably by oxidation of the reactive methylene group at position 4 in the initially formed cinnoline **26**. Its molecular formula was established by elemental analysis and mass spectrum. The structure was suggested by the presence of an extra C=O group in the ir spectrum and the absence of a CH_2 singlet at δ 2.35 ppm in the NMR spectrum. Cinnoline derivatives did not result from the reaction of ketone **1** with carbethoxyhydrazine, aminoguanidine, 4-pyridylhydrazine, and isonicotinic acid hydrazide. Only the uncyclized products **35–38** were formed. The tetrahydrocinnoline **39** has been reported by us earlier.[4] It may be noted that reaction of ketones of the type **1** with N,N-substituted hydrazines leads to 3-amino-4-oxo-4,5,6,7-tetrahydroindoles by a novel route.[5] Hexahydrocinnolines have been synthesized from 2-(2-oxocyclohexyl)acetophenone by reaction with hydrazine. These were unstable and were dehydrogenated to 5,6,7,-8-tetrahydrocinnolines.[6] Obviously, the enamino ketone system present in **13–32** renders these compounds stable.

Pharmacology. Compounds were administered orally (po) in 0.2% agar suspension or parenterally (ip) to CF male mice for evaluation of the CNS profile.[7] Scoring of CNS depressant effects was done at a dose of 500 mg/kg po at peak drug effect (test 1) on a 0–4+ basis and the scores were collectively assessed on the percentage inhibition of spontaneous motor activity (SMA),[8] ptotic index determined from percentage eye closure,[9] and on the degree of sedation[7] (Table II). Protection against seizures at 500 mg/kg po (test 2) and against chemoshock, strychnine, and metrazole[10] was also examined. The compounds were also tested at a dose of 25 mg/kg po for their activity in the mouse Dopa response potentiation test[11] (test 3) and for their ability to antagonize reserpine-induced hypothermia[12] (test 4). Tests 3 and 4 are commonly used in characterizing potential antidepressants.

Discussion of Results. The acyclic derivatives **35–38** showed moderate to good activity in the Dopa test and in antagonizing reserpine-induced hypothermia. They exhibited in addition a slight degree of sedation (test 1) but had no activity in the electroshock test (test 2). Hydrocinnolines **13–16** and **18** lacking a basic side chain at position 1 were generally devoid of sedative and anticonvulsant activity and were only weakly or moderately active in tests 3 and 4. Compound **17** with a hydroxyethyl side chain was an exception, showing additionally slight sedative activity. The more aromatic derivative **39** was comparable to **17** in tests 1, 3, and 4 and was also found to have some anticonvulsant activity.



The introduction of a diethylaminoethyl side chain at position 1 resulted in **19** with an interesting spectrum of activity. Cinnoline **19** was moderately sedative. It had good activity in the Dopa test and moderate activity in test 4. It was also active in the electroshock test, with an ED_{50} of 225 mg. One or more of these activities were lost to some extent upon introduction of a methoxy group in the phenyl ring at position 3 (compound **21**) or three methoxy groups (compound **24**), an additional methyl group at position 4 (compound **20**) or replacement of the phenyl by a methyl group at position 3 (compound **26**) or by the removal of the *gem*-dimethyl group at position 7 (compound **25**). Cinnoline **34** carrying a methyl group at position 3 and a keto group at 4 was moderately active in test 3 and more so in test 4, but it had no depressant or anticonvulsant properties. The introduction of a bromine atom in the phenyl group at position 3 (compound **22**) helped to increase the anticonvulsant activity (ED_{50} 100 mg) while other properties of **19** were retained. The *p*-fluorophenyl derivative **23** was a more potent CNS depressant showing sedation even at 25 mg/kg po; however, it was more toxic than the rest.

Replacement of the diethylaminoethyl side chain in **19** by a dimethylaminoethyl moiety (compound **27**) resulted in a significant improvement of depressant properties and retention of activities in tests 3 and 4; thus, **27** exhibited dose-dependent sedation at 25 mg/kg po and above, but it was only half as potent as **19** as an anticonvulsant.

Cinnoline **28** with an extra bromine atom in the para position of the phenyl group was less sedative. It was active in the Dopa test but inactive in test 4. However, the antielectroshock activity increased fivefold. The *p*-fluorophenyl compound **29** was toxic and had surprisingly no sedative or anticonvulsant properties. Compound **33**, the dimethylaminoethylhydrazone of **27**, was again totally uninteresting.

Upon increasing the length of the side chain in **27** from a two to a three carbon one (compound **30**), activities in tests 2, 3, and 4 were retained but depressant activity was significantly lowered. Compounds **31** and **32** carrying a piperazinoethyl side chain were both uninteresting.

Table II. CNS Activity of 5-Oxo-1,4,5,6,7,8-hexahydrocinnolines and Related Compounds

Compd no.	CNS depressant effect[a] (test 1)	Act. against electroshock (test 2), ED_{50}, mg/kg po	Dopa test[b] (test 3)	Antagonism of reserpine induced hypothermia[c] (test 4)
13	0	Nil	+++	+
14	0	Nil	++	++
15	0	Nil	++	+++
16	0	Nil	+	++
17	+	Nil	+++	++
18	0	Nil	+++	++
19	++[d]	225	+++	++
20	+[d]	400	++	+
21	+	300	++	+
22	++[d]	100	++	++
23	+++[d,e]	150	+++	++
24	0	Nil	++	+++
25	0[e]	200	+++	++
26	++	Nil	+	++
27	++++[d]	500	+++	++
28	+++	100	+++	Nil
29	0[d,e]	Nil	++	++
30	+	500	+++	++
31	++	Nil	+	++
32	0	Nil	+++	++
33	0	Nil	–	–
34	0	Nil	++	+++
35	+	Nil	++	+++
36	+	Nil	+++	++++
37	+	Nil	+++	++++
38	+	Nil	+++	+++
39	+[d]	500	++	++

[a] Scoring of CNS depressant effects in CF albino mice.

% inhibn, SMA	% eye closure (approx)	deg of sedation	final score
No change from baseline			0
1-25	25	Slight	+
26-50	50	Moderate	++
51-75	75	Marked; arousability present	+++
76-100	100	Marked; arousability absent	++++

[b] Scoring system: % potentiation, 0-25 = +, 26-50 = ++, 51-75 = +++, 76-100 = ++++. [c] Scoring system same as in footnote *b*. [d] Tremors, mild convulsions. [e] Toxic.

Conclusion

While no rigid structure–activity relationships were discernible in the hexahydrocinnoline series, the most

interesting profiles were exhibited by **23**, with a diethylaminoethyl side chain at position 1 and a *p*-fluorophenyl at position 3, and by **27** having a dimethylaminoethyl and phenyl group, respectively, at these positions. However, their toxicity precluded further development. Compounds **35–38** were moderately active in tests 3 and 4, commonly used for characterizing antidepressants, but these were not potent enough to merit follow-up studies.

Experimental Section

Melting points are uncorrected; all compounds were analyzed for C, H, and N and some for chlorine and gave results within ±0.4% of the theoretical values. Uv, ir, and NMR spectral data were consistent with the structures assigned.

2-(2-Hydroxy-6-oxo-1-cyclohexenyl)acetophenone. A slurry of dimedone (14 g, 0.1 mol), α-bromoacetophenone (19.9 g, 0.1 mol), and anhydrous potassium carbonate (13.8 g, 0.1 mol) in chloroform was kept stirred at room temperature for 48 h. The mixture was filtered; the insoluble salts were dissolved in water and the filtered solution was made acidic with concentrated HCl. The precipitate was filtered off, washed with water, and crystallized from aqueous alcohol to give 1 (23.8 g, 92%), mp 180–182°. Anal. ($C_{16}H_{18}O_3$) C, H. The original chloroform filtrate was evaporated and the residual gum rubbed with hexane to give **9** (1.2 g, 4.5%), mp 128° (transition 107°). Anal. ($C_{16}H_{18}O_3$) C, H. Similarly prepared were **2** [mp 143–145°, 15% (from MeOH). Anal. ($C_{17}H_{20}O_3$) C, H] along with **10** [mp 160–161°, 8% (from aqueous MeOH). Anal. ($C_{17}H_{20}O_3$) C, H], **3** [mp 135–137°, 51% (from aqueous alcohol). Anal. ($C_{11}H_{16}O_3$) C, H], **4** [mp 172–174°, 70% (from alcohol). Anal. ($C_{16}H_{17}BrO_3$) C, H], **5** [mp 167–168°, 44% (from aqueous alcohol). Anal. ($C_{17}H_{20}O_4$) C, H], **6** [mp 157–160°, 80% (from aqueous alcohol). Anal. ($C_{16}H_{17}FO_3$) C, H] along with **11** [mp 135–137°, 12% (from aqueous alcohol). Anal. ($C_{16}H_{17}FO_3$)], and **7** [as a gum (60%)] along with furan **12** [mp 280–282°, 5% (from alcohol). Anal. ($C_{19}H_{22}O_5$) C, H]. Compound **8** was prepared by a known procedure.[13]

5-Oxo-1,4,5,6,7,8-hexahydrocinnolines. Ketone 1 (2.6 g, 10 mmol) was mixed with 3-dimethylaminoethylhydrazine (3.5 g, 30 mmol) when an exothermic reaction occurred. After 15 min, alcohol (25 ml) was added and the solution heated under reflux for 2–4 h. Solvent was then evaporated off in vacuo and the residue taken up in ether. The ether layer was washed with water, dried, and evaporated to give **30** as an oil (3.5 g). The perchlorate salt was crystallized from aqueous alcohol (3.5 g, 76%), mp 110–112°.

Other derivatives were similarly prepared.

The total product from the reaction of 1 with dimethylaminoethylhydrazine was converted into the perchlorate which was crystallized from MeOH to give **33**·3$HClO_4$ (25%), mp 207–209°. Anal. ($C_{24}H_{41}Cl_3N_6O_{12}$) C, H, N, Cl. The desired product **27** was obtained as the monoperchlorate from the mother liquor and crystallized from aqueous alcohol: 42%; mp 179–181°.

The product from the reaction of **3** with diethylaminoethylhydrazine was extracted with ether and the ether solution concentrated to give (tentatively) **34** (8%): mp 119–121°; M^+ at *m/e* 305. Anal. ($C_{17}H_{27}N_3O_2$) C, H, N. The mother liquors were evaporated and the residue was converted to the perchlorate. Crystallization from MeOH gave **26** as the diperchlorate.

Uncyclized Derivatives 35–38 of Ketone 1. These were prepared by heating a solution of the appropriate hydrazine and ketone 1 in alcohol under reflux for 4–10 h. The following were obtained.

35 (using *N*-carbethoxyhydrazine): 50%; mp 161–163° (from benzene–hexane). Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

36 (using aminoguanidine): 48%; mp 242–244° (from alcohol). Anal. ($C_{17}H_{22}N_4O_2$) C, H, N.

37 (using 4-pyridylhydrazine): 71%; mp 232–234° (from $CHCl_3$–EtOH). Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

38 (using isonicotinic acid hydrazide): 58%; mp 212–213° (from alcohol). Anal. ($C_{22}H_{23}N_3O_3$) C, H, N.

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