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/mm³. 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-hexahydrocinnolines¹

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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



				ļ				
				ĸ		Sol-		
						vent		
Compd					Yield.	of		
no.	R	\mathbf{R}_{i}	R_2	R ₃	%	crystn ^a	Mp, °C	Mol formula
13	Н	CH	Н	CH	79	A	157-159	C ₁₁ H ₁₆ N,O
14	н	C.H.	Н	CH	80	В	235-238	$C_{1}H_{1}N_{2}O^{k}$
15	CH	C.H.	н	CH	33	С	105-108	C, H, N,O
16	C.H.	C.H.	Н	CH	80	С	141 - 142	C, H, NO
17	CH.CH.OH ^{b,c}	C.H.	н	CH	53	D	185-187	C, H, N,O,S
18	CONH	C.H.	H	CH	22	D	202-203	C, H, N,O,
19	CH.CH.NEt.d	Ċ.H.	Н	CH	55	D	186-189	C, H, CIN, O.
20	CH.CH.NEL e	Č.H.	CH.	CH	63	E	228-230	C,H,N,O
		-65	3		• -			1.5HClO, ^{1,m}
21	CH_CH_NEL ^d	n-MeO-C.H.	Н	CH	69	D	162-163	C, H, CINO
22	CH.CH.NEt.	p-Br-C.H.	Н	ĊH	60	F	124 - 125	C. H. BrN. O
23	CHICHINEL	p-F-C.H.	Н	CH	41	\mathbf{F}	78-79	C, H, FN, O
24	CH, CH, NEt, d	3.4.5-(MeO)	H	CH	5	D	205-207	C, H, CIN, O,
		C.H.		5				20 00 0 0
25	CH,CH,NEt,d	C, H,	н	Н	54	G	180-182	$C_{20}H_{28}CIN_{3}O_{5}$
26	CH, CH, NEt, ^f	CH	Н	CH,	25	D	189-191	$\mathbf{C}_{1},\mathbf{H}_{1},\mathbf{C}_{1},\mathbf{N},\mathbf{O}_{2}^{l}$
27	CH CH NMe d	C, H,	Н	CH	42	н	179-181	C, H, CIN, O,
28	CH, CH, NMe, d	p-Br-C, H,	Н	CH	46	н	202-204	$C_{20}N_{27}BrClN_{3}O_{5}$
29	CH, CH, NMe, ^g	p-F-C,H	Н	CH	45	D	145-148	C ₁₂ H ₂₈ FN ₃ O ₅
		- 0 -		5				0.5H,O
30	CH,CH,CH,NMe, ^h	C, H,	Н	CH,	76	н	110-112	C ₂₁ H ₃₀ ČlN ₃ O ₅ ·
		0,0		5				H ₂ Ô
31	CH,CH,-e-	p-Br-C ₆ H ₄	Н	CH,	45	D	185^{m}	$C_{22}H_{11}BrCl_{2}N_{4}O$
	N(CH,CH,),NH ⁱ	- 04		3				$2H_{i}O^{l}$
32	CH,CH,-e-	p-F-C ₆ H ₄	Н	CH,	37	D	165-175	C ₁₆ H ₄ , FN ₄ O ₇ S,
	N(CH ₂ CH ₂) ₂ NH ⁱ	- 0 -		3				Ĥ,Ö

^a The solvents are A, benzene; B, THF-EtOH; C, Et₂O-hexane; D, EtOH; E, MeOH; F, hexane; G, water; H, aqueous EtOH. ^b Tosylate salt. ^c Free base, mp 152-153° (from Et₂O-hexane). Anal. $(C_{1s}H_{22}N_2O_2)$ 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 -H₂O 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 CH₂ 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 3amino-4-oxo-4,5,6,7-tetrahydroindoles by a novel route.⁵ Hexahydrocinnolines have been synthesized from 2-(2oxocyclohexyl)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 sedation⁷ (Table II). Protection against seizures at 500 mg/kg po (test 2) and against chemoshock, strychnine, and metrazole¹⁰ 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 test¹¹ (test 3) and for their ability to antagonize reserpine-induced hypothermia¹² (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 ED50 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 (ED50 100 mg) while other properties of 19 were retained. The pfluorophenyl 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

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

Compd no.	CNS depressant effect ^a (test 1)	Act. against electro- shock (test 2), ED ₅₀ , mg/kg po	Dopa test ^b (test 3)	Antagonism of reserpine induced hypo- thermia ^c (test 4)
13	0	Ni1	+++	+
14	0	Ni1	+ +	+ +
15	0	Ni1	+ +	+ + +
16	0	Ni1	+	+ +
17	+	Ni1	+ + +	+ +
18	0	Ni1	+ + +	+ +
19	$++^{d}$	225	+ + +	+ +
20	$+^{d}$	400	+ +	+
21	+ .	300	+ +	+
22	$^{+ + d}$.	100	+ +	+ +
23	++++ ^d , ^e	150	+ + +	+ +
24	0	Ni1	+ +	+ + +
25	0^e	200	+ + +	+ +
26	++	Ni1	+	+ +
27	++++a	500	+ + +	+ +
28	+ + +	100	+ + +	Ni1
29	0 ^{a,e}	Ni1	+ +	+ +
30	+	500	+ + +	+ +
31	+ +	Ni1	+	+ +
32	0	Ni1	+ + +	+ +
33	0	Ni1		-
34	0	Nil	+ +	+ + +
35	+	Nil	+ +	+ + +
36	+	NIL	+ + +	+ + + +
37	+	NIL	+++	+ + + +
38	+	IN11 5.00	+++	+++
39	+ 4	500	++	++

^a Scoring of CNS depressant effects in CF albino mice.

% inhibn, SMA	% eye closure (approx)	deg of sedation	final score
No ch	ange		0
irom ba	senne		
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.

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.

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 $\pm 0.4\%$ 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. (C₁₆H₁₈O₃) 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. (C16H18O3) C, H. Similarly prepared were 2 [mp 143-145°, 15% (from MeOH). Anal. (C17H20O3) C, H] along with 10 [mp 160-161°, 8% (from aqueous MeOH). Anal. (C17H20O3) C, H], 3 [mp 135-137°, 51% (from aqueous alcohol). Anal. (C11H16O3) C, H], 4 [mp 172-174°, 70% (from alcohol). Anal. (C16H17BrO3) 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. (C16H17FO3) 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. (C19H22O5) 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 33.3HClO4 (25%), mp 207-209°. Anal. (C₂₄H₄₁Cl₃N₆O₁₂) 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 diethylaminoethyl-

hydrazine was extracted with ether and the ether solution concentrated to give (tentatively) **34** (8%): mp 119-121°; M⁺ at m/e 305. Anal. (C₁₇H₂₇N₃O₂) 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. (C₁₉H₂₄N₂O₄) 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 CHCl₃-EtOH). Anal. (C₂₁H₂₃N₃O₂) C, H, N.

38 (using isonicotinic acid hydrazide): 58%; mp 212–213° (from alcohol). Anal. (C₂₂H₂₃N₃O₃) C, H, N.

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