Table I—Twelve-Hour Area under the Blood Level *versus* Time Curve (AUC_0^{12}) Comparison for the Hard *versus* Soft Gelatin Capsule Formulations of I

Number	AUC_0^{12} (Hard Gelatin Capsule), μg hr/ml	AUC_0^{12} (Soft Gelatin Capsules), μg hr/ml	$\frac{AUC_0^{12} \text{ (Hard Gelatin Capsule)}}{AUC_0^{12} \text{ (Soft Gelatin Capsules)}}$
1	0.99	9.02	0.11
2	2.46	12.18	0.20
3	16.53	17.53	0.94
4	0.94	18.96	0.05
5	1.38	5.19	0.27
$\bar{x} \pm SD$	4.46 ± 6.77	12.58 ± 5.76 ($p < 0.05$)[b]	0.31 ± 0.36
$\bar{x} \pm SD$[a]	1.44 ± 0.71[a]	11.33 ± 5.83[a] ($p < 0.01$)[b]	0.16 ± 0.10[a]

[a] Numbers refer to the mean and standard deviation values if the data in each column for Dog 3 are disregarded. The AUC_0^{12} for Dog 3 given the hard gelatin capsule could be rejected using the Q test. [b] The AUC_0^{12} for the soft gelatin capsule formulation is significantly different from the AUC_0^{12} at the level indicated using the Student t test.

The results of the blood level–time studies for each dog for the two formulations are given in Fig. 1. Table I summarizes the area under the curve (AUC) data for the blood level–time profile. Also included is the relative AUC for the hard gelatin capsule *versus* the soft gelatin capsule formulation. Compound I was delivered significantly more efficiently from the oleic acid solvent soft gelatin capsule than from the hard gelatin capsule. For both formulations, there appears to be a significant lag time of 1–3 hr for I absorption.

The oleic acid formulation of the hydrophobic drug, I, in a soft gelatin capsule allowed the poorly water-soluble drug to enter the GI tract in a readily dispersible form, providing for more rapid and complete drug absorption. The mechanism for the increased I bioavailability can be postulated to be the emulsification of the oleic acid by the GI contents, resulting in the release of I which is then rapidly absorbed. Whether the drug is carried along by oleic acid absorption or whether it is actually released from oleic acid and subsequently absorbed is not known.

In summary, it appears that I as its hydrochloride is poorly bioavailable from its standard hard gelatin capsule formulation relative to I formulated in a soft gelatin capsule utilizing oleic acid as a solvent. The poor bioavailability of I from the hard gelatin capsule is probably due to its low aqueous solubility combined with a poor formulation design.

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Heterocyclic Tricycles as Potential CNS Agents I: 4-Aminoalkylindeno[1,2-*c*]pyrazoles

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Received November 7, 1977, from the **Department of Medicinal Chemistry and Pharmacognosy and the* [‡]*Department of Pharmacology, College of Pharmacy, University of Houston, Houston, TX 77004.* Accepted for publication January 31, 1978.

Abstract □ Series of 4-(3-dimethylaminopropyl)-4-hydroxyindeno[1,2-*c*]pyrazoles and 4-(1-methyl-4-piperidyl)-4-hydroxyindeno[1,2-*c*]pyrazoles were synthesized and identified. The compounds were evaluated as potential CNS agents using spontaneous and forced motor activity in mice as an initial test. 2-Ethyl-3-methyl-4-(1-methyl-4-piperidyl)-4-hydroxyindeno[1,2-*c*]pyrazole possessed significant biological activity.

Keyphrases □ Indenopyrazoles, substituted—synthesized, evaluated for CNS activity in mice □ CNS activity—evaluated in substituted indenopyrazoles in mice □ Structure–activity relationships—substituted indenopyrazoles evaluated for CNS activity in mice □ Heterocycles, tricyclic—substituted indenopyrazoles synthesized, evaluated for CNS activity in mice

Since the introduction of chlorpromazine, a potent central nervous system (CNS) depressant of the phenothiazine class, numerous tricyclic analogs have been investigated. Modification of the side chain and the central ring of the phenothiazines resulted in discovery of additional CNS depressants as well as CNS stimulants. A limited number of investigations involved replacement of one of the benzene rings with heterocyclic aromatic rings. The syntheses of 4-(3-dimethylaminopropylidene)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (I) derivatives (1) and 2-methyl-4-(3′-dimethylaminopropylidene)-9,10-dihydro-4*H*-benzo[5,6]cyclo-

Table I—1- and 2-Alkyl-3-substituted Indeno[1,2-*c*]pyrazol-4(1*H*)-ones

Compound	R_1	R_2	Melting Point	Yield, %[a]	Molecular Formula	Analysis, %	Calc.	Found
VI*a*	CH_3	C_6H_5	192–193°[b]	54	$C_{17}H_{12}N_2O$	C	78.44	78.58
						H	4.65	4.69
						N	10.76	10.74
VI*b*	C_2H_5	C_6H_5	136°[b]	45	—		—	—
VI*c*	$(CH_3)_2CH$	C_6H_5	176–177°[b]	38	$C_{19}H_{16}N_2O$	C	79.14	79.02
						H	5.59	5.61
						N	9.72	9.74
VI*d*	CH_3	$(CH_3)_3C$	147°[b]	46	$C_{15}H_{16}N_2O$	C	74.97	74.86
						H	6.71	6.72
						N	11.66	11.70
VI*e*	C_2H_5	$(CH_3)_3C$	116–118°[b]	50			—	—
VI*f*	$(CH_3)_2CH$	$(CH_3)_3C$	86°[b]	35	$C_{17}H_{20}N_2O$	C	76.09	76.13
						H	7.51	7.53
						N	10.44	10.44
VI*g*	CH_3	CH_3	140–142°[c]	19	$C_{12}H_{10}N_2O$	C	72.70	72.51
						H	5.08	5.12
						N	14.13	13.96
VI*h*	C_2H_5	CH_3	110°[d]	17	$C_{13}H_{12}N_2O$	C	73.56	73.69
						H	5.70	5.79
						N	13.20	13.18
VI*i*	$(CH_3)_2CH$	CH_3	145–146°[c]	23	$C_{14}H_{14}N_2O$	C	74.31	74.17
						H	6.24	6.25
						N	12.38	12.42
VII*a*	CH_3	CH_3	167°[c]	28	$C_{12}H_{10}N_2O$	C	72.70	72.46
						H	5.08	5.14
						N	14.13	14.16
VII*b*	C_2H_5	CH_3	94–96°[d]	26	$C_{13}H_{12}N_2O$	C	73.56	73.60
						H	5.70	5.72
						N	13.20	13.26
VII*c*	$(CH_3)_2CH$	CH_3	108–110°[d]	17	$C_{14}H_{14}N_2O$	C	74.31	74.25
						H	6.24	6.25
						N	12.38	12.41

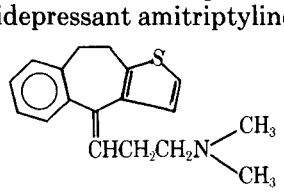
[a] Yield of VI*a*–VI*i* and VII*a*–VII*c* from V*a*–V*c*. [b] From 95% ethanol. [c] From ethanol. [d] From cyclohexane.

Table II—1- and 2-Ethyl-3-substituted 4-Alkylamino-4-hydroxyindeno[1,2-*c*]pyrazoles

Compound	R_2	Melting Point	Yield, %	Molecular Formula	Analysis, %	Calc.	Found
VIII*a*	C_6H_5	174–177°[a]	71	$C_{23}H_{27}N_3O$	C	76.41	74.46
					H	7.53	7.58
					N	11.62	11.66
VIII*b*	$(CH_3)_3C$	125–126°[a]	73	$C_{21}H_{31}H_3O$	C	73.85	73.81
					H	9.15	9.16
					N	12.30	12.24
VIII*c*	CH_3	139°[b]	46	$C_{18}H_{25}N_3O$	C	72.21	72.23
					H	8.42	8.42
					N	14.03	14.02
IX*a*	C_6H_5	249–252°[a]	54	$C_{24}H_{27}N_3O$	C	77.18	76.97
					H	7.29	7.33
					N	11.24	11.16
IX*b*	$(CH_3)_3C$	141–149°[b]	48	$C_{22}H_{31}N_3O$	C	74.74	74.55
					H	8.84	8.90
					N	11.89	11.83
IX*c*	CH_3	158–161°[c]	51	$C_{19}H_{25}N_3O$	C	73.28	73.08
					H	8.09	8.13
					N	13.49	13.44
X	—	124–126°[d]	79	$C_{18}H_{25}N_3O$	C	72.21	72.13
					H	8.42	8.45
					N	14.03	14.00
XI	—	211–213°[b]	58	$C_{19}H_{25}N_3O$	C	73.28	73.27
					H	8.09	8.12
					N	13.49	13.51

[a] From 95% ethanol. [b] From cyclohexane. [c] From ethyl acetate. [d] From benzene–cyclohexane.

hepta[1,2-*d*]thiazole, imidazole, and oxazole (II*a*–II*c*) derivatives (2) were reported. Both series are analogs of the antidepressant amitriptyline.



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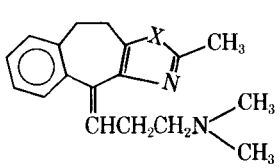


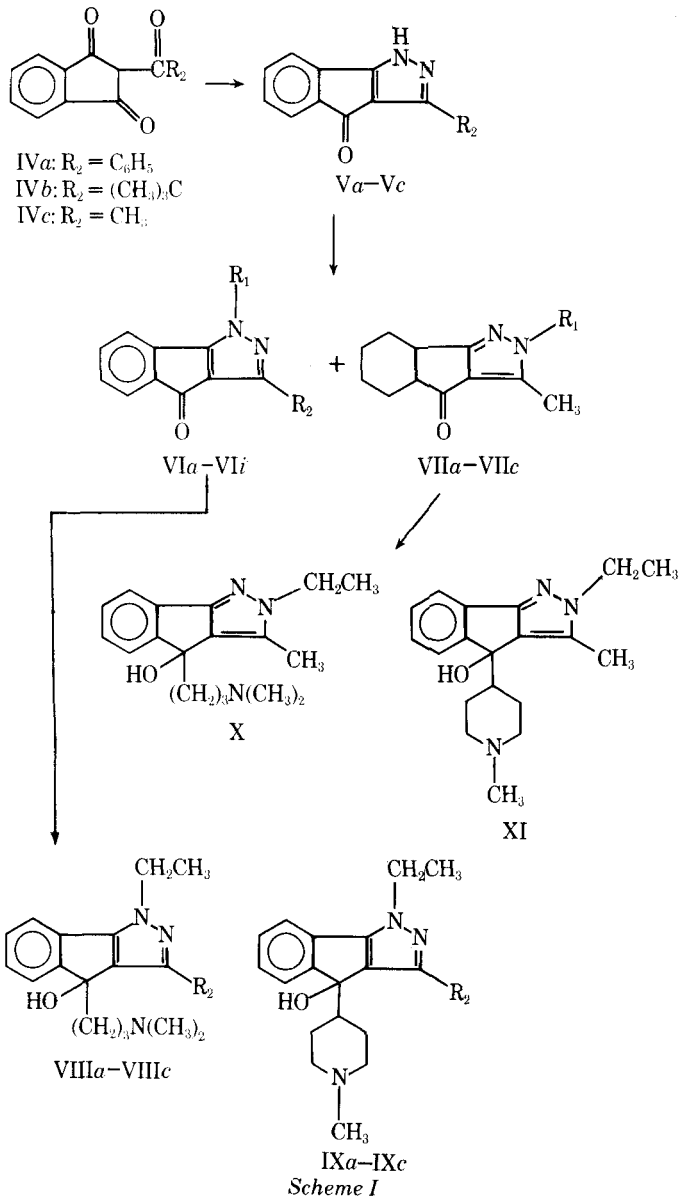
II*a*: X = S
II*b*: X = N
II*c*: X = O

The present investigation concerned the effect of novel heterocyclic tricyclic nuclei as potential CNS agents; synthesis, identification, and evaluation of substituted indeno[1,2-*c*]pyrazoles are reported.

EXPERIMENTAL[1]

Chemistry—The indeno[1,2-*c*]pyrazol-4(1*H*)-ones (V*a*–V*c*, Scheme

Melting points were taken with a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. NMR data were recorded on a Varian Associates model EM-360 spectrophotometer with tetramethylsilane as an internal standard. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Ga.



Scheme I

I) were prepared from the corresponding triketones (IV*a*–IV*c*) through the one- or two-step addition of hydrazine (3–6). Alkylation of the sodium salts of V*a*–V*c* with alkyl halides resulted in the preparation of 1-alkyl-3-substituted indeno[1,2-*c*]pyrazol-4(1*H*)-ones (VI*a*–VI*i*) when R_2 was *tert*-butyl or phenyl and the 1- and 2-alkyl-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-ones (VII*a*–VII*c*) when R_2 was methyl. The 1-ethyl- and 2-ethyl-3-substituted indeno[1,2-*c*]pyrazol-4(2*H*)-ones were converted to the 4-alkylated products (VIII*a*–VIII*c*, IX*a*–IX*c*, X, and XI) *via* reaction with Grignard reagents (Scheme I).

Table III—NMR Data for 1- and 2-Alkyl-3-substituted Indeno[1,2-*c*]pyrazol-4(1*H*)-ones

Compound	R_1			R_2
	CH_3	CH_2	CH	
VI*a*	3.85 (s)			6.90–8.24 (m) (C_6H_5)
VI*d*	3.92 (s)			1.38 (s) [$(CH_3)_3C$]
VI*g*	3.87 (s)			2.28 (s) (CH_3)
VII*a*	3.79 (s)			2.35 (s) (CH_3)
VI*b*	1.48 (t)	4.10 (q)		6.78–8.30 (m) (C_6H_5)
VI*e*	1.52 (t)	4.20 (q)		1.38 (s) [$(CH_3)_3C$]
VI*h*	1.50 (t)	4.17 (q)		2.29 (s) (CH_3)
VII*b*	1.43 (t)	4.02 (q)		2.41 (s) (CH_3)
VI*c*	1.62 (d)		4.60 (m)	6.80–8.38 (m) (C_6H_5)
VI*f*	1.59 (d)		4.60 (m)	1.39 (s) [$(CH_3)_3C$]
VI*i*	1.60 (d)		4.57 (m)	2.32 (s) (CH_3)
VII*c*	1.48 (d)		4.30 (m)	2.39 (s) (CH_3)

Table IV—LD_{50}, ED_{50}, and Safety Indexes of Indenopyrazole Derivatives

Compound	LD_{50}[a]	ED_{50}[a,b]	Safety Index (LD_{50}/ED_{50})
VIII*a*	148.2 (No interval)	42.3 (16.9–105.8)	3.50
VIII*b*	420.6 (268.9–657.9)	70.0 (45.2–108.5)	6.01
VIII*c*	468.6 (398.3–551.4)	>187.4	<2.5
IX*a*	168.3 (136.1–208.2)	89.0 (40.0–197.9)	1.89
IX*b*	318.6 (257.4–394.3)	86.2 (63.4–117.2)	3.70
IX*c*	421.9 (358.6–496.4)	>168.8	<2.5
X	449.3 (398.8–507.1)	104.2 (49.6–218.8)	4.32
XI	571.7 (383.2–853.0)	32.4 (12.0–87.5)	17.6
Haloperidol	49.7 (37.7–65.6)	1.55 (0.603–3.98)	32.1

[a] In milligrams per kilogram intraperitoneally (95% confidence interval in parentheses). [b] Determined using data on depression of spontaneous activity (Table V).

1-Ethyl-3-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one (VI*b*)—To 3 liters of 10% NaOH was added 18.7 g (0.075 mole) of V*a* (4), and the mixture was heated to boiling. Charcoal was added, the solution was filtered while hot, and the filtrate was cooled to yield 13.4 g (67%) of sodium 3-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one, mp >300°. The dried salt (0.05 mole) in 200 ml of ethanol was treated with 20.8 g of ethyl bromide (0.2 mole) and heated under reflux for 16 hr. The solution was filtered and cooled, and the crystalline product was collected by filtration. The residue was recrystallized from 95% ethanol.

A similar procedure was used to synthesize VI*a* and VI*c*–VI*f*. Melting points, recrystallization solvents, and yields are listed in Table I.

1-Ethyl-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (VI*h*) and 2-Ethyl-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (VII*b*)—To 3 liters of boiling 10% NaOH was added slowly 27.6 g (0.15 mole) of V*c* (6). After complete solution, the reaction mixture was boiled for 0.5 hr, filtered, and cooled. Then the solid was collected and dried to yield 19.1 g (62%) of sodium 3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one, mp >300°. The salt (10.3 g, 0.05 mole), 16.4 g (0.15 mole) of ethyl bromide, and 200 ml of ethanol were heated under reflux for 48 hr. The reaction mixture was filtered, concentrated *in vacuo*, diluted with 100 ml of water, and extracted with chloroform.

The combined chloroform extracts were dried. Solvent removal re-

Table V—Effects of Indenopyrazole Derivatives on Spontaneous Motor Activity in Mice

Compound	Dose[a] (*n*)	Activity Counts[b]	Percent of Control
Control[c]	— (18)	168.2 ± 21.3	100
VIII*a*	14.8 (6)	73.0 ± 19.9[d]	43.4
	29.6 (6)	100.5 ± 13.5	59.8
	59.3 (6)	68.3 ± 22.1[d]	40.6
VIII*b*	42.0 (6)	104.7 ± 40.6	62.2
	84.1 (6)	94.5 ± 24.7	56.2
	168.2 (6)	14.7 ± 5.4[d]	8.7
VIII*c*	46.9 (6)	280.2 ± 51.1[d]	166.6
	93.7 (6)	177.7 ± 46.1	105.6
	187.4 (6)	160.0 ± 32.0	95.1
IX*a*	16.8 (6)	164.0 ± 39.9	97.5
	33.7 (6)	162.3 ± 45.5	96.5
	67.3 (6)	109.8 ± 51.9	65.3
IX*b*	31.9 (6)	235.2 ± 49.8	139.8
	63.7 (6)	130.2 ± 34.1	77.4
	127.4 (6)	28.3 ± 11.1[d]	16.8
IX*c*	42.2 (6)	133.7 ± 42.6	79.5
	84.4 (6)	263.7 ± 145.9	156.8
	168.8 (6)	142.0 ± 44.1	84.4
X	45.0 (5)	119.8 ± 35.6	71.2
	89.9 (6)	145.0 ± 76.4	86.2
	179.9 (6)	66.2 ± 39.7	39.3
XI	57.2 (6)	55.7 ± 9.9[d]	33.1
	114.3 (6)	27.8 ± 7.2[d]	16.5
	228.7 (6)	31.2 ± 8.1[d]	18.5
Haloperidol	2.5 (3)	36.0 ± 22.0	21.4
	5.0 (3)	1.7 ± 0.9	1.0
	10.0 (3)	0.3 ± 0.3	0.18

[a] In milligrams per kilogram intraperitoneally; doses are 10, 20, and 40% of the LD_{50}. Number of mice tested is given in parentheses. [b] Activity counts (±*SE*) during 15-min test period. Drug was administered 40 min prior to initiation of activity counts. [c] Administered solvent instead of drug. [d] p *versus* control < 0.05 according to the Student t test.

Table VI—Effects of Indenopyrazole Derivatives on Forced Motor Activity in Mice

Compound	Dose[a] (*n*)	Third Trial[b]	Fourth Trial[b]	Percent of Control
VIII*a*	14.8 (6)	179.6 ± 13.0	170.1 ± 20.9	94.7
	29.6 (6)	205.2 ± 17.3	181.6 ± 10.6	88.5
	59.3 (6)	204.1 ± 13.1	113.7 ± 20.4[c]	55.7
VIII*b*	42.0 (6)	203.1 ± 23.7	191.4 ± 24.7	94.2
	84.1 (6)	222.6 ± 20.8	164.8 ± 44.1	74.0
	168.2 (6)	200.5 ± 18.5	59.5 ± 10.3[c]	29.7
VIII*c*	46.9 (6)	197.1 ± 18.2	152.2 ± 16.4	77.2
	93.7 (6)	215.9 ± 22.5	177.0 ± 16.1	82.0
	187.4 (6)	212.4 ± 15.8	175.6 ± 12.5	82.7
IX*a*	16.8 (6)	206.5 ± 8.9	203.8 ± 9.4	98.7
	33.7 (6)	223.7 ± 23.1	167.5 ± 13.9	74.9
	67.3 (6)	187.9 ± 15.4	146.1 ± 30.3	77.8
IX*b*	31.9 (6)	206.1 ± 22.2	187.7 ± 35.2	91.1
	63.7 (6)	208.8 ± 12.1	159.3 ± 19.7	76.3
	127.4 (6)	216.5 ± 23.2	127.4 ± 32.3[c]	58.8
IX*c*	42.2 (6)	193.2 ± 12.5	215.3 ± 22.7	111.4
	84.4 (6)	192.5 ± 11.1	184.7 ± 14.7	95.9
	168.8 (6)	211.6 ± 19.1	153.4 ± 28.1	72.5
X	45.0 (5)	207.9 ± 39.7	235.5 ± 27.7	113.3
	89.9 (6)	210.7 ± 21.3	215.4 ± 21.9	102.2
	179.9 (6)	191.0 ± 32.1	144.0 ± 35.7	75.4
XI	57.2 (6)	212.8 ± 16.2	215.9 ± 16.5	101.5
	114.3 (6)	195.1 ± 10.0	164.5 ± 21.4	84.3
	228.7 (6)	258.0 ± 14.7	115 ± 16.5[c]	44.8

[a] In milligrams per kilogram intraperitoneally; doses are 10, 20, and 40% of the LD_{50}. Number of mice tested is given in parentheses. [b] Seconds (± *SE*) mice remained on rotating rod. No drug was administered prior to the third (control) trial. Drug was administered 30 min prior to the fourth trial. [c] *p versus* control < 0.05 according to the Student *t* test.

Table VII—Effects of Indenopyrazole Derivatives on Rectal Temperature of Mice

Compound	Dose[a] (*n*)	Predrug[b]	Postdrug[b]	Change *versus* Control
VIII*a*	14.8 (6)	36.3 ± 0.2	35.3 ± 0.4[c]	−1.10
	29.6 (6)	36.4 ± 0.2	36.2 ± 0.4	−0.25
	59.3 (6)	36.7 ± 0.2	34.0 ± 0.4[c]	−2.70
XI	57.2 (6)	36.7 ± 0.2	36.4 ± 0.3	−0.25
	114.3 (6)	36.5 ± 0.3	35.3 ± 0.5[c]	−1.25
	228.7 (6)	36.1 ± 0.2	34.2 ± 0.5[c]	−1.92
VIII*b*	42.0 (6)	37.3 ± 0.8	36.5 ± 0.7	−0.83
	84.1 (6)	37.3 ± 0.3	35.4 ± 0.5[c]	−1.83
	168.2 (6)	35.9 ± 0.3	33.1 ± 0.2[c]	−2.83
X	45.0 (5)	35.8 ± 0.1	35.9 ± 0.4	+0.10
	89.9 (6)	35.0 ± 0.4	36.5 ± 0.4[c]	+1.50
	179.9 (6)	35.4 ± 0.3	33.8 ± 0.4[c]	−1.67
IX*b*	31.9 (6)	37.3 ± 0.2	37.0 ± 0.4	−0.25
	63.7 (6)	37.0 ± 0.3	36.5 ± 0.4	−0.50
	127.4 (6)	36.8 ± 0.2	34.2 ± 0.3[c]	−2.67
VIII*c*	46.9 (6)	37.7 ± 0.2	37.5 ± 0.7	−0.16
	93.7 (6)	37.5 ± 0.3	37.0 ± 0.3	−0.50
	187.4 (6)	37.0 ± 0.2	36.5 ± 0.3	−0.50
IX*c*	42.2 (6)	37.1 ± 0.1	37.3 ± 0.2	+0.25
	84.4 (6)	36.9 ± 0.2	37.1 ± 0.3	+0.17
	168.8 (6)	37.2 ± 0.2	35.6 ± 0.6[c]	−1.58
IX*a*	16.8 (6)	36.9 ± 0.3	37.0 ± 0.5	+0.08
	33.7 (6)	37.0 ± 0.3	37.3 ± 0.3	+0.25
	67.3 (6)	37.1 ± 0.2	35.7 ± 0.3[c]	−1.42

[a] In milligrams per kilogram intraperitoneally; doses are 10, 20, and 40% of the LD_{50}. Number of mice tested is given in parentheses. [b] Degrees (± *SE*) rectally. Predrug values were used as controls; postdrug temperature was taken 25 min after drug administration. [c] *p versus* control < 0.05 according to the Student *t* test.

sulted in recovery of 5.7 g of oil, which was chromatographed on 700 g of silica gel (on a 6 × 117-cm column) and eluted with chloroform; 100–150-ml fractions were collected. Compound VII*b* was eluted first, followed by VI*h*. The compounds were individually recrystallized as indicated in Table I.

A similar procedure was used to synthesize VI*g*, VI*i*, VII*a*, and VII*c*. Melting points, recrystallization solvents, and yields are listed in Table I.

1-Ethyl-3-phenyl-4-(3-dimethylaminopropyl)-4-hydroxyindeno[1,2-*c*]pyrazole (VIII*a*)—To 0.96 g (0.04 g atom) of magnesium and 25 ml of previously distilled tetrahydrofuran (dried over sodium hydride), stirred and maintained under nitrogen, was added dropwise 4.86 g (0.04 mole) of 3-dimethylaminopropyl chloride in 43 ml of tetrahydrofuran. The reaction was initiated with the aid of gentle heating and a few drops of methyl iodide. Grignard formation took 7 hr. To the reaction flask was added dropwise 5.48 g (0.02 mole) of VI*b* in 75 ml of tetrahydrofuran with stirring at 25°.

Following the addition, the reaction was heated under reflux for 3 hr and stirred at 25° for 12 hr. The reaction mixture was concentrated under reduced pressure, treated with 100 ml of 10% ammonium chloride, and stirred for 12 hr. Then the mixture was extracted with chloroform, and the combined extracts were dried. Solvent removal resulted in recovery of 5.1 g of VIII*a*.

A similar procedure was used for the synthesis of VIII*b*, VIII*c*, IX*a*–IX*c*, X, and XI. The melting points, recrystallization solvents, and yields are listed in Table II.

Pharmacological Evaluation—Acute 72-hr lethality was determined for each drug in male Swiss-Webster mice[2], 16–24 g. The LD_{50} values were determined using the method of Weil (7). All subsequent testing was done using three dose groups: 10, 20, and 40% of the LD_{50}. Rectal temperatures were measured using a telethermometer[3].

[2] Texas Inbred Mice Co., Houston, Tex.
[3] Yellow Springs Instrument Co., Yellow Springs, Ohio.

Effects on forced and spontaneous motor activity were determined as previously reported (8). The ED_{50} values for effects on spontaneous activity were determined by the method of Litchfield and Wilcoxon (9).

RESULTS AND DISCUSSION

The alkylation of Va–Vc with various alkyl halides to yield the 1-alkyl derivatives was uneventful when R_2 was the sterically large phenyl or *tert*-butyl group. This alkylation was successful when 3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one was alkylated since VI*a*–VI*i* and VII*a*–VII*c* formed. The isomers were separated by chromatography, and the products were identified by proton NMR spectroscopy.

As indicated in Table III, the protons of the alkyl at position 2 in VII*a*–VII*c* are shielded with respect to the protons of the alkyl at position 1 in VI*a*–VI*i*. The 1-methyl protons appear at approximately δ 3.9 ppm while the 2-methyl in VII*a* appears at δ 3.8 ppm. A similar trend is seen for the methyl and methylene protons in VI*b*, VI*c*, and VI*h* with respect to VII*b* and the methyl and methine protons in VI*c*, VI*f*, and VI*i* with respect to VII*c*.

As shown in Table IV, LD_{50} values in mice ranged from 148.2 (VIII*a*) to 571.7 (XI) mg/kg. 2-Ethyl-3-methyl-4-(1-methyl-4-piperidyl)-4-hydroxyindeno[1,2-*c*]pyrazole (XI) was the only one of the series to cause a significant depression of spontaneous motor activity at all doses tested (Table V). The safety index (LD_{50}/ED_{50}) for this compound was 17.6, remarkably higher than any other compound in the series although lower than that of haloperidol. Of the remaining compounds, VIII*b* and IX*b* depressed spontaneous activity, but the effect was significant only at the highest dose. Compounds VIII*a* and VIII*c* also produced significant decreases in spontaneous activity, but the dose–response relationship was inconsistent.

Statistically significant depression of forced motor activity was seen with VIII*a*, XI, VIII*b*, and IX*b*, but only at the highest dose tested (Table VI). The series of compounds tended to decrease rectal temperature, with XI and VIII*b* producing a clear dose-related decrease statistically significant at the middle and high doses (Table VII).

Of the compounds in this series, XI is the most appropriate candidate for further evaluation. Its high safety index, along with its preferential effect on spontaneous motor activity relative to that on forced motor activity, suggests potential utility as a psychotropic agent. A positional isomer of XI, IX*c*, was without noticeable biological activity.

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Interactions of Caffeine and Theophylline with *p*-Cresol: UV Studies

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Abstract □ UV absorption studies demonstrated the formation of weakly bonded charge transfer complexes between caffeine and theophylline with *p*-cresol in chloroform. The transitions involved were detected at wavelengths longer than those of the single pure substances. Equilibrium constants from the Benesi–Hildebrand equation could be measured together with other thermodynamic constants and molar extinction coefficients. In general, the equilibrium constants were very small while the entropies of formation were quite high. Even though the equilibrium constants of caffeine–*p*-cresol were independent of wavelength over a narrow range, the apparent enthalpies of formation of both complexes indicated wavelength dependence.

Keyphrases □ Caffeine—formation of charge transfer complexes with *p*-cresol, UV absorption study □ Theophylline—formation of charge transfer complexes with *p*-cresol, UV absorption study □ *p*-Cresol—formation of charge transfer complexes with caffeine and theophylline, UV absorption study □ Complexes, charge transfer—formed by caffeine and theophylline with *p*-cresol, UV absorption study

Phenols (1–4) and the purine and pyrimidine bases (5, 6) form charge transfer complexes with many organic compounds. The formation of these complexes between nucleic acid bases and catechol or epinephrine in aqueous solutions containing 0.1 *N* HCl was demonstrated (7–9). Evidence for the formation of charge transfer complexes between isoproterenol and nucleic acid bases in different solvents was described[1] (10). It was hypothesized (7–10) that the charge transfer phenomenon between the nucleic acid bases and catechol or catechol-containing substances might be involved in the mechanism of action of the biogenic amines at the molecular level as well as in their storage in the storage granules at the adrenal medulla and other nerve endings (11).

The present study concerns interactions of caffeine and theophylline with *p*-cresol in chloroform. The contribution of the aromatic nucleus is important information in tracing the mechanism of the formation of complexes between drugs having this nucleus and their receptors and may help explain the mechanism of action of the phenol-containing drugs. Chloroform was chosen as the solvent because of the solubility of the substances studied and the desire to exclude solvent effects in the formation of the complexes.

[1] Unpublished data.

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