ml). The $CHCl_3$ layer was dried (Na_2SO_4), filtered, and evapd under reduced pressure to give crude carbamate (253.1 mg, 91.7%); the nmr showed peaks at δ 1.24 and 4.15 for the Et group of the ethyl carbamate, ν_{max}^{KBr} (cm^{-1}) 3500 (OH,NH) and 1700 (C=O). This product was used for the subsequent reduction without further purification.

LAH reduction of crude **3b** in dioxane gave 92.0% yield of **25-aza-26-norlanost-8-en-3β-ol (3c)**: mp 164–166° (Me_2CO); $[\alpha]_D$ +54.7°; ν_{max}^{KBr} (cm^{-1}) 3615 (OH) and 3345 (NH); nmr δ 1.67 (**OH,NH**) and 2.49 (s, 3 H, **NCH**$_3$). *Anal.* ($C_{28}H_{49}NO$) C, H.

24ξ-Bromolanost-8-ene-3β,25-diol 3-Acetate (4a).—A soln of NBS (3 g) in H_2O and $HClO_4$ acid (70%, 3 ml) was added to a soln of lanosterol acetate[12] (7 g) in dioxane (300 ml), and the mixture was stirred for 1 hr, poured into H_2O, and filtered. The product was extd into $CHCl_3$, and the organic layer was washed successively with $Na_2S_2O_3$ soln, H_2O, dried, and evapd. The residue was composed of isomeric bromohydrins and dihydrolanosterol acetate. A portion of this mixture (2 g) was chromatographed on silica gel. Elution with hexane–$CHCl_3$ (8:2) gave dihydrolanosterol acetate (0.8 g). Further elution with $CHCl_3$ afforded bromohydrin **4a** (0.8 g): mp 168–169°; nmr δ 1.33 (s, 6 H, C-26, and C-27 Me protons). *Anal.* ($C_{32}H_{53}BrO_3$) C, H.

24,25-Epoxylanost-8-en-3β-ol 3-Acetate (4b).—A portion of the mixture of bromohydrins and dihydrolanosterol acetate (2 g) obtained above was chromatographed on Woelm neutral alumina (Activity II). Elution with hexane–$CHCl_3$ (9:1) gave dihydrolanosterol acetate (0.8 g). Further elution with hexane–$CHCl_3$ (8:2) gave the desired monoepoxide **4b** (0.6 g); mp 188–189°; $[\alpha]_D$ +53° (lit.[7] mp 181–182°; $[\alpha]_D$ +55°); nmr δ 1.25 and 1.30 (C-26 and C-27 Me protons).

Lanost-8-ene-3β,24ξ,25-triol 3-Acetate (4c).—$HClO_4$ (0.28 *N*, 10 ml) was added to a soln of the monoepoxide **4b** (1 g) in dioxane (100 ml), and the mixture was stirred at room temp for 1 hr prior to pouring into H_2O. The ppt was filtered, dried, and recrystd from hexane–CH_2Cl_2 to give diol **4c** (800 mg): mp 187–188°; $[\alpha]_D$ +45°; δ 1.15 and 1.20 (C-26 and C-27 Me protons). *Anal.* ($C_{32}H_{54}O_4$) C, H.

3β-Acetoxy-25,26,27-trisnorlanost-8-en-24-al (5).—$Pb(OAc)_4$ (800 mg) was added to a soln of diol **4c** (1 g) in THF (25 ml), and the mixture was stirred at room temp for 1 hr, filtered, and evapd. The residue was then extd into $CHCl_3$. The org layer was washed with $Na_2S_2O_3$ soln and H_2O, dried, and evapd. The residue was chromatographed on Woelm neutral Al_2O_3 (Activity II). Elution with hexane–Et_2O (1:1) gave the desired aldehyde **5** (730 mg) which was crystd from hexane: mp 144–145°; $[\alpha]_D$ +53° (lit.[7] mp 144–146°; $[\alpha]_D$ +58°); δ 9.72 (t, 1 H, J = 2 cps, CHO).

Leuckart Reductive Amination of 5.—A soln of aldehyde **5** (200 mg) in DMF (1 ml) and HCO_2H (90%, 1 ml) was heated at 140° for 2 hr. The mixture was then cooled, poured into H_2O, and extd into $CHCl_3$. The org layer was then washed with $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evapd. The residue was chromatographed on Al_2O_3, and elution with hexane–Et_2O (7:3) gave the desired azalanosterol derivative (120 mg). Recrystn from hexane gave a product identical in all respects with that obtained by acetylation of **3d**.

Centrally Acting Cyclic Urea, Thiourea, and Their *N,N'*-Dialkyl Derivatives. Structure–Activity Correlations[1a]

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Sixteen cyclic urea and thiourea derivatives were synthesized, 12 of which were new compounds and had not been reported previously. Six of the compounds showed potent convulsant activity, 3 showed potent CNS depressant activity, and 7 of them were found to possess potent respiratory stimulation activity. For these compounds the respiratory stimulation effect was tested in pentobarbital-depressed mice. The pharmacological activities, LD_{50}, HD_{50}, and CD_{50}, were correlated with the partition coefficient (log P) and the dipole moment (μ) by multiple regression analysis using an IBM 360/65 computer. The correlations obtained indicate that there is a parabolic relationship between the pharmacological activity and the partition coefficient of the congeneric cyclic ureas and thioureas. Inclusion of dipole moment further improves the correlations at the 99 percentile level.

Many of the CNS-acting drugs have amide or thioamide linkage as the common molecular structural units.[2,3] Cyclic urea and thiourea derivatives, which also have the same structural features, may be expected to possess CNS activities, although urea and thiourea molecules themselves do not have significant pharmacological activity.

It appears that the pharmacological inertness of urea and thiourea can be attributed to their very high solubility in water and poor solubility in lipid. If appropriate molecular modifications are made on the parent urea and thiourea molecules to raise their lipophilic character, pharmacologically active compounds may result. Relationship between biological activity of different classes of compounds and their lipid solubility has been demonstrated in many cases.[4–6] Meyer and Overton's classical work has been extended by Hansch and his coworkers.[7–10] They have shown that in general a parabolic relationship exists between the biological activity and partition coefficient of a wide variety of compounds. Linear relationship has been considered only as a special case.

Lien and Kumler[11] have reported the CNS activities of 5-, 6-, and 7-membered cyclic ureas, thioureas, and their *N,N'*-dimethyl derivatives. The methylated compounds were reported to be significantly more potent than the unmethylated ones. Also, they showed a

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(1) (a) Taken in part from the dissertation presented by Mehdi H. Hussain, June 1970, to the Graduate School, University of Southern California, in partial fulfillment of the requirements for the Doctor of Philosophy Degree. (b) R. M. and J. L. Converse Fund Fellow.

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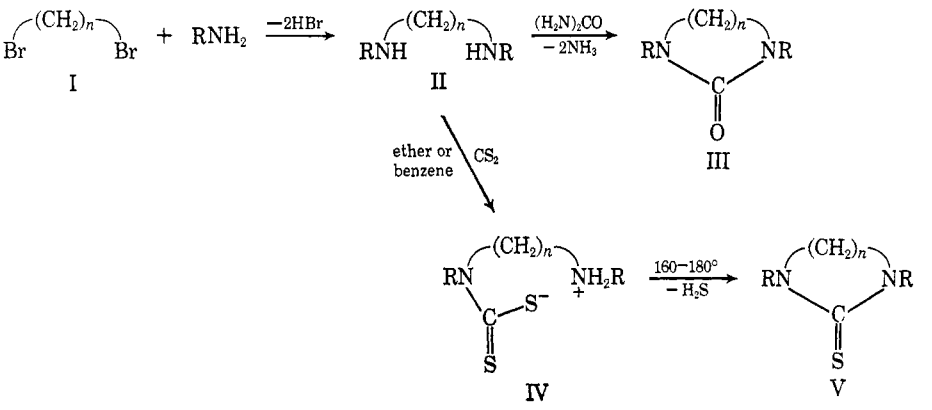
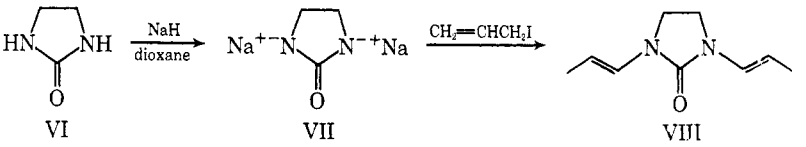
SCHEME I



SCHEME II



relationship between the respiratory stimulation activity and the dipole moment of the cyclic ureas and thioureas.

In order to obtain some information about the optimum structural requirements for maximum CNS stimulant or depressant activity, series of 5- and 6-membered cyclic urea and thiourea derivatives were synthesized, and their physicochemical properties and CNS activities were studied. The respiration stimulation effect of some of these compounds against sodium pentobarbital depression was also studied. The lethal toxicity and hypnotic or convulsant activity of these compounds are correlated with their physicochemical properties such as partition coefficient, dipole moment, and R_m values obtained from tlc.

Chemistry.—There are several routes available for the syntheses of N,N′-disubstituted cyclic ureas and thioureas.[12-18] In this study, both the cyclic ureas and cyclic thioureas were synthesized from *N,N′*-dialkylalkylenediamines, using the procedure described by Mistry and Guha,[14] Donia, *et al.*,[15] and Zienty.[16]

While alkylenediamines are bases strong enough to react with CS_2, arylenediamines are not. Therefore, in order to prepare *o*-phenylenethiourea, it is necessary to use a stronger inert organic base, such as Et_3N, to facilitate the initial nucleophilic attack on the CS_2 molecule. In this modified "Kaluza synthesis"[18] the intermediate dithiocarbamate salt IV is rather unstable and is not isolated. In C_6H_6 it decomposes at reflux temperature to form product V and gives off H_2S. The intermediate dithiocarbamate formed from phenylenediamine and CS_2 is probably the triethylammonium salt rather than the internal salt, since Et_3N is a much stronger base than phenylenediamine.

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Experimental Section

The elemental analyses are indicated only by symbols of the elements and were performed by the Elec Microanalytical Laboratories, Torrance, Calif., and by C. F. Geiger, Ontario, Calif. The analytical results obtained for these elements were within ± 0.4% of the theoretical values. The melting points were determined using a Fisher melting point block. Both the boiling points and the melting points given are uncorrected. The results are summarized in Table I.

***N,N′*-Dialkylalkylenediamines.**—The secondary diamines (II) were prepared from alkylene dibromide (I) and the primary alkylamines.[16] To 2.0 moles of alkylamine at 0°, 0.5 mole of the appropriate dibromide (I) was added dropwise with stirring. The reaction mixture was stirred for 1 hr at 0°, 4 hr at room temp, and an additional 1 hr at a gentle reflux temp. The reaction mixture was cooled and made strongly alk by addn of ice-cold 50% NaOH soln. The basic mixture was extd 3 times (Et_2O). The combined extracts were washed with cold H_2O and dried (Na_2SO_4), and the solvent was evapd using a rotatory evaporator. The product was purified by fractional distn under vacuum.

The *N,N′*-diethylethylenediamine, 1,2-diaminocyclohexane, *o*-phenylenediamine, and 1,8-diaminonaphthalene were purchased from K & K Laboratories, Inc., and used without further purification.

***N,N′*-Dialkylalkyleneurea (III).**—A mixture of 6.0 g (0.1 mole) of urea and 0.1 mole of II were stirred and heated to a gentle reflux. NH_3 evolved profusely indicating the reaction. Heating was discontinued after 6 hr when the evolution was not detectable. The reaction mixture was fractionally distd under vacuum or allowed to stand in a refrigerator until crystn occurred. The product was further purified either by distn or by recrystn.

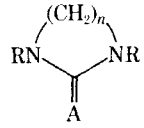
***N,N′*-Bis-(1-propenyl)ethyleneurea.**—The synthesis of *N,N′*-diallylethyleneurea was attempted using the alkylation procedure described by Lien and Kumler.[11] To 8.6 g (0.1 mole) of ethyleneurea (VI) in 500 ml of dry dioxane under N_2, 6.0 g (0.25 mole) of NaH (in 50% mineral oil) was added portionwise with stirring. The reaction temp was raised and maintained at 60–65° for 2 hr, then at room temp 32.0 g (0.25 mole) of allyl iodide in 100 ml of dry dioxane was added dropwise with stirring. After 2 hr stirring at room temp, the mixture was stirred 2 hr at reflux. The reaction mixture was filtered hot to remove pptd NaI. The solvent was evapd and the syrupy residue crystd by triturating with H_2O. The product was recrystd twice from EtOH–H_2O. The ir and nmr spectra indicated the product to be 1,3-bis-(1-propenyl)ethyleneurea (VIII).†

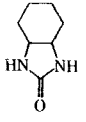
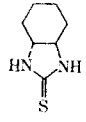
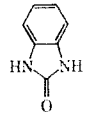
***N,N′*-Dialkylalkylenethioureas.**—To 0.1 mole of *N,N′*-dialkylenediamine (II) in 1 l. of anhyd Et_2O at 0°, 7.6 g (0.1 mole)

† The proof of the structure by nmr and ir and the proposed mechanism of isomerization will be published elsewhere in detail.

Table I

Cyclic Urea and Thiourea Derivatives



No.	n	A	R	Name (formula)	Bp (mm) or mp, °C	Yield, %	Analysis[a]	General observations: mg/kg LD_{50}	HD_{50}	CD_{50}	Dose	Signs observed
1	2	O	CH=CHCH$_3$	N,N'-Bis-(1-propenyl)ethyleneurea ($C_9H_{14}N_2O$)	82.3	68.0	C, H, N	690			500[b]	Ataxia, mild sedation, fearfulness, and fast respiration. Loss of righting reflex and convulsions at higher dose.
2	2	S	C_2H_5	N,N'-Diethylethylenethiourea ($C_7H_{14}N_2S$)	53.0	62.0	C, H, N, S	300		125	300	Straub tail, tremors, asphyxia, and convulsions.
3	2	S	$CH_2CH=CH_2$	N,N'-Diallylethylenethiourea ($C_9H_{14}N_2S$)	140–150 (1.2 mm)	22.0	C, H, N, S	195			300[b]	Ataxia, sedation, loss of righting reflex, death.
4	2	O	n-C_4H_9	N,N'-Dibutylethyleneurea ($C_{11}H_{22}N_2O$)	120–121 (0.9 mm)	46.0	C, H, N	378	120		250[b]	Loss of righting reflex in less than 1 min. No pre- and posthypnotic excitations.
5	2	S	n-C_4H_9	N,N'-Dibutylethylenethiourea ($C_{11}H_{22}N_2S$)	141–144 (4 mm)	55.0	C, H, N, S	632		390	500[b]	Straub tail, asphyxia, and convulsions
6	2	S	Cyclohexyl	N,N'-Dicyclohexylethylenethiourea ($C_{15}H_{26}N_2S$)	221–222	20.0	C, H, N, S				1000[b]	No effect.
7	3	O	C_2H_5	N,N'-Diethyltrimethyleneurea ($C_8H_{16}N_2O$)	90–91 (0.9 mm)	64.0	C, H, N	632	620		500	Mild sedation and ataxia.
8	3	S	C_2H_5	N,N'-Diethyltrimethylenethiourea ($C_8H_{16}N_2S$)	49.5	46.0	C, H, N, S	127		126	150	Straub tail, very fast respiration, violent convulsions, death.
9	3	O	n-C_3H_7	N,N'-Dipropyltrimethyleneurea ($C_{10}H_{20}N_2O$)	145 (1 mm)	21.5	C, H, N	310			200	Ataxia, mild sedation, fast respiration. Loss of righting reflex at higher doses.
10	3	S	n-C_3H_7	N,N'-Dipropyltrimethylenethiourea ($C_{10}H_{20}N_2S$)	204–208	55.0	C, H, N, S	385		252	300	Running fits, Straub tail, asphyxia, and convulsions.
11				Hexahydro-o-phenyleneurea ($C_7H_{12}N_2O$)	222–223	18.0	C, H, N	500		240	200	No depression, sensitive to auditory stimulation, fast respiration, and periodic convulsions.
12				Hexahydro-o-phenylenethiourea ($C_7H_{12}N_2S$)	162–163	69.0	C, H, N, S	82.2		37	50	Running fits, periodic convulsions. Violent convulsions and death at higher doses.
13				o-Phenyleneurea ($C_7H_6N_2O$)	>300	80.0	C, H, N		350		300[b]	Mild sedation and righting reflex loss.

14		*o*-Phenylenethiourea ($C_7H_6N_2S$)	>300	95.0	C, H, N, S	825	328	500[b]	Sedation, bulging eyeballs, asphyxia, and loss of righting reflex.
15		1,8-Naphthyleneurea (2,3-dihydroperimidin-2-one) ($C_{11}H_8N_2O$)	>300	85.0	C, H, N			1000[b]	Ataxia, mild sedation, and very fast respiration.

[a] All analytical values were within ±0.4% of the calculated values. [b] Injected as a suspension in 5% gum acacia.

of CS_2 in 100 ml of anhyd Et_2O was added dropwise with stirring. Reaction was indicated within 10 min by the formation of a white ppt of the inner salt IV. The reaction mixture was stirred for 2 hr at room temp. The inner salt was filtered, dried, and pyrolyzed at 160–180° (bath temp). Decomposition of the inner salt occurred at temperatures slightly above the melting points giving off H_2S. The heating was discontinued after 5 hr, and the dark brown residue was purified either by fractional distn or by crystn.

Ir and Uv Spectroscopic Studies.—The ir spectra were taken on a Perkin-Elmer Infracord spectrophotometer, Model 137. The spectra of the liq comps were run as thin film between NaCl disks. For cryst compds the spectra were taken in KBr pellets. Uv absorption spectra of the thioureas were recorded in 95% EtOH on a Cary-14 recording spectrophotometer.

Partition Coefficient and Tlc.—The 1-octanol–H_2O partition coefficients of *o*-phenyleneurea, *o*-phenylenethiourea, and *N,N'*-dipropyltrimethylenethiourea were measured according to published methods.[7,8] The partition coefficients of other compounds were calcd using Fujita and Hansch's substituent constant, derived from partition coefficients.[7-9]

The R_f values were determined on Eastman chromatogram silica gel thin-layer sheets (6061) in *n*-BuOH–AcOH–H_2O (4:2:1). After development the chromatograms were made visible by means of complexation with I_2, and the R_f values were calcd and converted into R_m using the following equation and the conversion table[19] obtained therefrom.

$$R_m = \log\left(\frac{1}{R_f} - 1\right)$$

Pharmacological Screening.—A group of 6 Swiss Webster albino mice (Simonsen Laboratories, Inc., Gilroy, Calif.), 3 male and 3 female, weighing 20–30 g were used for each dosage level tested. The groups were injected ip with a logarithmic series of doses, ranging from 25 to 1000 mg/kg of the drug. The drug was injected either in aq soln, or in a suspension in 5% acacia gum if the drug is not sol in H_2O. After injection the animals were observed constantly for at least 4 hr, then at intervals for 2 days. If no signs of effect were observed at 1000 mg/kg the drug was considered inactive.

Respiratory Stimulation Effect.—During the pharmacological screening, whenever possible, the respiration rate of the animals in each group was examined after the administration of drug, and compared with that of the control group which received normal saline alone. For the stimulant drugs the respiration rate was further measured in Na pentobarbital-treated mice. A group of 6 mice were given 60 mg/kg of Na pentobarbital (ip), and 10 min later the drug was administered. The respiration rate was counted periodically and compared with that of the group treated with Na pentobarbital alone. The results are summarized in Tables II and III.

Results and Discussion

The compounds synthesized in this study were screened for their general CNS depressant and stimulant activities, as may be predicted from the structural features common to many centrally acting drugs. Since the CNS depressant or stimulant activity and the degree of depression or stimulation vary according to the part of the nervous system affected, the observed overall effect may be a summation of several effects.[20] In order to have objective and reproducible measurements, the righting reflex, the respiration rate, the sleeping time, convulsions, and death are chosen as the criteria for measuring different degrees of CNS depression or stimulation. The median dose for loss of righting reflex (HD_{50}), the median convulsant dose (CD_{50}), and the median lethal dose (LD_{50}) were determined by

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TABLE II

RESPIRATION STIMULATION EFFECT OF SOME CYCLIC UREA DERIVATIVES

Compd	Dose, mg/kg	Number in group	Respiration rate: Time after injection, min	Respiration rate: Times/min ± stnd dev	Increase in respiration rate, %
Normal saline	1 ml	6	10	158 ± 26	
Hexahydro-*o*-phenylenethiourea	50	4	20	195 ± 23	23.4
Hexahydro-*o*-phenyleneurea	400	6	15	269 ± 22	70.3
N,N'-Dipropyltrimethyleneurea	200	4	10	246 ± 12	55.7
			15	248 ± 28	57.0
1,8-Naphthyleneurea	1000[a]	6	20	231 ± 34	46.3

[a] Injected as a suspension in 5% gum acacia.

TABLE III

RESPIRATION STIMULATION EFFECT OF SOME CYCLIC UREA AND CYCLIC THIOUREA DERIVATIVES AGAINST PENTOBARBITAL DEPRESSION

Compd	Dose, mg/kg	Number in group	Respiration rate: Min after sodium pentobarbitol	Respiration rate: Times/min ± stnd dev	Increase in respiration rate, %	Sleeping time, min (% increase)
Sodium pentobarbital	60	6	10	82 ± 23		44 ± 14
			15	81 ± 8		
			20	71 ± 9		
			25	67 ± 16		
			30	68 ± 11		
N,N'-Diethylethylenethiourea	150	6	20	91 ± 20	29	262 ± 103 (595)
Hexahydro-*o*-phenylenethiourea	30	6	10	99 ± 33	21	55 ± 31 (125)
N,N'-Diethyltrimethylenethiourea	50	6	15	101 ± 19	25	83 ± 20 (188)
			20	95 ± 10	34	
			30	93 ± 9	37	
N,N'-Dipropyltrimethylenethiourea	50	6	15	103 ± 13	27	93 ± 29 (211)
			20	80 ± 6	13	
			30	70 ± 12	3	
N,N'-Dipropyltrimethyleneurea	250	6	15	115 ± 10	42	132 ± 15 (300)
			20	97 ± 8	37	

the graphical calculation method of Miller and Tainter.[21] The results are summarized in Table I.

Besides observing the general CNS depression or stimulation, special attention was paid to the respiration rate after the administration of drug in search for potential respiratory stimulants. However, most stimulants have widespread activities, as indicated by tremors, running fits, and convulsions. These manifestations complicate the experimental observation of respiratory stimulation. For this reason, respiratory stimulation effect was further studied as antagonism to sodium pentobarbital induced depression in mice. Those compounds whose stimulant action was not masked by tremors, running fits, or convulsions were examined for their respiratory stimulation action directly without sodium pentobarbital pretreatment.

It can be seen from Table I that the cyclic thioureas have more pronounced CNS stimulation effect than depression. Potent convulsant activity was observed in 6 of the 8 cyclic thioureas. One of the compounds, cyclohexenylthiourea (hexahydro-2-benzimidazolidinthione) is even more potent (LD_{50} = 82.2 mg/kg) than pentylenetetrazole (LD_{50} = 92 mg/kg)[22] and niketha-mide (LD_{50} = 174 mg/kg).[22] At least 3 of the compounds indicated potent CNS depressant activity. *N,N'*-Di-*n*-butylethyleneurea (250 mg/kg, ip) induced rapid onset of sleep within 1 min after injection without pre- and posthypnotic excitation, which is commonly observed in pentobarbital-induced hypnosis. The sleep was very smooth and muscle relaxation was excellent.

Respiratory stimulation effect of some of the cyclic ureas and thioureas are summarized in Tables II and III. Significant respiratory stimulation was observed at high dosage levels for both hexahydro-*o*-phenylenethiourea (70.3% increase in respiration rate) and *N,N'*-dipropyltrimethyleneurea (57% increase). Noteworthy respiratory stimulation in pentobarbital-depressed animals was observed at much lower dosage levels (see Tables II and III). However, the sleeping time was increased rather than decreased. Whether this is due to biotransformation or due to direct action at the CNS is not certain at the present.

Structure–Activity Relationship.—The pharmacological data and the physicochemical constants used in deriving the equations in Table V are summarized in Table IV. The equations were derived by the method of least squares using an IBM 360/65 computer. The LD_{50}, HD_{50}, and CD_{50} values are from Table I and have been converted from mg/kg to moles/kg which gives the relative number of drug molecules that produce an equivalent biological response. The dipole moment values are those published by Lien and Kumler.[11] It is assumed that lengthening of the *N*-alkyl chain from Me to Et, Pr, Bu, etc., does not significantly change the resultant dipole moment.

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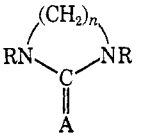
TABLE IV
PHARMACOLOGICAL DATA AND THE PHYSICOCHEMICAL CONSTANTS



						Log 1/LD_{50}					
						Calculated from:					
n	A	R	Log P	μ	$-R_m$	Observed	Eq 2	Eq 4	Eq 7	Eq 8	Eq 10	Eq 12
2	O	H	−1.41	4.01[a]	0.231							
2	O	CH_3	0.29	4.09[a]	0.650	1.51[a]			2.12	2.16	1.69	1.55
2	O	$CH{=}CHCH_3$	1.11	4.09[b]	1.453	2.39						2.61
2	O	n-C_4H_9	2.59	4.09[b]	1.235	2.67						2.41
2	S	H	−0.66	5.60[a]	0.183							
2	S	CH_3	0.46	5.32[a]	0.720	2.91[a]	2.77	2.85	2.66	2.79	2.90	
2	S	C_2H_5	1.46	5.32[b]	0.720	2.72	3.12	3.11	2.89	3.08	2.90	
2	S	$CH_2CH{=}CH_2$	1.86	5.32[b]	0.788	2.98						
2	S	n-C_4H_9	3.34	5.32[b]	0.760	2.51						
3	O	H	−1.01	4.67[a]	0.240							
3	O	CH_3	0.11	4.23[a]	0.393	2.00[a]			2.14	2.10	1.91	2.00
3	O	C_2H_5	1.11	4.23[b]	1.010	2.40			2.37	2.57	2.58	2.56
3	O	n-C_3H_7	2.11	4.23[b]	1.067	2.77			2.61	2.52	2.64	2.61
3	S	H	−0.29	5.79[a]	0.153	2.32[a]	2.13	2.43	2.67	2.43	2.55	
3	S	CH_3	0.83	5.63[a]		3.12[a]	2.96	3.12	2.87	3.09		
3	S	C_2H_5	1.83	5.63[b]	0.531	3.05	3.10	3.16	3.10	3.19	2.87	
3	S	n-C_3H_7	2.83	5.63[b]	0.757	2.72	2.66	2.62	3.34	2.76	3.11	
4	O	H	−0.59	4.43[a]		1.60[a]	1.78	1.67	2.05	1.54		
4	O	CH_3	0.53	3.75[a]	0.940	2.31[a]	2.81	2.40	2.04	2.15	2.22	
4	S	H	0.13	5.36[a]	−0.115	2.78[a]	2.52	2.65	2.59	2.60	2.56	
4	S	CH_3	1.25	5.29[a]		3.29[a]	3.09	3.10	2.83	3.05		
Hexahydro-*o*-phenyleneurea			0.24	4.01[b]	0.692	2.45	2.61	2.31	2.08	2.09		
Hexahydro-*o*-phenylenethiourea			1.01	5.60[b]	0.542	3.30	3.03	3.16	2.90	3.13	2.84	
o-Phenyleneurea			1.12	4.01[b]	0.767							
o-Phenylenethiourea			1.66	5.60[b]	0.845	2.27						

[a] From ref 11. [b] Estimated value.

Results

It can be seen from eq 1 and 2 in Table V that the parabolic equation of log P for the CNS stimulants gives much better correlation than the linear equation of log P (r = 0.849 *vs.* 0.564). A slight improvement in the correlation coefficient results for the linear equation when the dipole moment (μ) term is included in the correlation (eq 3). However, when both the $(\log P)^2$ and the dipole moment (μ) are taken into consideration an excellent correlation coefficient is obtained (eq 4, r = 0.942, s = 0.193). The improvement in correlation by addition of the dipole moment term to the parabolic equation is significant at the 99 percentile level ($F_{1,8}$ = 11.6; $F_{1,8_{0.99}}$ = 11.3).

When the data points for the CNS stimulants and depressants are grouped together the correlation coefficients obtained for both the linear and parabolic equations are not very high (eq 5 and 6). However, when the dipole moment term is added to the log P, the correlation coefficient is significantly improved (eq 7, $F_{1,13}$ = 8.04; $F_{1,12_{\alpha\,0.995}}$ = 6.55). High correlation coefficient is obtained when the dipole moment and the $(\log P)^2$ terms are added (eq 8, r = 0.882, s = 0.285). The improvement in correlation obtained upon the addition of the dipole moment term in the regression analysis strongly suggests the importance of the electrostatic interactions of the drug molecules with the receptor sites, such as the dipole–dipole interactions of the urea or thiourea function with the peptide linkage of a protein or lipoprotein membrane. The improvement in the correlation coefficient from linear to parabolic equation is significant (eq 7 and 8). An F test indicates that the addition of $(\log P)^2$ term is significant at 99.5 percentile level ($F_{1,12}$ = 11.4; $F_{1,12_{\alpha\,0.995}}$ = 11.8). The fairly good correlation (eq 8, r = 0.882) obtained for a group of both CNS stimulants and depressants strongly suggests that both may act at the same receptor sites in the CNS. However, this does not exclude the possibility that they may have different site of action, but the same rate-limiting step in approaching the receptors. This rate-limiting step may well lie in the penetration of the "blood–brain barrier" or other cellular membranes.

The R_m obtained from the R_f values of the tlc is also a measure of the lipohydrophilic character, since the chromatographic process is a process of partition and adsorption–desorption. Therefore, R_m should also give correlations similar to log P. Equation 10 is obtained when the log 1/LD_{50} of stimulants and depressants are correlated with their R_m values and the dipole moment (r = 0.878, s = 0.259). Similar good correlations are obtained for the depressants alone (eq 11 and 12).

From the correlations obtained for the CNS activities with the physicochemical constants, it is clear that the partition coefficient of the drug molecule appears to be the most important parameter which determines its relative pharmacological activities. The dipole moments of the compounds examined also play an impor-

TABLE V

No.	Equation	n^a	r^b	s^c	Log P_0 [d] (95% confidence interval)
	CNS stimulants injected in soln				
1	$\log (1/LD_{50}) = 0.290 \log P + 2.480$	12	0.564	0.423	
2	$\log (1/LD_{50}) = -0.288 (\log P)^2 + 0.902 \log P + 2.411$	12	0.849	0.285	1.569 (1.20–2.59)
3	$\log (1/LD_{50}) = 0.202 \log P + 0.305 \mu + 0.980$	12	0.688	0.392	
4	$\log (1/LD_{50}) = -0.291 (\log P)^2 + 0.819 \log P + 0.315 \mu + 0.862$	12	0.942	0.193	1.406 (1.14–1.83)
	CNS stimulants and depressants injected in soln				
5	$\log (1/LD_{50}) = 0.323 \log P + 2.309$	16	0.545	0.470	
6	$\log (1/LD_{50}) = -0.236 (\log P)^2 + 0.829 \log P + 2.236$	16	0.686	0.423	1.775 ($\pm\infty$)
7	$\log (1/LD_{50}) = 0.237 \log P + 0.401 \mu + 0.415$	16	0.752	0.383	
8	$\log (1/LD_{50}) = -0.262 (\log P)^2 + 0.792 \log P + 0.429 \mu + 0.197$	16	0.882	0.285	1.512 (1.16–2.51)
	CNS stimulants and depressants (R_m in BAW)				
9	$\log (1/LD_{50}) = 0.506 (-R_m) + 2.251$	12	0.305	0.487	
10	$\log (1/LD_{50}) = 1.086 (-R_m) + 0.579 \mu - 0.969$	12	0.877	0.259	
	Depressants (R_m in BAW)				
11	$\log (1/LD_{50}) = 0.821 (-R_m) + 1.547$	6	0.830	0.291	
12	$\log (1/LD_{50}) = 0.897 (-R_m) + 2.472 \mu - 8.808$	6	0.921	0.235	

[a] n = number of data points used in the analysis. [b] r = the correlation coefficient. [c] s = standard deviation. [d] Log P_0 is the ideal log P value for max activity. This can be obtained by setting $[d(\log 1/c)]/[d(\log P)] = 0$.

tant role. This may be due to the anchoring of the drug molecule onto the receptor sites by dipole–dipole interactions or by other type of electrostatic forces.

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Potential Nonequilibrium Analgetic Receptor Inactivators. Synthesis and Biological Activities of *N*-Acylanileridines[1]

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In a effort to prepare nonequilibrium analgetic receptor inactivators, a variety of *N*-acylanileridines having alkylating capacity were synthesized. The analgetic potencies of this series are reported together with experiments designed to detect receptor blockade. Ethyl *p*-(4-ethoxycarbonyl-4-phenyl-1-piperidinoethyl)fumaranilate (**5**) caused significant blockade of analgetic activity 2 hr after ip administration. Pretreatment with naloxone, a narcotic antagonist, blocked completely the analgetic activity of **5**. Naloxone also protected the analgetic receptors against inactivation. The data suggest that **5** has the capacity to alkylate analgetic receptors selectively.

Strong analgetics are generally believed to exert their effects by interacting with specific receptors located in the CNS. Three main bodies of evidence support this belief; (1) common structural features,[2,3] (2) large potency differences between enantiomers,[4] and (3) the existence of structurally related competitive antagonists.[5,6]

Although structural parameters required for high biological activity have been thoroughly delineated for many classes of strong analgetics and attempts have been made to explain their mechanism of action,[7] the

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