a Varian EM 360A spectrometer.

General Procedure for the Synthesis of Dichlorobenzaldehyde Alkylimines. While stirring and cooling in a water bath, the alkylamine (0.33 mol) was added slowly to a solution of the dichlorobenzaldehyde (0.30 mol) in a small volume of $CHCl_3$. After the solution stirred for 1 h at room temperature, the organic layer was separated and dried over $MgSO_4$. The solvent was removed and the residue was destilled in vacuo. The yields ranged from 65 to 95%.

General Procedure for the Synthesis of *N,N'*-Dialkyl-1,2-bis(dichlorophenyl)ethylenediamines (2). Spectral pure aluminum foil (21 g, 0.75 g-atom), cut in small pieces, was added to a solution of $HgCl_2$ (2.0 g) in EtOH (15 mL) and heated. When the gas evolution had started, a solution of dichlorobenzaldehyde alkylimine (0.25 mol) in toluene (250 mL) was added slowly under mechanical stirring. Finally, the mixture was kept for 4 h at 100 °C. HCl (6 N, 100 mL) was added; 30 min later, the solution was made alkaline by the addition of 6 N NaOH. The organic layer was separated and the aqueous solution was extracted several times with $CHCl_3$. After drying ($MgSO_4$), the solvent was removed under reduced pressure and the residue was dissolved in a small volume of MeOH. After filtration, the hydrochlorides were precipitated in fractions by addition of etheral HCl. Further separation and purification were achieved by factionated crystallization of the hydrochlorides from EtOH. The yields were 25–45% for the *d,l*-ethylenediamines, 15–30% for the *meso*-ethylenediamines, and 15–40% for the benzylamines. Melting points and recrystallization solvents of **2** are reported in Table I.

General Procedure for the Synthesis of *N,N'*-Dialkyl-4,5-bis(dichlorophenyl)imidazolidines (3). A solution of **2** (0.010 mol) and paraformaldehyde (0.015 mol) in benzene (25 mL) was refluxed for 7 h. The cold solution was filtered or decanted from a precipitate. After evaporation of the solvent, the residue was crystallized from EtOH. Compounds which resisted crystallization (*cis*-**3b**, *cis*-**3g**, and *cis*- and *trans*-3i) were chromatographed on alumina (activity I) with eluation by CH_2Cl_2/ligroin (1:1). The yields varied from 55 to 85%. For further data, see Table II.

Biological Methods. The applied methods (E2-receptor binding assay, Dorfman uterine weight test, and mammary tumor inhibition test) have been described in detail in a previous paper.[4] All diarylethylenediamines (**2**) and -imidazolidines (**3**) were tested for their affinity to the E2 receptor in concentrations ranging from 10^{-4} to 10^{-8} M. The association constants (K_a) for the inhibitor–receptor complexes were determined only for compounds which showed a strong affinity to the E2 receptor in preliminary tests (inhibition of the [^{3}H]E2 receptor interaction greater than 10% at a 10^4-fold excess of inhibitor; [^{3}H]E2 concentration 5×10^{-9} M). The reversibility test method has been described earlier.[5] *meso*-**2f** and the diastereomeric pairs of **2g**, **3f**, and **3g** (dissolved in arachis oil, application sc) were screened for their estrogenic[5,10] and antiestrogenic[5,11] properties by the Dorfman uterine weight test (Table III). *meso*-**2g** was tested as the hydrochloride in isotonic NaCl solution (application ip) for its effect on the DMBA-induced hormone-dependent mammary adenocarcinoma of the female Sprague–Dawley rat (Zentralinstitut für Versuchstierzucht, Hannover, Germany) according to published methods.[5]

Acknowledgment. Thanks are due to the Deutsche Forschungsgemeinschaft and to the Verband der Chemischen Industrie–Fonds der Chemischen Industrie, who supported this work by grants. The technical assistance of R. Ringshandl and Ch. Steinberger is gratefully acknowledged.

(10) B. L. Rubin, A. S. Dorfman, L. Black, and R. J. Dorfman, *Endocrinology*, **49**, 429 (1951).
(11) R. A. Edgren and D. W. Calhoun, *Proc. Soc. Exp. Biol. Med.*, **94**, 137 (1957).

Synthesis, Biological Evaluation, and Preliminary Structure–Activity Considerations of a Series of Alkylphenols as Intravenous Anesthetic Agents

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Following our discovery of the intravenous (iv) anesthetic activity of 2,6-diethylphenol in mice, a series of alkylphenols was examined in this species and the most active analogues were further evaluated in rabbits. The synthesis of compounds which were not commercially available was accomplished by adaptations of standard ortho-alkylation procedures for phenols. Structure–activity relationships were found to be complex, but, in general, potency and kinetics appeared to be a function of both the lipophilic character and the degree of steric hindrance exerted by ortho substituents. The most interesting compounds were found in the 2,6-dialkyl series, and the greatest potency was associated with 2,6-di-*sec*-alkyl substitution. In particular, 2,6-diisopropylphenol (ICI 35 868) emerged as a candidate for further development and has subsequently been shown to be an effective iv anesthetic agent in man.

The concept of total intravenous (iv) anesthesia has in recent years prompted attempts to improve on existing drugs, but alternative agents have not proved to be entirely satisfactory.[1] The use of the surfactant Cremophor EL for the formulation of compounds otherwise poorly soluble in water alone has enabled an examination of the anesthetic potential of numerous structural types with high lipophilic character which could not previously have been administered by the intravenous route. This paper describes the synthesis and biological evaluation of a series of alkyl-substituted phenols which resulted from the discovery of anesthetic activity in 2,6-diethylphenol (**8**) in mice, during the search for an agent which would demonstrate advantages over existing iv anesthetics.

Chemistry. Many of the phenols listed in Tables II–V were available either from commercial or ICI interdivisional sources and only required purification prior to biological evaluation. The remaining examples were synthesized by the introduction of alkyl groups into the ortho position of an appropriate phenol by the following methods (Schemes I–III).

Direct ortho alkylation of phenols by alkenes in the presence of the corresponding aluminum phenolate[2]

(1) B. Davies, *Adv. Drug. Res.*, 10, 1 (1975).
(2) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).

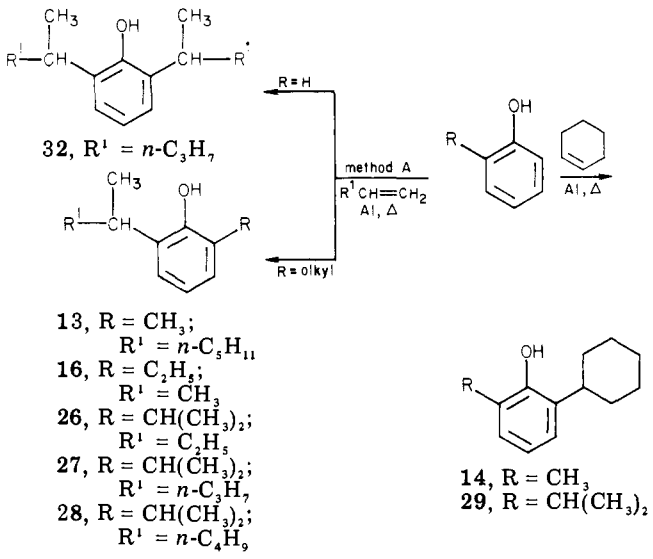
0022-2623/80/1823-1350$01.00/0

Table I. Results Obtained with Standard Compounds in the Mouse Test

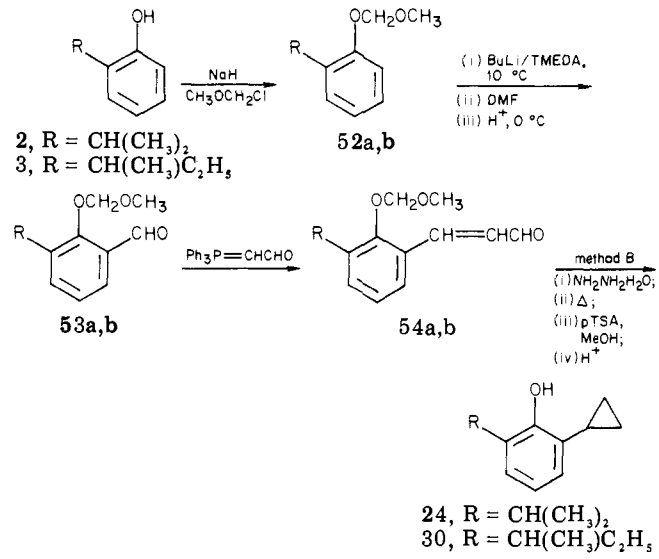
compd	HD_{50}[a]	LD_{50}[b]	speed of induction[c]	duration of action[d]	additional comments
thiopental sodium	20-25	80-90	I	B	prolonged duration of action at high doses
ketamine hydrochloride	10-15	60	S	B	
etomidate	1-1.5	40-45	I	B	excitatory side effects
methohexital sodium	5-10	30	I	B	excitatory side effects on recovery

[a] Median hypnotic dose, in mg/kg. [b] Median lethal dose, in mg/kg. [c] Abbreviations used: I = immediate, <10 s; S = slow, 10-15 s. [d] Abbreviation used: B = brief, <5 min.

Scheme I



Scheme II[a]



[a] 52-54: a, R = $CH(CH_3)_2$; b, R = $CH(CH_3)C_2H_5$

(Scheme I) was adopted with readily available starting phenols. The *sec*-alkyl analogues **13**, **16**, **26**–**28**, **32**, **47**, **48**, **50**, and **51** and the cyclohexylphenols **14** and **29** were prepared in this manner (method A). Inter- and intramolecular migration of the *sec*-alkyl groups was often observed, resulting in low yields of final products (>98% pure by GC) due to losses on fractional distillation.

The *o*-cyclopropylphenols **24** and **30** were synthesized via the benzaldehydes **53a,b** as summarized in Scheme II. Protection of the phenols **2** and **3** as their methoxymethyl ethers **52a,b** was followed by conversion to the corresponding ortho anions with *n*-butyllithium/tetramethylethylenediamine.[3] Treatment with DMF, followed by aqueous acid at ≤5 °C, gave the benzaldehydes **53a,b** which, in a Wittig reaction with formylmethylenetriphenylphosphorane,[4] afforded a cis/trans mixture of cinnamaldehydes **54a,b** in high yield. The major cis components were isolated by chromatography and treated with hydrazine hydrate and then pyrolyzed and deprotected to give the cyclopropylphenols **24** and **30** (method B).

o-*n*-Alkylphenols were prepared by the two approaches outlined in Scheme III. Phase-transfer O-alkylation[5] of **3** afforded the ether **55**, which was subjected to thermal Claisen rearrangement.[6] Chromatographic separation of the required *o*-allyl product **56** from its minor para-isomer **57** and subsequent hydrogenation over 10% Pd/C gave **20** in good overall yield (method C). Other *o*-propylphenols (**9**, **10**, and **19**) were prepared similarly, while **21** was separated from its para isomer after hydrogenation.

The preparation of other *n*-alkylphenols was initially attempted via the Fries rearrangement. The predominance of *p*-acyl products from hindered phenyl esters and the inter- and/or intramolecular migration of existing *o*-*sec*-alkyl moieties observed when the para position was blocked with halogen made this approach unattractive. The phenol **17** was therefore prepared by the Gassman procedure[7] (method D) in which **3** was converted to the oxasulfonium salt **58** with NCS and diethyl sulfide. This was converted to the ylide with NEt_3 at −25 °C, which was rearranged in situ, by warming to room temperature. The thioether **59** so formed was desulfurized with Raney nickel, affording **17**. Similarly obtained were the phenols **11**, **12**, **18**, **22**, **23**, and **49**. Yields were poor but no attempt was made to optimize the conditions for hindered phenols, and the regiospecificity of the reaction gave easy access to the desired products.

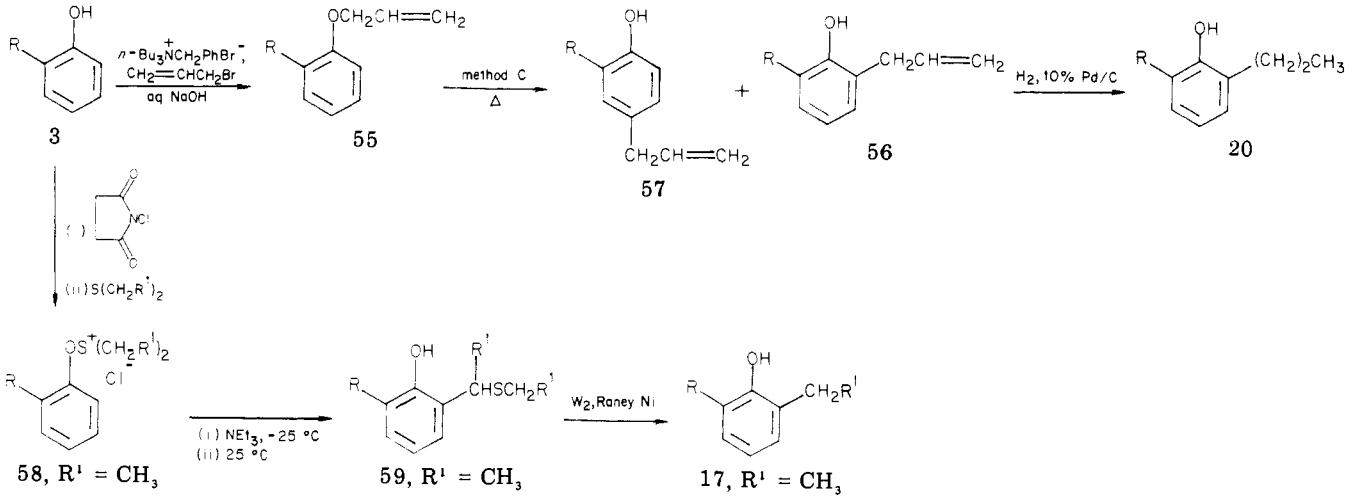
All novel phenols prepared during the course of this work were characterized by NMR and gave satisfactory analyses.

Results

Hypnotic activity (HD_{50}) and acute toxicity (LD_{50}) were estimated in mice for standard anesthetics (Table I) and the phenols examined. Sleeping times and the speed of induction and recovery were noted together with a qualitative assessment of muscle relaxation, analgesia, and any excitatory effects. Compounds with an $HD_{50} \leq 20$ mg/kg and a therapeutic ratio (LD_{50}/HD_{50}) ≥ 4 which were free from undesirable side effects were considered for further

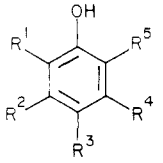
(3) H. Christensen, *Synth. Commun.*, **5**, 65 (1975).
(4) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1266 (1961).
(5) A. McKillop, J. C. Fiaud, and R. Hug, *Tetrahedron*, **30**, 1379 (1974).
(6) E. N. Marvell, B. Richardson, R. Anderson, J. L. Stephenson, and T. Crandall, *J. Org. Chem.*, **30**, 1032 (1965).
(7) P. G. Gassman and D. R. Amick, *J. Am. Chem. Soc.*, **100**, 7611 (1978).

Scheme III[a]



[a] 3, 17, 20, 55-59: R = $CH(CH_3)C_2H_5$

Table II. Monoalkylphenols



$R^2 = R^4 = R^5 = H$

no.	R^1	R^3	HD_{50}[a]	LD_{50}[b]
1[c]	H	H	70	100
2[c]	$CH(CH_3)_2$	H	30-40	100-120
3[c]	$CH(CH_3)C_2H_5$	H	30-40	60-80
4[d]	$CH(CH_3)$-n-C_3H_7	H	20-30	100
5[d]	H	$CH(CH_3)_2$	30-40	40-60
6[d]	H	$CH(CH_3)C_2H_5$		40-60

[a] Median hypnotic dose, in mg/kg. [b] Median lethal dose, in mg/kg. [c] From Aldrich Chemical Co. Ltd., checked by GPLC and NMR. [d] From ICI Petrochemicals Division, purified by distillation where necessary and then checked by GPLC and NMR.

evaluation of the quality of anesthesia produced in rabbits.

General trends in the primary mouse results were apparent when derivatives were arranged according to the pattern and type of substitution in the phenol ring as in Tables II–V. For supportive results on a further 39 compounds, see paragraph at the end of paper concerning supplementary material.

Monosubstituted Phenols (Table II). As a class, o-alkylphenols, e.g., **2–4**, showed only moderate activity and therapeutic ratios were poor. Corresponding para isomers, e.g., **5** and **6**, proved toxic, as did the parent compound, phenol (**1**). 2-(1-Methylbutyl)phenol (**4**) was evaluated in rabbits but rejected because poor muscle relaxation and marked respiratory depression were noted at anesthetic doses.

Di-ortho-substituted Phenols (Table III). Compounds in this series have been grouped together according to the degree of branching of the alkyl substituents, to facilitate discussion.

The 2,6-di-n-alkylphenols from 2,6-dimethylphenol (**7**) to 2-n-butyl-6-n-propylphenol (**11**) exhibited similar profiles with moderate potencies and therapeutic ratios. Induction of anesthesia with compounds **8**, **9**, and **11** was slow and sleeping times were short, though the latter increased with increasing alkyl chain length. The most active compound in this series, 2,6-diethylphenol (**8**), had a low therapeutic ratio in the rabbit, and induction of anesthesia at a dose of 20 mg/kg was slow in this species.

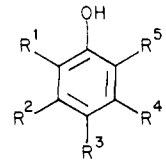
In the 2-n-alkyl-6-sec-alkyl subgroup, **12–23**, potency was again observed to increase as the total number of carbon units in the substituents ($\sum C$) increased, reaching a maximum at $\sum C = 7–8$, e.g., **13**, **18**, **20**, **22**, and **23**. The introduction of a cycloalkyl moiety, e.g., **14**, resulted in decreased activity in comparison with the sec-alkyl derivative **13**. When $\sum C \geq 8$, e.g., **13**, **21**, and **23**, induction was slow, and at high doses prolonged recovery, indicating a cumulative effect, was seen. With the exception of **20**, in the rest of the series therapeutic ratios were good, and induction and recovery were smooth and rapid. Compounds **13**, **16**, **17**, and **20** were selected for evaluation in rabbits and were subsequently eliminated because of slow induction of anesthesia, sometimes accompanied by excitement and poor muscle relaxation. 2-Ethyl-6-(1-methylbutyl)phenol (**18**) was also examined in this species and was found to produce good anesthesia, but profuse salivation at higher doses was noted as a significant side effect.

2,6-Di-sec-alkylphenols, **24–32**, were the most interesting group examined in the whole of this study. Activity was generally high, though cyclic analogues were again less active than their sec-alkyl equivalents, e.g., **24** cf. **25**, **30** cf. **26**, and **29** cf. **28**. Potency increased, with increasing chain length of the substituents reaching a maximum at $\sum C = 6–8$, e.g., **25–27** and **31**, appearing to plateau at $\sum C \geq 9$, e.g., **28** and **32**. Therapeutic ratios were good and induction times were rapid when $\sum C \leq 7$ but became slower thereafter. At $\sum C \geq 8$, e.g., **27**, **28**, **31**, and **32**, evidence of a cumulative effect was observed at higher doses. 2,6-Di-tert-butylphenol (**33**), included here for comparison, was essentially inactive as an anesthetic.

Analgesia was noted during the period when righting reflex was lost with a large proportion of compounds in this series, and the overall quality of anesthesia observed with the analogues **25–28**, **31**, and **32** was good. The results recorded in rabbits with these six compounds are summarized in Table VI. As with all phenols tested in this species, therapeutic ratios were generally lower than in mice. Excitement was frequently seen on induction, and muscle relaxation was sometimes poor. However, 2,6-diisopropylphenol (**25**; ICI 35 868) was exceptional in that it produced smooth rapid induction and recovery with good muscle relaxation and a short but useful period of anesthesia.

Phenols with a Para Substituent (Table IV). In the 2,4-dialkyl series, **34–40**, therapeutic ratios and po-

Table III. 2,6-Dialkylphenols[a]



$R^2 = R^3 = R^4 = H$

no.	R^1	R^5	HD_{50}[b]	LD_{50}[c]	speed of induction[d]	duration of action[e]	method or source	bp (mmHg) or mp, °C	yield, %
7	CH_3	CH_3	20-30	80	I	B	*f*		
8	C_2H_5	C_2H_5	15-20	100	S	B	*f*		
9	C_2H_5	*n*-C_3H_7	20-40	100	VS	B	C	60 (0.5)	75[g]
10	*n*-C_3H_7	*n*-C_3H_7	20-30	100	I	B	C	60 (0.5)	77[g]
11	*n*-C_3H_7	*n*-C_4H_9	20-40	100-120	VS	B	D	81 (0.03)	45[h]
12	CH_3	$CH(CH_3)_2$	20-30	80	I	B	D	63 (4.8)	23[h]
13	CH_3	$CH(CH_3)$-*n*-C_5H_{11}	15-20	100	VS	L	A	85 (0.2)	69[i]
14	CH_3		30-40	140-160	VS	B	A	64-66	47[i]
15	CH_3	$C(CH_3)_3$	40-60	120-140	I	B	*f*		
16	C_2H_5	$CH(CH_3)_2$	15-20	60-80	I	B	A	67 (0.7)	52[i]
17	C_2H_5	$CH(CH_3)C_2H_5$	10-15	80	I	B	D	62 (0.07)	28[h]
18	C_2H_5	$CH(CH_3)$-*n*-C_3H_7	10-20	100-120	I	B	D	60 (0.05)	17[h]
19	*n*-C_3H_7	$CH(CH_3)_2$	20-30	80	I	B	C	60 (0.5)	73[g]
20	*n*-C_3H_7	$CH(CH_3)C_2H_5$	10-20	120	S	B	C	66 (0.1)	66[g]
21	*n*-C_3H_7	$CH(CH_3)$-*n*-C_4H_9	50	140	VS	M	C	76 (0.05)	38[j]
22	*n*-C_4H_9	$CH(CH_3)_2$	20	100	I	B	D	101 (4.3)	17[h]
23	*n*-C_4H_9	$CH(CH_3)C_2H_5$	20-30	120	VS	M	D	74 (0.05)	25[h]
24	$CH(CH_3)_2$	-c-C_3H_5	20-30	120-140	I	B	B	85 (2.6)	12[k]
25	$CH(CH_3)_2$	$CH(CH_3)_2$	5-10	50-60	I	B	*f*		
26	$CH(CH_3)_2$	$CH(CH_3)C_2H_5$	5-10	50	I	B	A	92 (3.5)	50[i]
27	$CH(CH_3)_2$	$CH(CH_3)$-*n*-C_3H_7	10-15	80	S	L	A	77 (1.0)	46[i]
28	$CH(CH_3)_2$	$CH(CH_3)$-*n*-C_4H_9	10-15	100-120	S	L	A	104 (2.0)	73[i]
29	$CH(CH_3)_2$		30-40	100-120	S	L	A	114 (0.8)	61[i]
30	$CH(CH_3)C_2H_5$	-c-C_3H_5	20-40	120-140	S	B	B	65 (0.15)	8[k]
31	$CH(CH_3)C_2H_5$	$CH(CH_3)C_2H_5$	5-10	60	S	M	*f*		
32	$CH(CH_3)$-*n*-C_3H_7	$CH(CH_3)$-*n*-C_3H_7	15-20	160-180	VS	L	A	143 (5)	23[i]
33	$C(CH_3)_3$	$C(CH_3)_3$	80-100	120			*f*		
	thiopentone sodium		20-25	80-90	I	B			
	ketamine hydrochloride		10-15	60	S	B			
	etomidate		1-1.5	40-45	I	B			
	methohexitone sodium		5-10	30	I	B			

[a] All samples synthesized gave satisfactory analysis for C and H (±0.4% of calculated values) and were checked by GPLC and NMR. [b] Median hypnotic dose, in mg/kg. [c] Median lethal dose, in mg/kg. [d] Abbreviations: I = immediate, <10 s; S = slow, 10-15 s; VS = very slow, >15 s. [e] Abbreviations: B = brief, <5 min; M = moderate, 5-10 min; L = long, >10 min. [f] From Aldrich Chemical Co. Ltd., checked by GPLC and NMR. [g] Calculated from the corresponding *o*-allylphenol. [h] Overall yield based on 1 mol equiv of starting phenol. [i] GPLC yields based on analysis of crude reaction mixtures. [j] Calculated from the corresponding allyl ether. [k] Calculated from the corresponding monoalkylphenol.

tencies were generally poor, while in the 2,4,6-trialkyl analogues, **41**, **42**, and **43**, bearing two α-branched ortho substituents, these parameters were reasonable. Again, activity fell dramatically with the introduction of two *o*-*tert*-butyl groups, e.g., **44**. A significant feature of this group was that delayed deaths were noted on the 5th–7th day after dosing with most *p*-methyl derivatives, e.g., **36**, **41**, and **44**, at doses substantially less than the original LD_{50} level. It seems probable that these compounds undergo a different mode of metabolism, which may involve a *p*-quinonemethide intermediate, as they cannot be eliminated via a *p*-hydroquinone conjugate, such as that identified for ICI 35 868 in the rat.[8]

4-Ethyl-2,6-diisopropylphenol (**42**) was examined in rabbits but gave poor muscle relaxation at 10 mg/kg and was lethal at 30 mg/kg.

Phenols with a Meta Substituent (Table V). Di-, tri-, and tetraalkylphenols in this group, **45–51**, appeared very similar. Potencies and therapeutic ratios were generally poor. 3,6-Diisopropyl-2-methylphenol (**47**) was tested in rabbits but produced excitement on induction at a dose of 20 mg/kg.

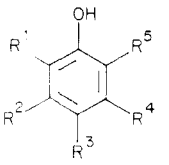
Partition coefficients between octanol and water (log *P*) for selected analogues were determined by a high-pressure liquid chromatographic technique.[9] The results are shown in Figure 1 in which log *P* has been plotted against the total number of carbon atoms in the substituent chains ($\sum C$). To a first approximation, log $P \propto \sum C$.

The slope of the graph implies a π value of 0.36 unit per methylene group for *o*-alkyl substituents in this environment compared with 0.5 unit per methylene commonly

(8) C. Rhodes, unpublished results.

(9) M. S. Mirrlees, S. J. Moulton, C. T. Murphy, and P. J. Taylor, *J. Med. Chem.*, **19**, 615 (1976).

Table IV. Para-Substituted Phenols[a]



$R^2 = R^4 = H$

no.	R^1	R^3	R^5	HD_{50}[b]	LD_{50}[c]
34	CH_3	CH_3	H	30-40	100-120
35	CH_3	$C(CH_3)_3$	H	80	180-200
36	$C(CH_3)_3$	CH_3	H	30	100-120[d]
37	$CH(CH_3)_2$	C_2H_5	H	40	120
38	$CH(CH_3)_2$	$CH(CH_3)_2$	H	40-60	120
39	$CH(CH_3)C_2H_5$	$CH(CH_3)C_2H_5$	H	20-30	120
40	$C(CH_3)_3$	$C(CH_3)_3$	H	40-60	100-120
41	$CH(CH_3)_2$	CH_3	$CH(CH_3)_2$	20	80-100[e,f]
42	$CH(CH_3)_2$	C_2H_5	$CH(CH_3)_2$	20	80-100
43	$CH(CH_3)C_2H_5$	CH_3	$CH(CH_3)C_2H_5$	30	140
44	$C(CH_3)_3$	CH_3	$C(CH_3)_3$	80-100	180-200[g]

[a] All samples obtained from CIC Petrochemicals Division were purified by distillation where necessary and then checked by GPLC and NMR. [b] Median hypnotic dose, in mg/kg. [c] Median lethal dose, in mg/kg. [d,e,g] Delayed deaths observed, dose in mg/kg (day after dosing) as follows: *d*, 100 (5); *e*, 40 (7); *g*, 80 (5). [f] At 20 mg/kg in rabbits, severe lung damage was observed on postmortem at day 3.

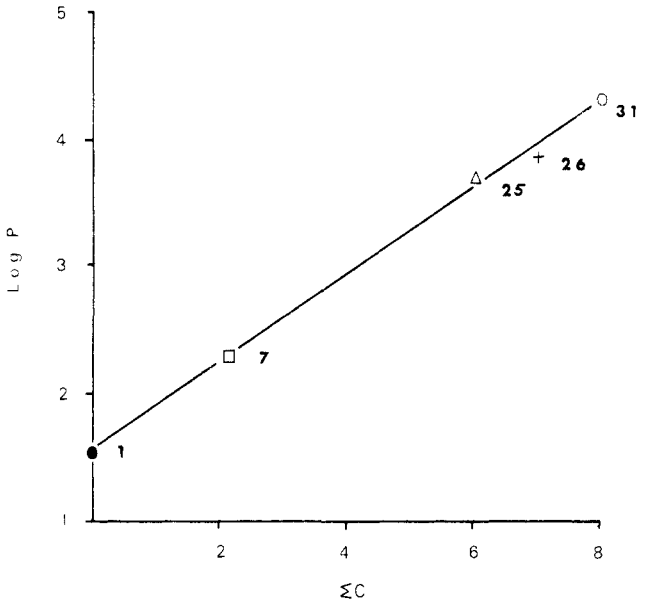


Figure 1. $\sum C$ vs. log *P* for selected phenols.

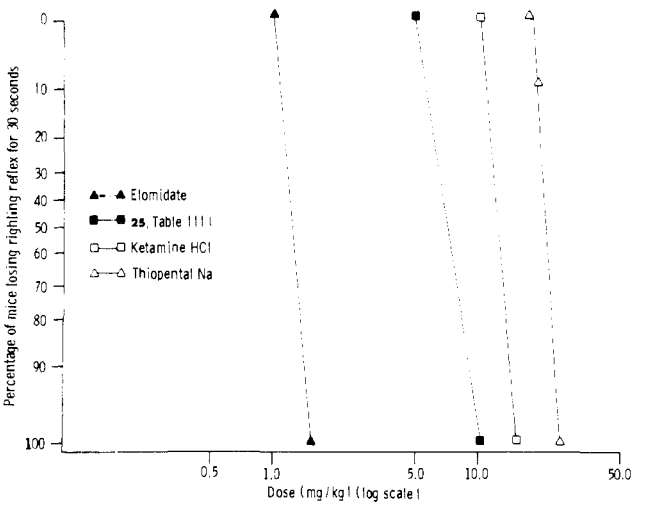


Figure 2. Dose-response lines used for the estimation of HD_{50} with 2,6-diisopropylphenol (**25**) and standard intravenous agents in mice.

found for alkyl chains not exerting a steric effect on an adjacent H-bonding site. It must be emphasized, however, that the value obtained for **31** is only approximate, being close to the upper extreme of the measurable range.

Discussion

A preliminary attempt has been made to correlate the observed anesthetic activity with the physicochemical properties of the members of this series. The steep slope of the dose–response curves for standards in the mouse primary screen is illustrated in Figure 2. In dealing with the data it is not therefore possible to make accurate comparisons of potency or kinetics across the series. Consideration of structure–activity relationships has thus been limited to a semiquantitative approach.

In any series of alkylphenols in which the steric effect of the substituents is held approximately constant, potency and kinetics appear to be related to $\sum C$ and, hence, log *P*. Thus, in the 2,6-dialkylphenols bearing one or two sec-substituents (**12–23** and **24–32**, respectively), potency increases with increasing $\sum C$, reaching a maximum or plateau when $\sum C = 6$–8. Kinetics are rapid and sleeping times short when $\sum C \leq 7$, but induction becomes slow and duration of anesthesia and recovery become prolonged at $\sum C \geq 8$.

The degree of steric compression experienced by the phenolic –OH is governed by the nature and extent of ortho substitution. The importance of this parameter can be seen in every class of phenol examined in this study. Thus, therapeutic ratios are higher for *o*-alkylphenols than for their para isomers, e.g., **2** cf. **5** and **3** cf. **6**. Comparison of isomers in the 2,6-dialkyl series reveals the general trend:

Di-*sec*-alkyl > *n*-alkyl, *sec*-alkyl > di-*n*-alkyl

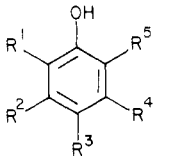
potency increasing

steric hindrance decreasing

e.g., 31 > 23; 26 > 22 ≈ 20 > 11; 25 > 19 = 10; 16 > 9

Further there seems to be an optimum value for this parameter which is exceeded by 2,6-di-*tert*-butyl substitution. This is illustrated by comparison of 2,6-di-*tert*-butylphenol (**33**), in which anesthetic activity is essentially lost, with

Table V. Meta-Substituted Phenols

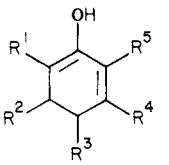


$R^3 = H$

no.	R^1	R^2	R^4	R^5	HD_{50} [a]	LD_{50} [b]	method or source	bp (mmHg) or mp, °C	% yield
45	CH_3	H	$CH(CH_3)_2$	H	30-40	80-100	*c*		
46	$CH(CH_3)_2$	H	CH_3	H	30	100	*d*		
47	CH_3	$CH(CH_3)_2$	H	$CH(CH_3)_2$	20	100	A[e]	90-92 (1.7)	12
48	$CH(CH_3)_2$	CH_3	H	$CH(CH_3)_2$	40	100-120	A[e]	70-72 (1)	35
49	n-C_4H_9	CH_3	H	$CH(CH_3)_2$	50	150	D[e]	74 (0.15)	20
50	$CH(CH_3)_2$	CH_3	CH_3	$CH(CH_3)_2$	120	160-180	A[e]	95	16
51	C_2H_5	CH_3	CH_3	C_2H_5	60-80	160	A[e]	130 (2)	35

[a] Median hypnotic dose, in mg/kg. [b] Median lethal dose, in mg/kg. [c] From ICI Petrochemicals Division, purified by distillation where necessary and checked by GPLC and NMR. [d] From Aldrich Chemical Co. Ltd., checked by GPLC and NMR. [e] All samples synthesized were checked by GPLC and NMR and gave satisfactory analyses for C and H (±0.4% calculated values).

Table VI. 2,6-Dialkylphenols: Test Results in Rabbits



$R^2 = R^3 = R^4 = H$

			mouse		
no.	R^1	R^5	HD_{50} [a]	LD_{50} [b]	summary of rabbit result
25	$CH(CH_3)_2$	$CH(CH_3)_2$	5-10	50	7.5-15 mg/kg: rapid induction, good muscle relaxation, short duration of anesthesia (4-7 min) and rapid recovery. 20 mg/kg: lethal
26	$CH(CH_3)_2$	$CH(CH_3)C_2H_5$	5-10	50	5 mg/kg: slow induction with some excitement. 15 mg/kg: lethal
27	$CH(CH_3)_2$	$CH(CH_3)$-n-C_3H_7	10-15	80	5-10 mg/kg: rapid induction, poor muscle relaxation. 20 mg/kg: lethal
28	$CH(CH_3)_2$	$CH(CH_3)$-n-C_4H_9	10-15	100-120	10 mg/kg: excitement at induction, Poor muscle relaxation. 15 mg/kg: lethal
31	$CH(CH_3)C_2H_5$	$CH(CH_3)C_2H_5$	5-10	60	5 mg/kg: rapid induction, prolonged duration of action (13 min). 10 mg/kg: lethal
32	$CH(CH_3)$-n-C_3H_7	$CH(CH_3)$-n-C_3H_7	15-20	160-180	5-15 mg/kg: marked excitement at induction, poor muscle relaxation. 30 mg/kg: lethal
	thiopental sodium		20-25	80-90	10 mg/kg: righting reflex retained. 20-30 mg/kg:[c] rapid induction, good muscle relaxation, moderate duration of action (6-11 min). 30 and 46 mg/kg: lethal

[a] Median hypnotic dose, in mg/kg. [b] Median lethal dose, in mg/kg. [c] Three rabbits per dose.

the corresponding di-sec-analogue **31** and is attributed to the marked decrease in H-bond donor properties known to occur in the series **2** > **25** ≫ **33**, as indicated by the association constants with 1,4-dioxane estimated spectroscopically.[10]

2,6-Disubstituted phenols are also more potent than their less hindered 2,4-isomers, e.g., **7** cf. **34**; **15** cf. **35**; **16** cf. **37**; **31** cf. **39**. Again the concept of an optimum value for steric crowding is suggested by the di-*tert*-butyl isomers **33** and **40** in which the latter, though less hindered, is more potent. Within the para-substituted group, comparison of isomeric pairs suggests that, normally, the more hindered is the more potent, e.g., **36** cf. **35**, but once more the exception occurs with the *tert*-butyl analogues, **44** cf. **43**.

To explore this concept further, the tri- and tetraalkylphenols **47**–**51** were prepared to evaluate the effect of increased steric crowding at the phenolic –OH, by restricting the rotational freedom of existing ortho substituents. It is apparent that the magnitude of the changes affected by the introduction of *m*-methyl groups is relatively large. Thus, 2,6-diisopropyl-3,5-dimethylphenol (**50**), although less active, has a similar profile to 2,6-di-*tert*-butylphenol (**33**), as does the corresponding 2,6-diethyl analogue **51** which is slightly more potent and less toxic. The trisubstituted compounds **47**–**49** appear intermediate in potency between the corresponding 2,6-di-*sec*-alkylphenols **12**, **25**, and **22** and the di-*tert*-butyl analogue **33**.

Conclusion

It is evident that the structure–activity relationship in this series of alkylphenols is complex. However, despite

(10) B. G. Somers and H. S. Gutowsky, *J. Am. Chem. Soc.*, **85**, 3065 (1963).

the number of biological parameters considered and the nature of the preliminary results, the importance of lipophilic character and H-bond donor/acceptor properties is apparent. It is concluded that the optimum requirement for overall anesthetic activity is fulfilled by di-*sec*-alkyl substitution, where $\sum C = 6–8$. Less steric hindrance results in lower potency, while greater crowding leads to complete loss of anesthetic activity and increased lipophilicity gives slower kinetics.

2,6-Diisopropylphenol (**25**) has emerged from the primary study in mice and rabbits as a potent iv anesthetic suitable for both induction and maintenance of anesthesia. In both species this compound is superior in its overall profile to other analogues evaluated, though some proved at least as potent, e.g., **26** and **31**. Following extensive biological follow-up, 2,6-diisopropylphenol has been evaluated in the clinic and shown to be an effective iv anesthetic agent in man.[11]

Experimental Section

Chemistry. Boiling points were determined during high-vacuum distillation and pressures were recorded with a Vacustat gauge. Where necessary, distillations were performed using a Büchi spinning-band apparatus equipped with a 60-cm column. All products gave proton NMR spectra which were compatible with the assigned structures and were recorded on either a Varian A60 or a Perkin-Elmer R12 spectrometer. Microanalyses were within ±0.4% of the theoretical values. GC analyses of both crude reaction mixtures and final products were performed with 2% OV17 and/or 5% FFAP on Gaschrome Q using Perkin-Elmer 900 and Pye 104 instruments. Column chromatography was conducted on E. Merck silica (70–230 mesh ASTM).

Method A. 2-Methyl-6-(1-methylhexyl)phenol (13). *o*-Cresol (54 g, 0.5 mol) was heated to 120 °C with Al turnings (0.7 g, 0.26 g-atom) under an atmosphere of N_2 until all the metal was dissolved and the evolution of H_2 ceased (2 h). After the mixture cooled to 40 °C, hept-1-ene (49 g, 0.5 mol) was added and the reaction mixture was transferred to a steel autoclave under N_2. The sealed vessel was heated to 200 °C over a period of 4 h and maintained at that temperature for a further 2 h. The crude product was dissolved in Et_2O (200 mL), washed with 2 N HCl, water, and brine (100 mL each), dried ($MgSO_4$), and evaporated. Distillation of the residue through a 45-cm glass helix packed column afforded 28.2 g of an oil, bp 92–93 °C (1 mm), which was further purified by spinning-band distillation to give 17.1 g (17%, >99% pure by GC) of **13**, bp 85 °C (0.2 mm). Anal. ($C_{14}H_{22}O$) C, H.

Method B. 2-Isopropylphenyl Methoxymethyl Ether (52a). 2-Isopropylphenol (136 g, 1.0 mol) was added to a stirred slurry of a 50% oil dispersion of NaH (55 g, 1.15 mol) in dry DMF (300 mL) at a rate which maintained the internal temperature at 55 °C. When evolution of H_2 ceased (1 h), the reaction vessel was cooled to 30–40 °C. Freshly distilled chloromethyl methyl ether (84.5 g, 1.0 mol) was slowly added (30 min) and, after 1 h, excess NaH was destroyed by the cautious addition of methanol (40 mL). Toluene (300 mL) and water (600 mL) were added, and the aqueous phase was separated and extracted with toluene (200 mL). The combined organic extracts were backwashed with 5% aqueous NaOH, water, and brine (200 mL each) and dried (Na_2SO_4). Evaporation of the solvent afforded a brown oil, which was distilled in vacuo to give 136.1 g (76%) of **52a**, bp 68–69 °C (3.0 mm). Anal. ($C_{11}H_{16}O_2$) C, H.

3-Isopropyl-2-methoxymethoxybenzaldehyde (53a). Tetramethylethylenediamine (44 mL, 0.28 mol) was added to a 1.43 N solution of *n*-butyllithium in *n*-hexane (200 mL, 0.286 mol) at 25 °C with stirring and under an argon atmosphere, which was maintained throughout the experiment. 2-Isopropylphenyl methoxymethyl ether (50 g, 0.28 mol) was then added slowly (20 min) at 10 °C and, after 1 h, the reaction mixture was transferred under pressure of argon into DMF (25.8 mL, 0.375 mol) in dry xylene (300 mL) at 0 °C. The reaction mixture was decomposed after a further 30 min by addition to a vigorously stirred solution of concentrated HCl (60 mL) and ice (500 g), keeping the internal temperature at ≤5 °C. Hydrolysis was completed by stirring at 0 °C, and the xylene phase was separated. The aqueous layer was extracted with toluene (200 mL), and the combined organic extracts were washed with 1 N NaOH (100 mL), water (100 mL), and brine (200 mL), then dried (Na_2CO_3), and evaporated. The resulting oil was distilled in vacuo, affording 39.7 g (68%) of **53a**, bp 84–86 °C (0.05 mm). Anal. ($C_{12}H_{16}O_3$) C, H.

3-Isopropyl-2-methoxymethoxycinnamaldehyde (54a). 3-Isopropyl-2-methoxymethoxybenzaldehyde (14.6 g, 0.07 mol) was dissolved in dry toluene (350 mL) and formylmethylenetriphenylphosphorane[4] (23 g, 0.075 mol) was added in one portion. The reaction mixture was stirred and heated to reflux under argon for 24 h. Evaporation, followed by trituration with ether at 0 °C, gave triphenylphosphine oxide, which was filtered off and washed with ice-cold ether (20 mL). The filtrate was evaporated and distilled in vacuo to remove unreacted starting aldehyde (6.3 g). The fraction, bp 110–150 °C (0.05 mm), was chromatographed on silica, eluting with petroleum ether (60–80 °C)/ether (3:1), affording 5.3 g of *cis*-3-isopropyl-2-methoxymethoxycinnamaldehyde (**54a**) as an oil, which was utilized in the next stage. Subsequent elution gave 3.3 g of a cis/trans mixture of the cinnamaldehyde. The total yield based on unrecovered starting material was 93%.

2-Cyclopropyl-6-isopropylphenol (24). *cis*-3-Isopropyl-2-methoxymethoxycinnamaldehyde (4.8 g, 0.022 mol) in absolute EtOH (10 mL) was slowly added (30 min) to a solution of 95% hydrazine hydrate (3.1 mL, 0.062 mol) in absolute EtOH (15 mL) heated to reflux. After a further 30 min at reflux, EtOH and excess hydrazine were distilled off, gradually raising the external bath temperature to 150 °C over the next hour. Finally, the crude product was pyrolyzed at 320 °C for 30 min and the remaining material flash distilled. Redistillation in vacuo afforded 2.0 g of 2-cyclopropyl-6-isopropylphenyl methoxymethyl ether, bp 79–81 °C (0.2 mm), which was dissolved in methanol (40 mL) and *p*-TSA (20 mg) added. The reaction mixture was heated with stirring in an oil bath at 110 °C beneath a 25-cm Vigreux column and methanol/dimethyl acetal azeotrope was slowly distilled over until the volume of the solution in the distillation flask was ~5 mL (1 h). Methanol (5 mL) and aqueous 2 N HCl (10 mL) were added, and the solution was stirred and heated to reflux for 30 min. After the solution cooled, ether (40 mL) and water (10 mL) were added and the aqueous phase was separated and extracted with ether (2 × 30 mL). Combined ether extracts were backwashed with saturated aqueous $NaHCO_3$ solution (25 mL), then dried (K_2CO_3), and evaporated. The residue was distilled in vacuo to give 1.0 g (26%) of **24**, bp 85–86 °C (2.6 mm). Anal. ($C_{12}H_{16}O$) C, H.

Method C. Allyl 2-*sec*-Butylphenyl Ether (55). 2-*sec*-Butylphenol (22.5 g, 0.15 mol) and allyl bromide (36.3 g, 0.3 mol) were dissolved in CH_2Cl_2 (225 mL) and added to a 1 N solution of NaOH in water (255 mL) containing benzyltri-*n*-butylammonium bromide (5.1 g, 0.015 mol). The reaction mixture was stirred rapidly at the phase interface for 2 h at room temperature and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (200 mL), and the combined organic phases were washed with water and brine (200 mL each), dried ($MgSO_4$), and evaporated. Distillation of the resulting oil in vacuo afforded 25.8 g (86%) of **55**, bp 56–58 °C (0.2 mm). Anal. ($C_{13}H_{18}O$) C, H.

2-Allyl-6-*sec*-butylphenol (56). Allyl 2-*sec*-butylphenyl ether (9.5 g, 0.05 mol) was heated to 250 °C under a nitrogen atmosphere for 1.5 h. On cooling, the reaction mixture was chromatographed on silica, eluting with toluene, and the major component distilled in vacuo to give 6.0 g (72.5%) of **56**, bp 64 °C (0.06 mm). Anal. ($C_{13}H_{18}O$) C, H.

2-*sec*-Butyl-6-propylphenol (20). 2-Allyl-6-*sec*-butylphenol (3.8 g, 0.02 mol) was dissolved in absolute EtOH (100 mL) and hydrogenated at 25 °C (atmospheric pressure) over 10% Pd/C. Total uptake of H_2 (530 mL) was completed within 15 min, and the catalyst was removed by filtration through a Celite pad. Evaporation of the solvent gave an oil which was distilled in vacuo, affording 3.1 g (66%) of a colorless liquid **20**, bp 66 °C (0.1 mm). Anal. ($C_{13}H_{20}O$) C, H.

Method D. 2-*sec*-Butyl-6-ethylphenol (17). Freshly recrystallized NCS (13.4 g, 0.1 mol) was dissolved in dry CH_2Cl_2 (500 mL) and stirred magnetically under an argon atmosphere,

(11) B. Kay and G. Rolly, *Acta Anaesthesiol. Belg.*, **28**, 303 (1977).

which was maintained throughout the experiment. Diethyl sulfide (11.25 g, 0.125 mol) was added over 15 min at −5 °C. The internal temperature was adjusted to −25 °C and 2-*sec*-butylphenol (30 g, 0.2 mol) in dry CH_2Cl_2 (50 mL) was added slowly (20 min). After a further 30 min, triethylamine (10.2 g, 0.1 mol) was added in one portion and the reaction mixture was allowed to warm to room temperature (4 h). Evaporation afforded a brown oily solid, which was triturated with petroleum ether (60–80 °C) and filtered to remove salts. The filtrate was evaporated, and unreacted starting phenol was separated by distillation in vacuo. The residue was chromatographed on silica, eluting with petroleum ether/ether (3:1), to give an oil which was distilled in vacuo, affording 9.3 g of the intermediate thioether **59**, bp 91–93 °C (2.0 mm). This material (2.0 g, 0.0085 mol) was desulfurized by heating to reflux in EtOH (100 mL), together with W2 Raney nickel (20 g) for 24 h. When the solution cooled, the catalyst was removed by filtration through Celite and the solvent was evaporated. Vacuum distillation of the residue afforded 1.1 g (28% based on NCS) of **17**, bp 62 °C (0.07 mm). Anal. ($C_{12}H_{18}O$) C, H.

Pharmacology. Cremophor EL (BASF, Germany), a polyoxyethylated castor oil derivative with surfactant properties, in a 10% (v/v) concentration in water was used to prepare solutions for intravenous injection containing 10 mg/mL of a test compound. In some instances, ethyl alcohol (6%, v/v) and dimethyl sulfoxide (6%, v/v) were required as additional solubilizing agents.

The compounds were administered intravenously (iv) to S.P.F. albino mice (Alderley Park Strain) weighing 18–22 g. Groups of five male mice were used for each dose investigated. Most compounds were injected at a rate of 0.1 mL/10 s, the maximum volume injected being 0.4 mL. In tests performed toward the end of this study, our technique was altered in such a way that all doses were given over a standard injection time of 10 s. This alteration allowed a more accurate assessment of speed of onset of effect[13] and had minimal influence on the figures obtained for the activity and acute toxicity of standard compounds. A range of 6–8 doses was administered, including a dose producing 100% lethality and one which failed to produce loss of righting reflex for a minimum period of 30 s. The median hypnotic dose (HD_{50}) was estimated by interpolation as that dose which would be expected to cause loss of righting reflex for a minimum period of 30 s in 50% of mice. This technique is based on the method of probit analysis.[12] To achieve an accurate estimate with this method it is necessary to examine doses producing effects in the range of 40 to 60%. In many instances, because of the steep slope of the dose–response lines obtained, these estimates were expressed as a dose range giving 0 and 100% effects with closely spaced doses. The dose–response lines used in the estimation of HD_{50} values for compound **25** and a number of standard intravenous anesthetic agents are shown in Figure 2.

The median lethal dose (LD_{50}) was estimated in the same way, as that dose which would be expected to produce a lethal effect in 50% of mice, and therapeutic ratio was calculated as the ratio LD_{50}/HD_{50}. The definition of HD_{50} and LD_{50} values within a 5–10 mg/kg dose range was sufficiently accurate to allow the activity and toxicity of a range of compounds to be compared. In a preliminary testing situation it is not necessary to use additional animals to further define the HD_{50} value.

In the group of di-ortho-substituted phenols (Table III), where the most active compounds were found, note was taken of the speed of onset of anesthesia and the duration of the period of loss of righting reflexes. Since these features were noted at doses equal to two times the estimated HD_{50}, the HD_{50} being taken in some instances as the median dose within a defined dose range, it was not always possible to be certain that these observations were made at exactly equipotent doses. For this reason, limits were defined within which speed of induction was classed an immediate (<10 s; i.e., mice lost righting reflexes by the end of an injection), slow (10–15 s), or very slow (>15 s) and duration of action was classed as brief (<5 min), moderate (5–10 min), or long (>10 min). A nonlinear decrease in the duration of anesthesia with increasing doses indicated that a particular compound was accumulating in body tissues to a significant extent.

Analgesia was assessed by noting the response to tail pinching. Muscle tremors and myoclonia were noted as excitatory side effects, and compounds producing poor muscle relaxation were those which failed to abolish muscle tone during anesthesia. Mice were observed for 10 days following the test to allow any delayed deaths to be noted.

Compounds without serious side effects, with an $HD_{50} \leq 20$ mg/kg and a therapeutic ratio ≥ 4, were selected for further testing in rabbits (Dutch strain) weighing 2–3 kg. Test agents were prepared as solutions containing 25 mg/mL in Cremophor EL 10%, v/v, and injected into a marginal ear vein over a period of 20 s. A range of doses was examined to give some indication of minimum hypnotic and lethal doses and to assess the quality of the anesthesia obtained. Each dose was generally given to only a single rabbit, and four to six rabbits were used to study each compound. Speed of onset and duration of anesthesia, muscle relaxation, and any excitatory effects were noted. In addition, compounds which produced a period of respiratory arrest lasting more than 20 s at anesthetic doses were classed as potent respiratory depressants. Results obtained with thiopental sodium in this test are included in Table VI.

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Supplementary Material Available: Biological results on 39 phenols not included in the text (1 page). Ordering information is given on any current masthead page.

(12) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).

(13) J. B. Glen, *Br. J. Anaesthesiol.*, **49**, 545 (1977).