Model 240 spectrophotometer equipped with an automatic sample-changing accessory. Reactions were initiated by adding a given amount of *l*-NE from a stock solution to a $2.5 \times 10^{-4}$ *M* solution of PLP in the appropriate buffer and decreases in absorption at 388 nm were recorded continuously until no further change was observed. Pseudo-first-order rate constants were calculated on a Hewlett-Packard 2100A digital computer, using a program designed to calculate a least-squares evaluation of a plot of $\ln (A_{inf} - A_o/A_{inf} - A_T)$ *vs.* time. The correlation coefficients were usually greater than 0.999.

**Purification and Assay of COMT.** COMT was purified from rat liver (male, Sprague Dawley, 180–200 g) and assayed according to the methods previously described.[14,15] Kinetic data processing was also achieved as previously described.[14,15]

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# Synthesis of New Bis(1-aziridinyl) Phosphinate Alkylating Agents Containing *O*-Phenyl *N*-Phenylcarbamate Side Chains†,[1]

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In view of the previously observed unusually high therapeutic indices of certain aromatic carbamate nitrogen mustards against the Walker 256 tumor, suggesting the possibility of selective uptake of these agents by the tumor cells, several new compounds were synthesized in which the same *O*-phenyl *N*-phenylcarbamate side chains were linked to bis(1-aziridinyl)- and bis(2,2-dimethyl-1-aziridinyl)phosphinyl alkylating groups. The syntheses of these compounds, requiring selective reactions of bifunctional molecules, are described. The biological test results do not show any increase in the therapeutic indices of these alkylating agents and thus do not support the suggested "selective carrier" action of the *O*-phenyl *N*-phenylcarbamate moiety.

In a previous study[2] of the structure-activity relationships of a variety of aromatic nitrogen mustards and aziridine-type alkylating agents, it was observed that the "carbamate mustards" (synthesized by Owens, *et al.*[3,4]) and the 2,2-dimethylaziridine derivatives (synthesized in our laboratory[5-7]) represented two striking classes of selective-acting alkylating agents. It was suggested that the unusually high therapeutic indices shown by the carbamate mustards against Walker carcinosarcoma 256 in rats may be due to the action of their *O*-phenyl *N*-phenylcarbamate moieties as "selective carrier" structures, capable of mediating preferential "uptake" of these cytotoxic agents by the tumor cells. On the other hand, the favorable antitumor spectra of the 2,2-dimethylaziridine derivatives have been attributed to the unique chemical reactivity pattern of their alkylating functions.[2,8-10]

It appeared, therefore, of interest to synthesize new compounds in which 2,2-dimethylaziridine-containing alkylating functions are linked to *O*-phenyl *N*-phenylcarbamate carrier structures similar to those of the "carbamate mustards," hoping that a combination of the favorable properties of both types of antitumor agents may be achieved. Furthermore, it was of interest to test our hypothesis concerning the extraordinary selectivity of the carbamate mustards against the Walker 256 tumor by synthesizing agents in which the same carrier structures are linked to an alkylating function other than nitrogen mustard. For the latter purpose, it seemed more appropriate to employ the ring-unsubstituted bis(1-aziridinyl)phosphinyl as the alkylating function, since this is considerably more reactive with nucleophiles than the corresponding 2,2-dimethylaziridine derivative and is more similar in both structure and pharmacologic properties to the nitrogen mustard moiety.[8]

The present paper describes the successful syntheses of bis(1-aziridinyl)phosphinyl and bis(2,2-dimethyl-1-aziridinyl)phosphinyl analogs **4**, **5**, **15**, and **16** corresponding to both the "carbamate" and "reverse carbamate" series[2] of the aromatic carbamate nitrogen mustards and of two additional derivatives, **19** and **20**, in which the two phenyl groups of the side chain are linked by $OCH_2$ rather than carbamate moieties. The latter were designed to permit estimation of the "structurally nonspecific" component of the effect of the long lipophilic side chains on the activities of these agents. Finally, our unsuccessful attempts aimed at the syn-

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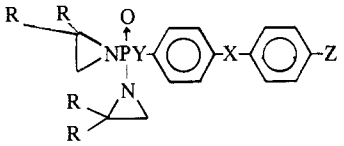
thesis of the even more complex bis(carbamatophenyl) derivatives **7a** and **7b** which would contain the entire structures of the "dual antagonists" AB-100 and AB-132,[5,8] respectively, linked to the *O*-phenyl *N*-phenylcarbamate moiety, are also reported in this paper.



| | X | Y | Z | R |
|---|---|---|---|---|
| **4** | NHCOO | O | $CO_2CH_3$ | $CH_3$ |
| **5** | NHCOO | O | $CO_2CH_3$ | H |
| **15** | OCONH | O | $CO_2CH_3$ | $CH_3$ |
| **16** | OCONH | O | $CO_2CH_3$ | H |
| **19** | $OCH_2$ | O | H | $CH_3$ |
| **20** | $OCH_2$ | O | H | H |
| **7a** | NHCOO | NHCOO | $CO_2CH_3$ | H |
| **7b** | NHCOO | NHCOO | $CO_2CH_3$ | $CH_3$ |

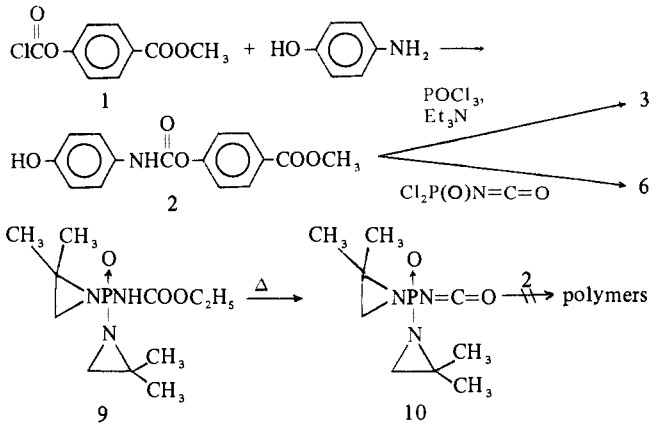
In the method employed by Owen, *et al.*,[3,4] for the synthesis of the aromatic carbamate nitrogen mustards, it was possible to build the carbamate side chain onto the amino or hydroxyl group, respectively, of the previously synthesized *p*-anilino and *p*-phenol nitrogen mustards, since the latter are relatively stable in the form of their hydrochloride salts. In contrast, the aziridine rings of the bis(1-aziridinyl)phosphinyl and bis(2,2-dimethyl-1-aziridinyl)phosphinyl groups are extremely labile to trace amounts of acid and even to water (containing absorbed $CO_2$ from the air) and readily undergo polymerization or hydrolysis.[9] Therefore, the introduction of the aziridine functions could be carried out only in the last step of the synthetic schemes, and the *O*-phenyl *N*-phenylcarbamate moieties had to be synthesized first, with a free amino or hydroxyl group in the para position for the attachment of the alkylating moiety. Due to this necessity, three major synthetic problems arose: (1) in the synthesis of the carbamates **2** and **12** (Schemes I and II), a bifunctional compound (*p*-aminophenol or *p*-hydroquinone, respectively) had to be reacted in a *selective* manner with the chloroformate or isocyanate reactants (**1** and **11**, respectively); (2) in the final reaction step, the aziridines had to be reacted selectively with the dichlorophosphinyl groups of **3**, **6**, and **14** (Table II) without splitting the carbamate linkages *via* transamidation (tendency to form urea derivatives[6]); and (3) in an alternative synthetic route to **7b**, attempts to couple the *p*-hydroxyphenyl carbamate **2** with bis(2,2-dimethyl-1-aziridinyl)isocyanatophosphine oxide (**10**) resulted in opening of the aziridine rings due to the acidity of the phenolic hydroxyl group of **2**.

In the synthesis of **2** (Scheme I), selective reaction of the amino group of *p*-aminophenol with the chloroformate **1** could be achieved by using, as hydrochloride acceptor, a second equivalent of *p*-aminophenol, which upon salt formation immediately precipitated from the solution. The "reverse" carbamate **12** (Scheme II) could be synthesized by reacting the isocyanate **11** at −10 to −15° with a twofold excess of *p*-hydroquinone, in the presence of a catalytic amount of triethylamine (which dramatically increased the otherwise very slow reaction rate at the low temperatures employed). The reaction temperature, as well as the solvent used, was found to be a critical factor in determining the ratio of the products obtained; low temperature, using ether as solvent, favored the formation of the desired product **12** which precipitated from the ether solution, while at room temperature or above, *both* hydroxyls of *p*-hydroquinone reacted with the isocyanate **11** to give a large amount of the unwanted by-product **13**. The latter was the major product even at low temperature when the reaction was conducted in DME or THF.

The reactions of the carbamates **2** and **12** with equivalent amounts of phosphorus oxychloride and triethylamine proceeded in almost quantitative yields to give the phosphorodichloridate derivatives **3** and **14**, respectively. In reacting these with the respective aziridines, conducting the reactions at very low temperatures (−10 to −15°) successfully prevented transamidation of the carbamyl groups (which was a major side reaction at temperatures in the neighborhood of 0°, as indicated by the infrared spectra). Thus, the desired aziridine derivatives **4**, **5**, **15**, and **16** could be obtained in satisfactory yields and purity. The synthesis of **19** and **20**, containing no carbamate moieties, presented no problems. On the other hand, the phosphorodichloridate **6**, which contains two carbamate moieties, underwent degradation upon treatment with the aziridines even at −15°; thus, our efforts to synthesize **7a** and **7b** were unsuccessful.

**Biological Activity.** All new compounds were tested against Walker carcinosarcoma 256 in rats according to the procedure used previously in the comparative study of a large series of alkylating agents[11] and, subsequently, in the original study of the carbamate mustards.[12] At the highest employable dose levels (1000–2000 μmol/kg), none of the

Scheme I



Scheme II

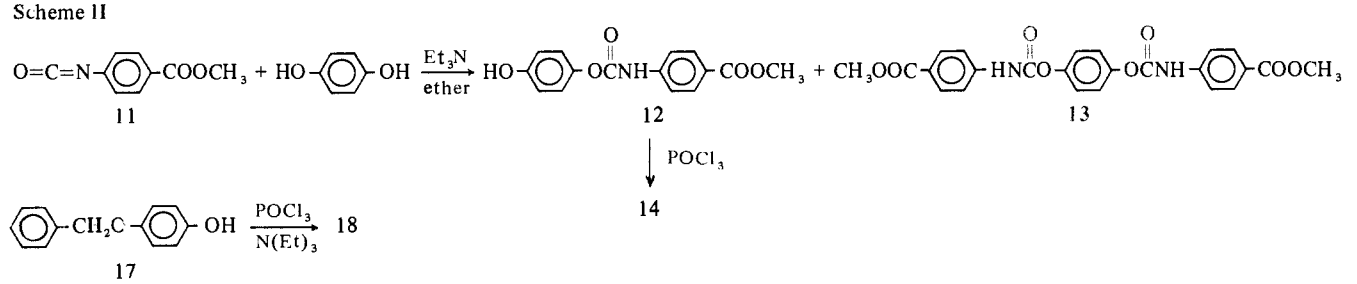


Table I. Toxicity and Chemotherapeutic Activity of Bis(1-aziridinyl)phosphinyl Derivatives

| Compd no. | Toxicity,[a] $LD_{50}$, μmol/kg | Antitumor activity[b] $ED_{90}$, μmol/kg | $LD_{50}/ED_{90}$ |
|---|---|---|---|
| **5** | 539 | 96 | 5.6 |
| **16** | 2400 | 1198 | 2.0 |
| **20** | 1800 | 970 | 1.9 |

[a]In Holtzman rats (ref 11). [b]Walker carcinosarcoma 256 (ref 11).

new 2,2-dimethylaziridine derivatives **4**, **15**, and **19** showed either toxicity or antitumor activity. Active dose levels could be attained only with the unsubstituted aziridine derivatives **5**, **16**, and **20** (Table I), and of these only **5** showed significant antitumor selectivity in the Walker tumor assay, having a therapeutic index of 5.6. This compound has the same carrier structure as the nitrogen mustard which gave the *highest* therapeutic index (*i.e.*, a surprising 137) in the previously reported series of "alkylating carbamates,"[2,12] and, yet, its selectivity against the Walker tumor is of the same order as those of some other bis(1-aziridinyl)phosphinyl derivatives having much simpler urethane or ester side chains.[2]

Thus, the results of our present study demonstrated that, at least in the bis(1-aziridinyl) phosphinate series of alkylating agents, the *O*-phenyl *N*-phenylcarbamate moiety does not increase the selectivity of "uptake" by the Walker tumor cells. Since there are sufficient differences between the overall structures of these agents and those of the analogous nitrogen mustard derivatives to account for possible differences in the mechanisms of their uptake by the cells, the negative result obtained with the bis(1-aziridinyl) phosphinate analogs cannot be regarded as definitive evidence *against* the carrier hypothesis in relation to the carbamate nitrogen mustards; a positive result would have constituted a more satisfactory evidence *in support* of this hypothesis. Definitive conclusions concerning the mode of action of the carbamate mustards cannot be based on structure-activity relationship studies only. However, the results presented in this paper seem to lend more prominence to an alternative hypothesis, proposed by Hebborn.[12] It should be pointed out that the "chemical alkylating activities" ($k' \times 10^3$ values)[11] of the bis(1-aziridinyl)phosphinyl derivatives are in the range of 3.0–3.5, while the corresponding values for the "reverse carbamate" series of nitrogen mustards are ten times higher.[2] It is possible that the unusual selectivity of the carbamate mustards could be due to their ability to alkylate a "specific site" in the Walker tumor cells[12] and that this same site might not be sufficiently nucleophilic to be alkylated by the much less reactive aziridine agents. Thus, the *O*-phenyl *N*-phenylcarbamate moiety could possibly contribute to the binding of the highly reactive carbamate nitrogen mustards to an intracellular receptor at the site of alkylation rather than act as a "carrier" providing for the preferential uptake of these agents by the tumor cells.

## Experimental Section‡

*p*-Carbomethoxyphenyl *N*-*p*-(Hydroxyphenyl)carbamate (2). To a solution of *p*-aminophenol (31.28 g, 0.286 mol) in dry THF (500 ml) was added under stirring *p*-carbomethoxyphenyl chloroformate (I)[13] (30.76 g, 0.143 mol) in THF (200 ml), keeping the temperature below 10° (ice bath). After addition, the reaction mixture was stirred for 3 hr at 10°, and the precipitated *p*-aminophenol hydrochloride salt was filtered (20.7 g, 99%). The filtrate was evaporated to dryness, and the residue (41 g) was extracted (Soxhlet) with ether and then recrystallized from ether–hexane: yield 35.5 g (87%); mp 176–178°; nmr ($CD_3COCD_3$) δ 3.33 (s, 3 H), 6.28 (d, 2 H, $J$ = 9 Hz), 6.72 (d, 2 H, $J$ = 5 Hz), 6.91 (d, 2 H, $J$ = 5 Hz), 7.50 (d, 2 H, $J$ = 9 Hz); carbamate linkage clearly shown by ir (1722 and 1695 $cm^{-1}$); formation of a carbonate product was not detected. *Anal.* ($C_{15}H_{13}NO_5$) C, H, N.

*p*-Hydroxyphenyl *N*-*p*-(Carbomethoxyphenyl)carbamate (12). A suspension of *p*-hydroquinone (11.0 g, 0.10 mol) in dry ether (400 ml) was cooled to −10 to −15° (ice–salt bath) and 5 drops of triethylamine was added as a catalyst. Methyl *p*-isocyanatobenzoate (11)[14] (9.0 g, 0.05 mol) in ether (200 ml) was added dropwise; then stirring was continued for 2 hr. The precipitated crude product (12.8 g) was extracted at room temperature with 1,2-dimethoxyethane (DME) (400 ml); about 3 g of insoluble residue was separated by filtration. The DME-soluble fraction was recrystallized from DME–$CHCl_3$ (1:1): yield 8.7 g (61%) of 12; mp 146–148°; nmr (TFA) δ 3.63 (s, 3 H), 6.65 (s, 4 H), 7.17 (d, 2 H, $J$ = 8.5 Hz), 7.68 (d, 2 H, $J$ = 8.5 Hz). *Anal.* ($C_{15}H_{13}NO_5$) C, H, N.

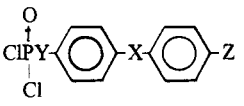
The DME-insoluble residue was identified as 13, *i.e.*, a by-product formed by the reaction of two molecules of **11** with one molecule of *p*-hydroquinone, mp 289–293° dec. *Anal.* ($C_{24}H_{20}N_2O_8$) C, H, N.

Phosphorodichloridate Intermediates (See Table II). Procedure A. A solution of $POCl_3$ (purchased from Allied Chemical Co. and freshly distilled; 2.134 g, 13.92 mmol) in dry THF (30 ml) was cooled to 0–5° (ice bath), and the *p*-hydroxyphenyl carbamate **2** or **12**, respectively (4.0 g, 13.92 mmol), in THF (30 ml) was added dropwise, under stirring, keeping the temperature of the reaction mixture below 5°. After addition, stirring was continued for 2 hr. Triethylamine (1.409 g, 13.92 mmol) in THF (10 ml) was added slowly; then the solution was stirred for an additional hour at 0–5°. The precipitated triethylamine hydrochloride was separated by filtration. The filtrate was evaporated and the residue was washed with petroleum ether (20 ml) and dried *in vacuo* ($P_2O_5$) to give quantitative yields of the *O*- (and *N*-) (*p*-carbomethoxyphenyl)carbamato-*N*- (and *O*-) *p*-phenyl phosphorodichloridates (3 and 14), respectively: ir (3) 3360 (CONH), 1747 (C=O, ester), 1725 (C=O, carbamate), 1280 (P→O), 1210 $cm^{-1}$ (POAr).

Procedure B. A solution of freshly distilled dichloroisocyanatophosphine oxide[6] (2.06 g, 13.92 mmol) in dry THF (30 ml) was cooled to 0–5° (ice bath). A solution of **2** (4.0 g, 13.92 mmol) in THF (30 ml) was added dropwise, under stirring. The temperature was maintained below 5°. After addition was completed, the reaction mixture was stirred for another 2 hr. The solvent was removed under reduced pressure at room temperature, and the residue was washed with petroleum ether (30 ml) and then dried *in vacuo* to give the [bis(carbamatophenyl)] phosphorodichloridate (6); ir 3346 (CONH), 3100 (PNH), 1760 (C=O, ester), 1730 and 1725 (2 C=O, carbamates), 1275 $cm^{-1}$ (P→O).

Procedure C. To a solution of $POCl_3$ (7.667 g, 50 mmol) in dry ether (100 ml) a solution of *p*-(benzyloxy)phenol (17, 10.0 g, 50 mmol) and triethylamine (5.06 g, 50 mmol) in ether (150 ml) was added dropwise at a temperature below 5°. Stirring was continued for 3 hr, and the precipitated triethylamine hydrochloride was filtered. The filtrate was evaporated and the residue was crystallized from petroleum ether to give *p*-(benzyloxy)phenyl phosphorodichloridate (18). All phosphorodichloridates appeared to be unstable and were used immediately for the next reaction step.

Table II. Phosphorodichloridate Intermediates[a]



| No. | X | Y | Z | Procedure | Yield, % | Mp, °C |
|---|---|---|---|---|---|---|
| 3 | NHCOO | O | $CO_2CH_3$ | A | 95 | 120–122 |
| 6 | NHCOO | NHCOO | $CO_2CH_3$ | B | 61 | 159–161 |
| 14 | OCONH | O | $CO_2CH_3$ | A | 93 | 122–125 |
| 18 | $OCH_2$ | O | H | C | 65 | 58–60 |

[a]Very hygroscopic, unstable compounds; identity and purity based on satisfactory ir and nmr spectra in lieu of elemental analysis.

‡Ir and nmr spectra of all compounds were recorded and used for confirmation of structure. The ir spectra were taken in KBr pellet in a Beckman IR-8; the nmr spectra were recorded on Varian A-60 in an appropriate solvent ($CD_3COCD_3$, TFA, or $CDCl_3$), using TMS as standard. All melting points were taken in capillary tubes (Mel-Temp) and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Atlantic Microlab, Atlanta, Ga.

[Bis(2,2-dimethyl-1-aziridinyl) and Bis(1-aziridinyl)] Phosphinates. (A) *O*-(*p*-Carbomethoxyphenyl)carbamato-*N*-*p*-phenyl Esters (4 and 5). A solution of 2,2-dimethylaziridine (1.423 g, 0.02 mol) and triethylamine (2.024 g, 0.02 mol) in dry ether (80 ml) was cooled to −10 to −15° (ice-salt bath), and 3 (4.042 g, 0.01 mol) in dry DME (20 ml) was added dropwise keeping the temperature below −8°. After continued stirring for 2 hr, the precipitated solids were collected and repeatedly extracted with DME. The combined extracts were evaporated and the residue was dried *in vacuo* and then recrystallized from a mixture of methylene chloride and ether (1:1) to yield 4 in analytical purity: yield 61%; mp 142–144°; nmr δ 1.43 (s, 12 H), 2.26 (d, 4 H, $J$ = 14 Hz), 3.93 (s, 3 H), 7.08–8.17 (m, 8 H). *Anal.* ($C_{23}H_{28}N_3O_6P$) C, H, N, P.

Compound 5 was synthesized in the same manner, using unsubstituted aziridine instead of 2,2-dimethylaziridine: yield 72%; mp 140–142°; nmr δ 2.26 (d, 8 H, $J$ = 14 Hz), 3.93 (s, 3 H), 7.07–8.17 (m, 8 H). *Anal.* ($C_{19}H_{20}N_3O_6P$) C, H, N, P.

(B) *N*-*p*-(Carbomethoxyphenyl)carbamato-*O*-*p*-phenyl Esters (15 and 16). These compounds were synthesized in an analogous manner as 4 and 5, respectively, using the phosphorodichloridate 14. However, the products 15 and 16 remained in solution after precipitation of the triethylamine hydrochloride and were obtained from the filtrates by evaporation of the solvent and recrystallization of the residues from methylene chloride–ether (1:1). 15 gave a yield of 57%; mp 101–104°; nmr δ 1.42 (s, 12 H), 2.25 (d, 4 H, $J$ = 14 Hz), 3.86 (s, 3 H), 6.86–8.01 (m, 8 H). *Anal.* ($C_{23}H_{28}N_3O_6P$) C, H, N, P. 16 gave a yield of 38%; mp 153–154°; nmr δ 2.32 (d, 8 H, $J$ = 15 Hz), 3.95 (s, 3 H), 6.95–8.08 (m, 8 H). *Anal.* ($C_{19}H_{20}N_3O_6P$) H, N, P; C: calcd, 54.68; found, 54.14.

(C) *p*-(Benzyloxy)phenyl Esters (19 and 20). These compounds were prepared by reacting 18 with 2,2-dimethylaziridine and aziridine, respectively, in the presence of an equivalent amount of triethylamine, under similar conditions as described in the synthesis of 4, except that ether was used as the only solvent. After separation of the precipitated triethylamine hydrochloride, the desired products, 19 and 20, respectively, were crystallized from the filtrates and then recrystallized from ether. 19 gave a yield of 58%; mp 83–85°; nmr δ 1.42 (s, 12 H), 2.24 (d, 4 H, $J$ = 14 Hz), 5.04 (s, 2 H) 7.07 (q, 4 H), 7.39 (s, 5 H). *Anal.* ($C_{21}H_{28}N_2O_3P$) C, H, N. 20 gave a yield of 73%; mp 38–40°; nmr δ 2.30 (d, 8 H, $J$ = 15 Hz), 5.10 (s, 2 H), 7.13 (q, 4 H, $J$ = 9 Hz), 7.48 (s, 5 H). *Anal.* ($C_{17}H_{19}N_2O_3P$) C, H, N.

Attempted Syntheses of 7a and 7b (Scheme I). Method A. Reaction of the phosphorodichloridate 6 with aziridine (or 2,2-dimethylaziridine), at −15°, led to mixtures of partially polymerized degradation products, from which only tris(1-aziridinyl)phosphine oxide[15] (TEPA) could be isolated and identified.

Method B. A solution of ethyl bis(2,2-dimethyl-1-aziridinyl)-phosphinylcarbamate (9, AB-132)[7] in dry toluene was heated to boiling. Immediate formation of the isocyanate 10 was observed [ir 2225 $cm^{-1}$ (C=N=O)]. Reaction of the latter with 2 resulted in opening of the aziridine rings (nmr) and polymerization.

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# Local Anesthetic Azabicyclo-*N*-alkylanilides

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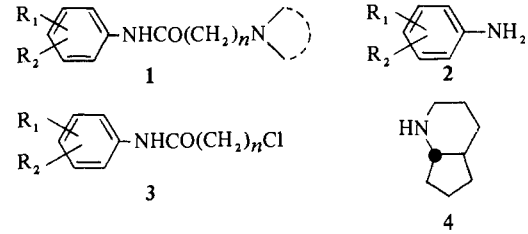
The synthesis of a series of azabicyclo-*N*-alkylanilides and the preliminary evaluation of their local anesthetic activities are described. The azabicyclic moieties are *cis*- and *trans*-octahydro-1*H*-pyrindine, *cis*- and *trans*-decahydroquinoline, *cis*- and *trans*-decahydro-1*H*-cyclohepta[*b*]pyridine, and *trans*-hexahydro-1*H*-cyclopenta[*b*]pyrrole. *trans*-6′-Chloro-2,3,4,4a,5,6,7,7a-octahydro-1*H*-1-pyrindine-1-propiono-*o*-toluidide (14a, rodocaine) was approximately four times more potent than lidocaine and had a considerably longer duration of action.

Since the introduction of lidocaine,[1] the literature has recorded many derivatives containing the aminoalkylanilide grouping.[2–4] Most local anesthetics[5–7] are characterized by a lipophilic portion and a hydrophilic moiety linked together by an intermediate chain.[1] Relatively little structural modification has been introduced into the amine portion or hydrophilic moiety.[5–7]

As part of an effort to develop new local anesthetic agents, with properties corresponding to chemical stability, high potency, low toxicity, rapid onset of action, and absence of local irritation, a series of azabicyclo-*N*-alkylanilides of general formula 1 was prepared. One of the objectives of this study was to incorporate the amine portion into a bicyclic ring system. Thus in 1, -N< corresponded to *cis*- or *trans*-octahydro-1*H*-pyrindine, *cis*- or *trans*-decahydroquinoline, *cis*- or *trans*-decahydro-1*H*-cyclohepta[*b*]pyridine, or *trans*-hexahydro-1*H*-cyclopenta[*b*]pyrrole, *n* was either methylene or ethylene, and $R_1$ and $R_2$ were methyl or chlorine.

**Chemistry.** The compounds were synthesized by conventional methods. Reaction of appropriate anilines 2 with




either chloracetyl chloride or 3-chloropropionyl chloride afforded the corresponding ω-chloroalkylanilides (3). Displacement of the ω-chlorine of 3 with various bicyclic sec-