(22) N. Petragnani and G. Schill, *Chem. Ber.*, **97**, 3293 (1964).
(23) M. Fieser, L. Fieser, E. Toromanoff, Y. Hirata, H. Heymann, M. Tefft, and S. Bhattacharya, *J. Am. Chem. Soc.*, 78, 2825 (1956).
(24) A. Aszalos, P. Lemanski, and B. Berk, *J. Chem. Eng. Data*, 11, 429 (1966).
(25) G. Tong, W. W. Lee, D. R. Black, and D. W. Henry, *J. Med. Chem.*, **19**, 395 (1976). Modified procedures for measuring ΔT_m used 0.010 M phosphate buffer containing 10^{-5} M EDTA at pH 7.0 plus 5% Me_2SO to solubilize the compound. Modified procedures for measuring DNA–RNA inhibition added 1% Me_2SO for improved solubility. The in vitro tests were done at SRI by Dorris Taylor, Charlotte Elder, Nancy Charbeneau, and Keith Hohlfeldt.
(26) We are indebted to Dr. Harry B. Wood, Jr., Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, NCI, and to Mr. S. J. Lucania, E. R. Squibb & Sons, Inc., for supplying samples of 1.
(27) B. N. Ames, W. E. Durston, E. Yamasaki, and F. D. Lee, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2281 (1973); B. N. Ames, J. McCann, and E. Yamasaki, *Mutat. Res.*, 31, 347 (1975). We are indebted to Dr. V. F. Simmon of SRI for these determinations.
(28) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Am. Chem. Soc.*, 85, 2497 (1963).
(29) J. L. Frahn and J. A. Mills, *Aust. J. Chem.*, 18, 1303 (1965).
(30) E. B. Rathbone, A. M. Stephen, and K. G. R. Pachler, *Carbohydr. Res.*, **20**, 357 (1971).
(31) G. F. Vesley and V. I. Stenberg, *J. Org. Chem.*, **36**, 2548 (1971).
(32) C. R. Fordyce and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 3368 (1933).
(33) R. E. Leslie and H. R. Henze, *J. Am. Chem. Soc.*, 71, 3480 (1949).
(34) J. Andrako, J. D. Smith, and W. H. Hartung, *J. Pharm. Sci.*, **50**, 337 (1961).

Biologically Active Polycycloalkanes. 4.[1] Phosphoric Esters of Trimethylenenorbornyl Alcohols

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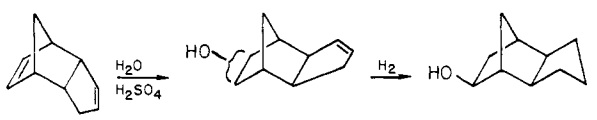
Secondary (**6**) and tertiary (**8**) phosphates of *exo*-5,6-trimethylenenorborn-*exo*-2-yl alcohol (*exo*-tricyclo-[5.2.1.$0^{2,6}$]dec-*exo*-8-yl alcohol, **3**) and a secondary ester (**9**) of a mixture of *exo*-tricyclo[5.2.1.$0^{2,6}$]dec-3-en-8- and -9-yl alcohol (**2**) were prepared. The most convenient route to **6** was direct esterification of phosphoric acid with **3**. **9** was obtainable by the addition of phosphoric acid to *endo*-dicyclopentadiene (**1**). These phosphates were tested in vitro for antiviral activity against Newcastle disease virus using a monolayer culture of chick embryo fibroblasts. **6** was found ca. twice more potent than, while **8** was as active as, amantadine hydrochloride under the present test conditions.

endo-Dicyclopentadiene (*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene, **1**) is one of the most easily accessible tricyclic hydrocarbons. The compound comes out in the C_5 fraction in petrochemical processes and may be regarded as a by-product of isoprene production because of its limited industrial use. Sulfuric acid catalyzed hydration, accompanied by Wagner–Meerwein rearrangement, of **1** has been known[2] to proceed with high yield, giving a mixture of monohydric alcohols, *exo*-tricyclo[5.2.1.$0^{2,6}$]dec-3-en-*exo*-8- and -9-yl alcohol (**2**). The alcohols were catalytically hydrogenated to an identical tricyclodecanol, *exo*-5,6-trimethylenenorborn-*exo*-2-yl alcohol (*exo*-tricyclo-[5.2.1.$0^{2,6}$]dec-*exo*-8-yl alcohol, **3**).[2] We prepared new phosphates of these tricyclic alcohols and tested them for antiviral activity, in the hope of discovering some other utility of dicyclopentadiene.



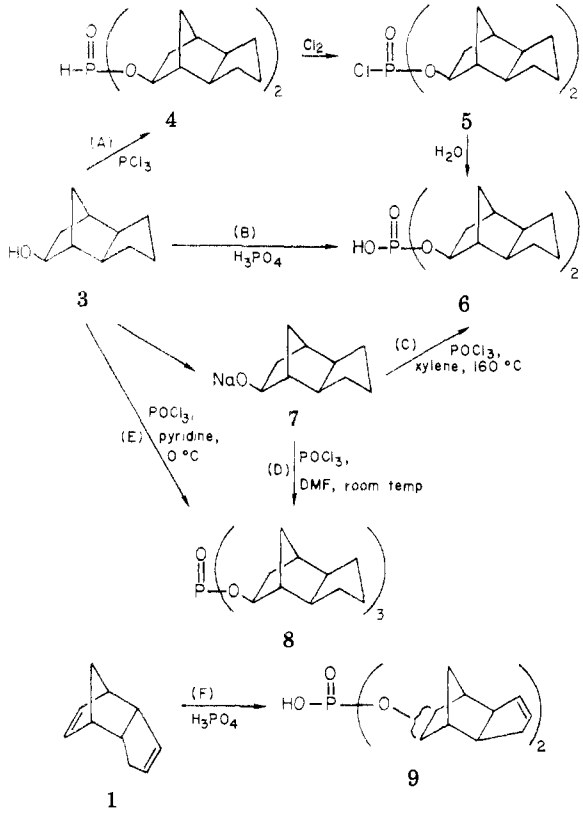
1 2 3

Synthesis. Bis(*exo*-5,6-trimethylenenorborn-*exo*-2-yl) hydrogen phosphate (**6**) was prepared[3] by an established method (route A, Scheme I) which consists of hydrolysis[4] of the corresponding ditricyclodecyl chlorophosphate (**5**). The chlorophosphate **5** was obtained through chlorination by chlorine gas[5] of the ditricyclodecyl hydrogen phosphite (**4**) which in turn was synthesized by the reaction[6] of the tricyclodecanol **3** with phosphorus trichloride. The secondary phosphate **6** was also obtainable either by direct esterification of phosphoric acid with the tricyclodecanol **3** at 200 °C for 8 h (route B)[3] or by reaction[7c] of the sodium alcoholate (**7**) of **3** and excess free alcohol **3** with phosphorus oxychloride in xylene at 160 °C for 3.5 h (route C).[8] However, yield and purity of **6** obtained by these methods (B and C) were somewhat inferior to those obtained via route A. It is to be noted that practically no tertiary phosphate [tris(*exo*-5,6-trimethylenenorborn-*exo*-2-yl) phosphate, **8**] was formed in either of these reactions.

Direct esterification of phosphoric acid by aliphatic alcohols has never been found as any practical application to the preparation of phosphates, as the reaction usually gives rise to a complex mixture comprising primary, secondary, and tertiary phosphates.[7a] Prolonged heating at elevated temperature in order to complete the esterification eventually leads to decomposition of alcohols as well as phosphates to form olefins.[7d] The tricyclodecanol **3** and the product phosphate **6** should be resistant to β-elimination, in which a considerably strained norborn-2-ene structure is to be resulted. Therefore, esterification of **3** could be effected under more drastic conditions than are applicable to ordinary aliphatic alcohols, and these reaction conditions are considered to have allowed the esterification to proceed definitely. Another intriguing aspect of this esterification is halt of the reaction at the stage of the secondary ester. A possible cause for this effect will be discussed later in this paper, in connection with addition of phosphoric acid to *endo*-dicyclopentadiene.

Reaction of the alkoxide **7** in the presence of excess alcohol **3** with phosphorus oxychloride at room temperature for 12 h in dimethylformamide (route D) gave mainly the tertiary ester **8**, together with a small amount of the

Scheme I



secondary ester 6. As was stated above, the same reaction at elevated temperature in nonpolar solvent offered a method of preparing 6. Whether this reaction proceeds toward the formation of the secondary (6) or the tertiary (8) ester seems to be determined chiefly by the reaction temperature rather than by the nature of the solvent, since raising the temperature to 100 °C for the reaction in DMF considerably increased the proportion of the secondary ester 6.

These results seem to be best interpreted with the competition between the nucleophilic substitution of the chlorine atom in 5 by the alkoxide 7 on one hand and the hydroxylation of 5 with the alcohol 3, that is, a reaction analogous to the well-known formation of phosphorus acid and alkyl halides from phosphorus halides and alcohols, on the other. It also appears that substitution of chlorine atoms in phosphorus oxychloride and chlorophosphates is fast for the first two tricyclodecyloxy anions, while it is fairly slow for the third alkoxide (completed in 12 h at room temperature in DMF). Therefore, within the molecule of 5, the hydroxylation giving 6 may well compete with the substitution to form 8. Particularly at high temperatures, the hydroxylation could be prevalent over the substitution, resulting in the predominant formation of 6.

Nucleophilic substitution in 5 is greatly assisted by pyridine.[7b] Reaction of the alcohol 3 with phosphorus oxychloride in the presence of pyridine at 0 °C (route E) gave a high yield of the tertiary ester without contamination by the secondary ester 6.[9]

The secondary phosphate (9) of the unsaturated tricyclic alcohol 2 could be obtainable via neither route A nor route B. In the former method, hydrogen phosphite (corresponding to 4) was obtained as expected, but chlorination gave only tarry materials. On the other hand, extensive carbonation took place by heating 2 with phosphoric acid in the latter method. The compound was finally prepared by the addition of phosphoric acid to *endo*-dicyclopentadiene (1) (route F).[10] This successful method is a variation in well-known additions of proton acids, such as hydrochloric, hydrobromic, hydroiodic, and formic acids, to 1.[11] It is again to be noted that the addition of phosphoric acid to 1 stops at the stage of the secondary ester.

Table I. Antiviral Activity and Cytotoxicity of Tricyclodecyl Phosphates

Compd	MIC,[a] nmol/mL	MCC,[b] nmol/mL
6	550	550
8	1000	400
9	2100	2100
1-NH_2-Ad·HCl[c]	1300	1300

[a] Minimum inhibitory concentration. [b] Minimum cytotoxic concentration. For definitions, see text. [c] Amantadine hydrochloride.

The fact was recognized through these preparation reactions that the bonding was precluded of the third tricyclodecyl moiety to secondary phosphate residues which were already substituted with two tricyclodecyl groups. This effect seems to be of steric origin (steric approach control), since the phenomenon was observed in various reactions involving both tetrahedral (route F) and trigonal-bipyramidal (routes B and D) electronic hybridization of the phosphorus atom at the transition state (or unstable intermediate). Space around the phosphorus atom, irrespective of its transition state hybridization, would be highly congested by substitution with two bulky tricyclodecyl groups, so that the room may be quite limited for the third one to access nearby.

Antiviral Activity. Antiviral activity and cytotoxicity were measured in the same way as in the previous report[1b,12] (tube assay method employing the Miyadera strain of Newcastle disease virus and monolayer culture of chick embryo fibroblasts). Antiviral activity was expressed by minimum inhibitory concentration (MIC, nmol/mL), as defined by that concentration of the test compound at which the virus multiplication measured by hemagglutinating activity was suppressed to 1% or less of the control experiment. Cytotoxicity was determined by microscopic examination of the host cell and represented by minimum cytotoxic concentration (MCC, nmol/mL). Amantadine hydrochloride was used as the reference. The results are listed in Table I.

The secondary phosphate (6) of the saturated tricyclodecanol was found to be moderately active, ca. twice as potent as amantadine hydrochloride. In contrast to this, the secondary phosphate (9) of the unsaturated alcohol was only half as active as the reference compound. Thus saturation of the ethylenic bond in the tricyclodecyl moiety brought about a four times enhancement in the activity.

In the adamantane[12] and 4-homoisotwistane[1b] series, carboxylic acids were found to be generally quite inactive (MIC ~5000), whereas their *exo*-5,6-trimethylenenorborn-*exo*-2-yl esters were moderately potent (MIC 300–960). The opposite is true for the present secondary and tertiary phosphates; esterification of 6 to form 8 lowered the activity to one-half.

Experimental Section

All melting points are uncorrected. IR and ^1H NMR spectra were measured on the same instruments as in the previous report.[1b,12] The tricyclic alcohols 2 and 3 were prepared according to the method in the literature.[2] Analyses of the elements indicated by the symbols were within ±0.4% of the calculated values for all the compounds.

Bis(*exo*-5,6-trimethylenenorborn-*exo*-2-yl) Hydrogen Phosphite (6). Route A. (i) **Bis(*exo*-5,6-trimethylenenor-**

born-*exo*-2-yl) Hydrogen Phosphite (4). Phosphorus trichloride (41.2 g, 0.3 mol) was dropped in a period of 1 h into a solution of 137 g (0.9 mol) of *exo*-trimethylenenorborn-*exo*-2-yl alcohol (3) in 200 mL of carbon tetrachloride kept below 10 °C, while the mixture was stirred vigorously. Dry nitrogen gas was bubbled for 2 h into the reaction mixture, kept at the same temperature. Dry ammonia gas was then introduced into the mixture until no more ammonia was absorbed. Precipitated ammonium chloride was filtered, and the filtrate was concentrated at 170 °C, finally under reduced pressure (0.5 mm), to remove solvent and unreacted alcohol 2. Crude phosphite 4 (104.2 g, 99% yield) was obtained as the distillation residue. Chromatographic purification on a silica gel column eluted with *n*-hexane gave a pure sample: n^{20}_D 1.5138; IR (neat) 2440 (ν_{P-H}), 1265 ($\nu_{P=O}$), 980 cm^{-1} (ν_{O-C}); ^{1}H NMR (CCl_4) δ 0.6–2.5 (complex m, 28 H), 4.10–4.55 (br s, 2 H, *endo*-2-H), 6.89 (s, 1 H, P–H). Anal. ($C_{20}H_{31}O_3P$) C, H, P.

(ii) Bis(*exo*-5,6-trimethylenenorborn-*exo*-2-yl) Chlorophosphate (5). To the solution of 94.5 g (0.27 mol) of the phosphite 4 obtained above in 200 mL of carbon tetrachloride kept below 10 °C was introduced dry chlorine gas for 3 h at a rate of 2 mL/s. Dry nitrogen was bubbled for 30 min through the reaction mixture at ambient temperature. Concentration of the solution at 150 °C (0.1 mm) gave 100.2 g (96% yield) of the chlorophosphate 5. Purification by chromatography (silica gel, *n*-hexane) gave a pure sample: n^{20}_D 1.5233; IR (neat) 1290 ($\nu_{P=O}$), 1010 (ν_{O-C}). Anal. ($C_{20}H_{30}O_3ClP$) C, H, Cl, P.

(iii) Bis(*exo*-5,6-trimethylenenorborn-*exo*-2-yl) Phosphate (6). A mixture of 85 g (0.22 mol) of the chlorophosphate 5, 200 mL of dioxane, and 36 mL of water was refluxed with stirring for 2.5 h. After being cooled, the reaction mixture was neutralized to pH 3 with 10% sodium hydroxide solution and evaporated to dryness at 100 °C under slightly diminished pressure. The residue was extracted with three 50-mL portions of dioxane. Combined dioxane extracts were concentrated to give 78.8 g (97% yield) of crude hydrogen phosphate 6, which was recrystallized from fresh dioxane to afford 69.9 g (86% yield) of a pure sample: mp 148–150 °C; IR (KBr) 2650 (ν_{O-H}), 1250 ($\nu_{P=O}$), 1010 cm^{-1} (ν_{O-C}); ^{1}H NMR (CCl_4) δ 0.6–2.8 (complex m, 28 H), 4.19 and 4.32 (AB q, J = 5 Hz, 2 H, *endo*-2-H). Anal. ($C_{20}H_{31}O_4P$) C, H, P.

Route B. A mixture of 11.5 g (0.1 mol) of 85% phosphoric acid, 152.2 g (1.0 mol) of the alcohol 3, 0.35 g (0.0025 mol) of potassium carbonate, and 15 mL of xylene was refluxed at 195 °C for 8 h in a flask equipped with a water separator,[13] while water formed was continuously distilled off as an azeotropic mixture. The reaction mixture was evaporated at 180 °C (0.4 mm), and the residue was recrystallized from dioxane to give 27.6 g (76% yield) of 6: mp 148–150 °C. The melting point was not depressed by admixture with the authentic specimen obtained via route A. IR and ^{1}H NMR spectra were also identical with those of the authentic specimen.

Route C. In a flask equipped with the water separator,[13] a mixture of 152.2 g (1.0 mol) of the alcohol 3, 12.8 g (0.32 mol) of sodium hydroxide, and 20 mL of xylene was refluxed with stirring until no more water was distilled out (~3 h). Phosphorus oxychloride (15.4 g, 0.1 mol) was added dropwise in a period of 30 min into the mixture kept at 160–170 °C. The reaction was stirred for an additional 3.5 h at the same temperature. Sodium chloride was filtered off from the cooled reaction mixture, and the filtrate was concentrated at 180 °C (0.2 mm). Recrystallization of the residue from dioxane gave 12.0 g (33% yield) of pure 6: mp and mmp 148–150 °C. IR and ^{1}H NMR spectra agreed with those of the authentic specimen.

Tris(*exo*-5,6-trimethylenenorborn-*exo*-2-yl) Phosphate (8). Route D. The alkoxide 7 dissolved in excess 3, as prepared from 152.2 g (1.0 mol) of 3 and 12.8 g (0.32 mol) of sodium hydroxide by the same procedure as in the route C (preceding paragraph), was mixed with 150 mL of DMF at room temperature and stirred until dissolution resulted. Phosphorus oxychloride (15.4 g, 0.1 mol) was added dropwise into the solution kept below 25 °C in a period of 30 min, and the reaction was stirred at room temperature for 12 h. The reaction mixture was evaporated to dryness at 150 °C (0.1 mm), and the residue was extracted with three 100-mL portions of benzene. Combined benzene extracts were washed with three 100-mL portions of 2% sodium hydroxide solution and then with water. The benzene solution was dried over anhydrous sodium sulfate and concentrated at 150 °C (0.1 mm) to give crude 8. Purification by chromatography (silica gel, *n*-hexane) gave 26.5 g (53% yield) of a pure sample: n^{25}_D 1.5208; IR (neat) 1270 ($\nu_{P=O}$), 1040, 1000 cm^{-1} (ν_{O-C}); ^{1}H NMR (CCl_4) δ 0.5–2.5 (complex m, 52 H), 4.0–4.5 (m, 3 H, *endo*-2-H). Anal. ($C_{30}H_{45}O_4P$) C, H, P.

Combined sodium hydroxide extracts and water washings were acidified to pH 1 with concentrated hydrochloric acid. The mixture was extracted with benzene, and the benzene extract was evaporated to dryness. The residue was recrystallized from dioxane to give 2.6 g (7%) of 6.

Route E. A solution of 45.7 g (0.3 mol) of 3 and 26.1 g (0.33 mol) of pyridine in 100 mL of benzene was kept at 0–5 °C, and 15.3 g (0.1 mol) of phosphorus oxychloride was added dropwise with stirring in a period of 4 h. The reaction was stirred for an additional 30 min at the same temperature and then refluxed for 2 h. The mixture was washed with three 50-mL portions of water, dried over anhydrous sodium sulfate, and concentrated at 140 °C (0.1 mm). Purification by chromatography gave 41.8 g (84% yield) of pure 8 which showed the same IR and ^{1}H NMR spectra as those of 8 prepared by route D.

Mixture of Bis(*exo*-tricyclo[5.2.1.0^{2,6}]dec-3-en-8- and -9-yl) Hydrogen Phosphates (9). Route F. A 100% phosphoric acid (9.8 g, 0.1 mol) was prepared by warming with stirring 7.03 g of 85% phosphoric acid and 2.77 g of phosphorus pentoxide on a water bath. The phosphoric acid thus obtained was cooled to 55 °C and mixed with 132 g (1.0 mol) of *endo*-dicyclopentadiene (1). The reaction was stirred for 13 h at the same temperature. After being washed with two 200-mL portions of water, the mixture was stirred with 300 mL of water and neutralized to pH 7–8 with 5% sodium carbonate solution. The water layer was separated and acidified to pH 1 by the addition of 5% hydrochloric acid. The organic layer formed was taken up in ether, and the aqueous layer was extracted with two 50-mL portions of ether. Combined organic layer and ether extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated at 150 °C (0.2 mm) to give crude unsaturated secondary phosphate 9. Recrystallization from petroleum benzine gave 14.8 g (63% yield) of a pure sample: mp 132 °C; IR (KBr) 3050 ($\nu_{=C-H}$), 2600 (ν_{O-H}), 1240 ($\nu_{P=O}$), 1020 (ν_{O-C}), 800, 700 cm^{-1} ($\delta_{=C-H}$); ^{1}H NMR (CCl_4) δ 1.2–2.8 (complex m, 24 H), 4.10–4.55 (br s, 2 H, *endo*-8- or -9-H), 5.46 and 5.66 (AB q, J = 6 Hz, HC=CH). Anal. ($C_{20}H_{27}O_4P$) C, H, P.

References and Notes

(1) (a) For paper 3, see K. Aigami, Y. Inamoto, N. Takaishi, and Y. Fujikura, *Phytochemistry*, **16**, 41 (1977); (b) for paper 2, see K. Aigami, Y. Inamoto, N. Takaishi, Y. Fujikura, A. Takatsuki, and G. Tamura, *J. Med. Chem.*, **19**, 536 (1976).

(2) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **67**, 723 (1945).

(3) Y. Inamoto and T. Kadono, Japanese Patent 752 206 (Dec 14, 1974) [Japan 74 11 223 (March 15, 1974)]; U.S. Patent 3 786 033 (Jan 15, 1974).

(4) R. A. McIvor, G. D. McCarthy, and G. A. Grant, *Can. J. Chem.*, **34**, 1819 (1956).

(5) N. K. Bliznyuk, A. F. Kolomiets, P. S. Khokhlov, and S. G. Zhemchuzhin, *Zh. Obshch. Khim.*, **37**, 1353 (1967); *Chem. Abstr.*, **67**, 108126t (1967).

(6) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 381 (1945).

(7) (a) E. Cherbuliez in "Organophosphorus Compounds", Vol. 6, G. M. Kosolapoff and L. Maier, Ed., Wiley, New York, N.Y., 1973, p 222; (b) p 227; (c) p 228; (d) p 335.

(8) Y. Inamoto, T. Kadono, and H. Nakayama, Japan Kokai 74 135 959 (Dec 27, 1974); *Chem. Abstr.*, **83**, 9612x (1975).

(9) Y. Inamoto and T. Kadono, Japanese Patent 752 208 (Dec 14, 1974) [Japan 74 11 225 (March 15, 1974)]; U.S. Patent 3 784 651 (Jan 8, 1974).

(10) Y. Inamoto and T. Kadono, Japanese Patent 752 207 (Dec 14, 1974) [Japan 74 11 224 (March 15, 1974)]; U.S. Patent 3 773 863 (Nov 20, 1973).

(11) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **67**, 1178 (1945); **68**, 8 (1946); P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946); F. Bergman and J. H. Japhe, *ibid.*, **69**, 1826

(1947); P. D. Bartlett and I. S. Goldstein, *ibid.*, **69**, 2553 (1947); S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. Jurale, *ibid.*, **84**, 3918 (1962); S. K. Cristol and G. C. Fusco, *J. Org. Chem.*, **33**, 106 (1968).

(12) K. Aigami, Y. Inamoto, N. Takaishi, K. Hattori, A. Takatsuki, and G. Tamura, *J. Med. Chem.*, **18**, 713 (1975).
(13) S. Natelson and S. Gottfried, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 382.

Synthesis and Pharmacological Activity of Some *N*-Alkyl-Substituted 9α-Ethyl-2′-hydroxy-5-methyl-6,7-benzomorphans[1,2]

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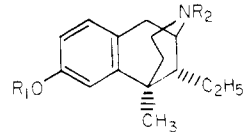
A series of N-substituted 9α-ethyl-2′-hydroxy-5-methyl-6,7-benzomorphans was synthesized and evaluated for their narcotic analgesic and antagonistic activities. Compounds **2a** and **22** were as potent as morphine in the writhing (PPQ) and hot-plate tests, while a number of compounds demonstrated antagonistic activities greater than nalorphine. Generally, the compounds in this series show activities somewhat greater than the comparable compounds in the 5,9α-dimethyl-6,7-benzomorphan series for analgesic effect and similar or slightly less antagonistic potency.

Due to the interesting analgesic and antagonistic activities of benzomorphans[3-6] and continuing the search for better, longer acting, orally active medicinal agents in the series, the title compounds were synthesized. The synthesis, the narcotic analgesic and the antagonistic activity in rodents, and single dose suppression (SDS) and precipitated withdrawal test (PPT) in monkeys are herein described.

Chemistry. Norbenzomorphan (1) was chosen as the key intermediate for the synthesis of various N analogues. This intermediate was obtained in 94% yield by N-demethylation of the 6,7-benzomorphan compound **2a** via a modification of the procedure of Rice.[8] It was unnecessary, for example, to hydrolyze the *N,O*-dicarbonyl compound **2b** to the carbamate **2c** or to eliminate the phenol formed in both steps of the process until the final crystallization of **1**. The fragmentation pattern of **1** (M^+ 231) was that expected for a 9α-6,7-benzomorphan.

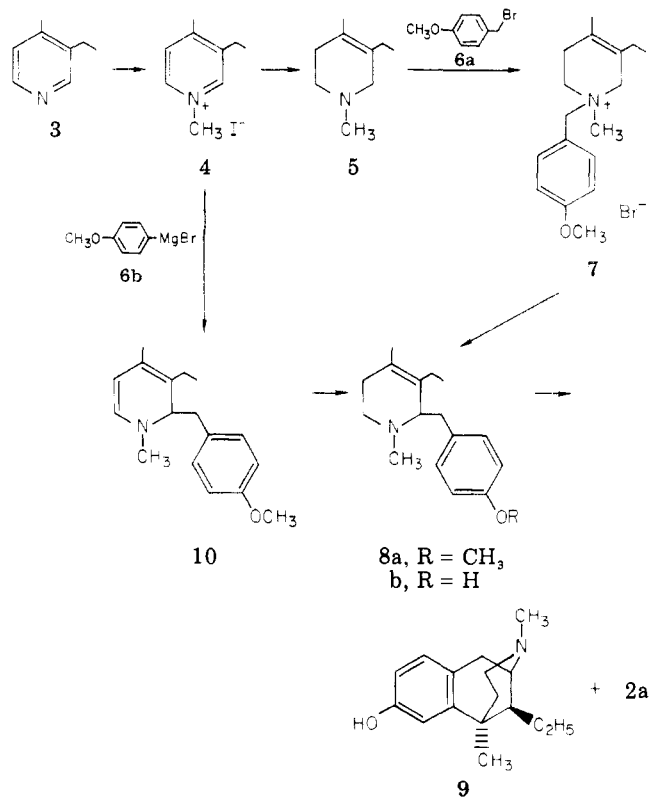


1, $R_1 = R_2 = H$
2a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = R_2 = OCOPh$
c, $R_1 = H$; $R_2 = OCOPh$

The synthetic routes to **2a** are those of May et al.[7] (Scheme I) except that anisyl bromide[9] and anisylmagnesium bromide[10] were used rather than the corresponding chlorides.

Quaternization of **3** with methyl iodide, followed by $NaBH_4$ reduction, gave the tetrahydropyridine **5**. Reaction of **5** with anisyl bromide (**6a**)[11] gave the quaternary bromide **7** in 50% yield (based on **4**). Stevens rearrangement of **7** (PhLi) gave **8a** (51% yield) and other undesirable side products.[12] Pure **8a** could be obtained readily through the HBr or picrate salt. Cyclization of **8a** with refluxing 48% HBr gave a 10:1 mixture of the 9α- and 9β-benzomorphans **2a** and **9**.[7] The two isomers were separated by fractional crystallization (Me_2CO) and their stereochemistry was established by mass spectroscopy (M^+ 245). The fragmentation pattern of each isomer, upon electron impact (70 eV), is characteristic. The relative intensity of the (M^+) and ($M^+ - C_5$) ions varies for each isomer (70 and 50% for the 9α isomer and 50 and 100% for the 9β isomer, respectively).[13]

Scheme I



Compound **8a** was also synthesized by treating **4** with anisylmagnesium bromide (**6b**) to give the dihydropyridine **10** which is then reduced by $NaBH_4$.[14] Further, when **8b** was cyclized with 85% phosphoric acid at 185 °C,[15] a 5:1 mixture of **2a** and **9** was obtained.

To get the various analogues (Table I), two procedures were used. (a) The Archer and Harris procedure[4b] was followed for the synthesis of compounds **11–20**. In this procedure, the norbenzomorphan **1** was refluxed with the desired alkyl halide in dimethylformamide (DMF) and $NaHCO_3$ for 4–5 h. The products were crystallized from $CHCl_3$–Et_2O, Me_2CO, or MeOH. (b) Compounds **21** and **22** were synthesized following established literature procedures for the acylation of secondary amines and the subsequent reduction of the resulting amides or *N,O*-dicarbonyl compounds.[16,17] Thus, compound **1** was refluxed with the appropriate cycloalkylcarbonyl halide in triethylamine and methylene chloride. The resulting adduct