purposes, quinine is included in Table I. No synthetic intermediates from this work displayed any antimalarial effects.

Experimental Section[8]

2-Allyloxy-5-*t*-butylbiphenyl.—4-*t*-Butyl-2-phenylphenol[9] (22.6 g, 0.10 mole) in 200 ml of DMF was converted to the Na salt by slow addition (with cooling) of 4.5 g (0.12 mole) of 53% NaH in oil. After dropwise addition of 14.4 g (0.12 mole) of allyl bromide, the mixture was heated for 3 hr at 90°, cooled, and extracted with pentane to remove mineral oil. Dilution with H_2O and extraction with Et_2O gave 24.8 g (93%) of essentially pure oil. A sample collected by glpc was analyzed. *Anal.* ($C_{19}H_{22}O$) C, H.

2-Allyl-4-*t*-butyl-6-phenylphenol.—Crude 2-allyloxy-5-*t*-butylbiphenyl (24.8 g, 0.083 mole) was heated under N_2 for 3 hr at 206–220°. Distillation of the dark mixture (104°, 0.03 mm) gave 15.7 g (59%). *Anal.* ($C_{19}H_{22}O$) C, H.

3-Allyl-2-benzyloxy-5-*t*-butylbiphenyl (7).—Alkylation as above, using benzyl chloride instead of allyl bromide, gave an 89% yield (bp 181°, 0.05 mm). *Anal.* ($C_{26}H_{28}O$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(3-hydroxypropyl)biphenyl (8).—Using the general procedure of Brown and Subba Rao,[10] 71.3 g (0.2 mole) of **7** was hydroborated with 1 *M* borane in THF (Metal Hydrides, Inc.) and oxidized to give 73.4 g of crude **8**. A sample (viscous oil) was distilled and then chromatographed over silica gel for analysis. *Anal.* ($C_{26}H_{30}O_2$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(3-tosyloxypropyl)biphenyl.—Crude **8** (71.2 g, 0.19 mole), dissolved in 700 ml of pyridine, was treated with 109 g (0.57 mole) of *p*-toluenesulfonyl chloride in small portions while stirred at 0°. Slow addition of ice–H_2O to the mixture, adjustment of the solution pH to 3–5 with HCl, and extraction with $CHCl_3$ gave 96 g of crude product. Recrystallized (39 g, 37%) from MeOH it melted at 122–124°. *Anal.* ($C_{33}H_{36}SO_4$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(3-diethylaminopropyl)biphenyl.—After refluxing for 2 hr, a solution of the above tosylate (10.6 g, 20 mmoles) in 100 ml of Et_2NH was diluted with H_2O and extracted with Et_2O to give a quantitative yield of oily product; oxalate salt mp 147–149°. *Anal.* ($C_{30}H_{39}NO \cdot H_2C_2O_4$) C, H, N.

4-*t*-Butyl-2-(3-diethylaminopropyl)-6-phenylphenol (4).—Hydrogenation of 8.5 g (19.8 mmoles) of 2-benzyloxy-5-*t*-butyl-3-(3-diethylaminopropyl)biphenyl in EtOH with 1.7 g of 10% Pd–C resulted in the theoretical uptake of H_2. The reaction mixture was filtered hot and diluted with H_2O to give 4.6 g of crude crystalline product. Recrystallized (EtOH–H_2O), it melted at 69–71° (3.4 g, 50%). *Anal.* ($C_{23}H_{33}NO$) C, H, N.

2-Benzyloxy-5-*t*-butyl-3-[3-(N,N-diethylcarbamyl)propyl]-biphenyl.—A solution of 21.2 g (40 mmoles) of 2-benzyloxy-5-*t*-butyl-3-(3-tosyloxypropyl)biphenyl in 250 ml of boiling EtOH was treated with 5.2 g (80 mmoles) of KCN in 15 ml of H_2O. After refluxing for 3 hr, H_2O was added and the crude, oily nitrile (15 g) was isolated by $CHCl_3$ extraction. This was hydrolyzed to the carboxylic acid with alcoholic NaOH. The crude acid (15.3 g) was converted to the acid chloride with $SOCl_2$ and treated with excess Et_2NH in Et_2O to give the crude amide product (17.7 g). Purification by chromatography over silica gel gave 14.3 g (82%) of oily product. *Anal.* ($C_{31}H_{39}NO_2$) C, H, N.

4-*t*-Butyl-2-(4-diethylaminobutyl)-6-phenylphenol (5).—2-Benzyloxy-5-*t*-butyl-3-[3-(N,N-diethylcarbamyl)propyl]biphenyl (13.7 g, 30 mmoles) was reduced to 2-benzyloxy-5-*t*-butyl-3-(4-diethylaminobutyl)biphenyl with excess borane–THF by the method of Brown and Heim.[11] Catalytic debenzylation as with **4** gave crude **5**. It was isolated by Et_2O extraction and recrystallized from Me_2CO–H_2O (mp 93–96°). *Anal.* ($C_{24}H_{35}NO$) C, H, N.

2-Benzyloxy-5-*t*-butyl-3-(1-propenyl)biphenyl (9) was formed from 2-allyl-4-*t*-butyl-6-phenylphenol and benzyl chloride when a 50–60% excess of NaH was used under the reaction conditions employed for preparing **7**. The excess NaH served to isomerize the allyl side chain to propenyl; yield 58% (bp 199°, 0.10 mm). Glpc and pmr served to distinguish it from **7**.

2-Benzyloxy-5-*t*-butyl-3-biphenylcarboxaldehyde (10).—A solution of 16.1 g (45.0 mmoles) of **9** in 80 ml of CH_2Cl_2 was ozonized (Welsbach generator) until a 50% excess of ozone had been passed in. The ozonolysis solution was added *carefully* to a suspension of 3 g of Zn dust in 75 ml of 50% aqueous AcOH. The CH_2Cl_2 was boiled off and the aqueous residue was heated on the steam bath for 1 hr. It was cooled and diluted (H_2O), and the crude, oily product was isolated by $CHCl_3$ extraction. Addition of petroleum ether (bp 30–60°) effected crystallization: yield 7.8 g (50%, mp 86–90°), mp 90–92° after recrystallization from EtOH. *Anal.* ($C_{24}H_{24}O_2$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(2-nitrovinyl)biphenyl (11).—A solution of 1.2 g of NaOH in 36 ml of 95% EtOH was added slowly to a stirred solution of 4.13 g (12 mmoles) of **10** in 138 ml of 95% EtOH, 1.5 ml of THF, and 1.464 g (24 mmoles) of $MeNO_2$. The reaction temperature was held below 10° throughout the addition by ice cooling. The cold, cloudy solution was poured into a stirred solution of 18 ml of concentrated HCl and 27 ml of H_2O. The yellow precipitate of product was collected and washed with EtOH; yield 3.6 g (78%), mp 110.5–113°. *Anal.* ($C_{25}H_{25}NO_3$) C, H, N.

3-(2-Aminoethyl)-2-benzyloxy-5-*t*-butylbiphenyl.—To a stirred suspension of 12.3 g (0.322 mole) of powdered LAH in 170 ml of THF was added (dropwise) a solution of 17.8 g (46 mmoles) of **11** in 170 ml of THF. After refluxing for 18 hr, H_2O (*ca.* 50–75 ml) was added carefully until the gray color of the solids changed to white. After filtering, the filtrate and several washings of the solids (Et_2O) gave 14.5 g of crude, oily product. It was purified *via* the oxalate salt (15.4 g, 74%, mp 195–196°). *Anal.* ($C_{29}H_{29}NO \cdot H_2C_2O_4$) C, H, N.

2-(2-Aminoethyl)-4-*t*-butyl-6-phenylphenol (6).—Hydrogenolysis of 3-(2-aminoethyl)-2-benzyloxy-5-*t*-butylbiphenyl (1.0 g, 2.8 mmoles, obtained by extraction from the neutralized oxalate salt) in the manner used for **4** gave this compound. It was isolated by removal of solvent from the filtered reaction mixture and crystallized from heptane; yield 0.5 g (67%, mp 89–93°). *Anal.* ($C_{18}H_{23}NO$) C, H, N.

2-Benzyloxy-5-*t*-butyl-3-(2-dimethylaminoethyl)biphenyl.—A mixture of 8.5 g (2.4 mmoles) of 3-(2-aminoethyl)-2-benzyloxy-5-*t*-butylbiphenyl, 25 ml of 90% formic acid, and 25 ml of 37% HCHO was refluxed for 18 hr. The reaction mixture was cooled, diluted (H_2O), made basic with 20% NaOH, and extracted with Et_2O to give 8.4 g (92%) of pure oily product; oxalate salt mp 164–167°. *Anal.* ($C_{27}H_{33}NO \cdot H_2C_2O_4$) C, H, N.

4-*t*-Butyl-2-(2-dimethylaminoethyl)-6-phenylphenol (3).—Debenzylation of 2-benzyloxy-5-*t*-butyl-3-(2-dimethylaminoethyl)biphenyl, using Pd black catalyst, gave **3**. The work-up was the same as that used to obtain **4** from its O-benzyl precursor; yield 72% (mp 132–133°). *Anal.* ($C_{20}H_{27}NO$) C, H, N.

(8) Melting points were taken on a Mel-Temp apparatus and are corrected. Microanalyses were performed in the Stanford Research Institute Analytical Laboratory by Miss Betty McCarthy. Pmr spectra, used to confirm the structures of most of the compounds reported herein, were obtained on a Varian A60 instrument. Where analyses are indicated only by the symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

(9) A. J. Dietzler and F. Bryner, U. S. Patent 2,784,239 (1957). The authors are grateful to Mr. A. J. Dietzler of the Dow Chemical Co. for a generous sample of this compound.

(10) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6433 (1959).

(11) H. C. Brown and P. Heim, *ibid.*, **86**, 3566 (1964).

Synthesis and Antiviral Properties of 1-Adamantylguanidine. A Modified Method for Preparing *t*-Alkylguanidines

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The influenza virus inhibiting properties of 1-adamantanamine (I)[1] (Scheme I) prompted us to synthesize some of its derivatives. It seemed worthwhile, for instance, to enhance its basicity by replacing the amino group by the guanidino group. This substitution was the more interesting since guanidine itself has note-

(1) R. R. Grunert, J. W. McGaben, and W. L. Davies, *Virology*, **26**, 262 (1965).

SCHEME I

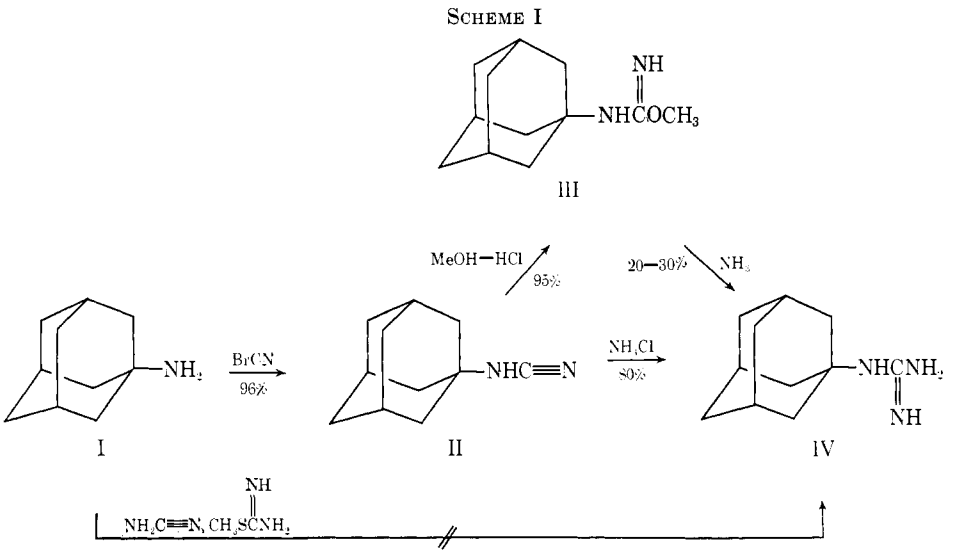
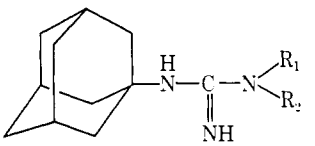


TABLE I: 1-ADAMANTYLGUANIDINES



R_1	R_2	Formula	Analyses[13]	Mp,[a] °C	Yield, %
H	H	$C_{11}H_{19}N_3 \cdot HNO_3$	C, H, N, O	151–153	80
CH_3	H	$C_{12}H_{21}N_3 \cdot HCl$	C, H, N, Cl	265–267.5	63
C_2H_5	H	$C_{13}H_{23}N_3 \cdot HCl$	C, H, N, Cl	227–230	72
i-C_3H_7	H	$C_{14}H_{25}N_3 \cdot HCl$	C, H, N, Cl	249–251	60
Cyclohexyl	H	$C_{17}H_{29}N_3 \cdot HCl$	C, H, N, Cl	267–268	69
Benzyl	H	$C_{18}H_{25}N_3 \cdot HCl$	C, H, N, Cl	196–197	65
1-Adamantyl	H	$C_{21}H_{33}N_3 \cdot HCl$	C, H, N, Cl	288–290[b]	52
$CH_2CH_2OCH_2CH_2$		$C_{15}H_{25}N_3O \cdot HNO_3$	C, H, N, O	209–211	33

[a] Crystallized from ethanol by addition of ether. [b] Crystallized from ethanol–methanol.

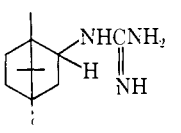
worthy inhibiting properties against a number of enteroviruses[2] and its mode of action differs from that of alkylamines.[3]

We have synthesized a number of 1-adamantylguanidines and investigated them for antiviral activity. We have found that only 1-adamantylguanidine significantly inhibits the multiplication of influenza virus (A_2 Japan) *in vitro* as well as *in vivo*.

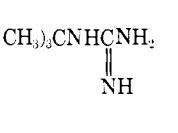
The synthesis of 1-adamantylguanidine (IV) offered some difficulties because the conventional synthetic methods failed. Cyanamide or S-methylisothiourea, for instance, did not react with 1-adamantanamine even under forcing conditions. As reactions *via* the adamantyl cation commonly proceed smoothly, the method to alkylate guanidine in H_2SO_4[4] might be expected to be attractive, especially for the synthesis of 1-adamantylguanidine. The adamantyl cation, however, is preferably isomerized and oxidized to adamantanone as we have reported previously.[5,6]

The attempted aminolysis of N-1-adamantyl-O-methylisouronium chloride[7] (III) proved successful for the preparation of 1-adamantylguanidine, although the yield was poor (20–30%).

Another method of preparing alkyl- or dialkylguanidines consists in heating of the appropriate alkyl cyanamide with NH_4Cl or an amine hydrochloride in EtOH or in the corresponding amine as the solvent.[8] 1-Adamantylcyanamide (II), readily obtained from 1-adamantanamine and BrCN, did not react under the conditions cited. Upon heating the reactants without



V



VI

a solvent, however, surprisingly good yields of 1-adamantylguanidines were obtained (Table I).

We also applied this method to the synthesis of *dl*-2-bornylguanidine[9] (V) and to the unknown *t*-butylguanidine (VI), since there are indications in the

(2) A. Lwoff, *Biochem. J.*, **96**, 289 (1965), and references cited therein.

(3) R. D. Fletcher, J. E. Hirschfield, and M. Forbes, *Nature*, **207**, 664 (1965).

(4) S. I. Burmistrov and Yu. V. Sukhoruchkin, *J. Gen. Chem. USSR*, **33**, 1202 (1963).

(5) H. W. Geluk and J. L. M. A. Schlatmann, *Tetrahedron*, **24**, 5361 (1968).

(6) Even 1-adamantylguanidine itself is split into guanidine and the adamantyl cation. This was found in an attempt to dehydrate 1-adamantylguanidine nitrate in 96% H_2SO_4. Only a poor yield of 1-adamantylnitroguanidine was obtained, whereas most of the starting material had been transformed into 1-hydroxyadamantane and adamantanone.

(7) Houben-Weyl, "Methoden der Organischen Chemie," Band VIII, Sauerstoffverbindungen III, Georg Thieme Verlag, Stuttgart, 1952, p 187.

(8) H. Schotte, H. Priewe, and H. Roescheisen, *Hoppe-Seyler's Z. Physiol. Chem.*, **174**, 172 (1928); H. C. Bhatnagar, N. N. Chopra, K. S. Narang, and J. N. Ray, *J. Indian Chem. Soc.*, **14**, 345 (1937); H. King and I. M. Tonkin, *J. Chem. Soc.*, 1063 (1946).

(9) R. B. Fearing and S. W. Fox, *J. Am. Chem. Soc.*, **76**, 4382 (1954).

literature[9,10] that it is difficult to synthesize guanidines from sterically hindered amines. Both guanidines were obtained in a satisfactory yield.

Biological Results.—1-Adamantylguanidine inhibits the growth of the influenza virus strains A Swine S-15/1930 and A_2 Japan 305/1957 in chick embryo fibroblast cultures to an extent comparable with 1-adamantanamine.[11] We obtained evidence that 1-adamantylguanidine has the same mode of action as 1-adamantanamine. They probably inhibit the penetration of the host cell.[12] It is noteworthy that this mode of action is unaffected upon substitution of the amino group by the guanidino group.

It has been established that 1-adamantylguanidine also exhibits an *in vivo* antiviral activity.[11] The lifetime of mice infected with influenza virus A_2 Japan 305/1957 was prolonged significantly on oral administration. A quantitative comparison, however, showed the amine to be superior to the guanidine.

Introduction of a second substituent at N-3 of the guanidino group (Table I) resulted in complete suppression of the activity *in vivo*.

Experimental Section[13]

1-Adamantylcyanamide (II).—To I[15] (11.78 g, 78 mmol) dissolved in Et_2O (200 ml) was added a solution of BrCN (5.10 g, 48 mmol) in Et_2O (50 ml) while stirred and cooled with cold H_2O. A white crystalline precipitate of I·HBr was formed rapidly. This was filtered off with suction after 1 hr (9.0 g). The filtrate was concentrated to dryness and the residue (6.82 g) was crystallized from EtOH–H_2O (1:1) to give II (6.04 g), mp 147–149°, total yield 96%. Recrystallization from MeOH–H_2O (1:2) raised the melting point to 150–151°. *Anal.* ($C_{11}H_{16}N_2$) C, H, N.

N-Adamantyl-O-methylisouronium Chloride (III).—The cyanamide II (5.30 g, 30.1 mmol) was dissolved in MeOH (30 ml). A 1 *N* solution of HCl in MeOH (80 ml) was added. The mixture turned slightly warm. After standing at room temperature for 1.5 hr, the clear and colorless solution was concentrated to about 30 ml. The substance crystallized upon gradual addition of Et_2O. The crystals were filtered off and dried to give III (5.43 g), mp 255° dec. From the mother liquor a second crop (1.27 g), mp 255° dec was obtained, total yield 91%. *Anal.* ($C_{12}H_{21}ClN_2O$) N, Cl.

1-Adamantylguanidine (IV) **from III.**—Liquid NH_3 (75 ml) was added to a cooled solution (−40°) of III (4.90 g, 20 mmol) in MeOH (25 ml). A precipitate of NH_4Cl was formed. The mixture was heated at 65° in a stainless steel bomb for 5 hr. After removal of the NH_3 and the MeOH a foamy residue (4.78 g) was obtained. H_2O (20 ml) was added and the mixture was neutralized with 2 *N* HCl. The undissolved fraction was removed by filtration and washed with H_2O. After drying, 1-adamantylurea[16] (0.82 g), mp 251–261°, was obtained. (The formation of 1-adamantylurea is probably due to competing hydrolysis by moisture introduced with the liquid NH_3.) NaOH (50%, 5 ml) was added to the aqueous filtrate. A viscous liquid (mixture of I and IV) separated which solidified after a few minutes. Et_2O (25 ml) was added, the remaining solid was filtered off, washed with Et_2O and a little H_2O, and dried to give IV (1.09 g), mp 195° dec, yield 28%. The Et_2O layer was found to contain I (1.39 g).

1-Adamantylguanidine (IV) **from II.**—The cyanamide II (7.04 g, 40 mmol) was mixed thoroughly with finely divided NH_4Cl (6.60 g, 123 mmol) and heated in an oil bath at 225° for 15 min. After cooling and grinding the mixture was extracted twice with hot H_2O. An insoluble fraction was filtered off. The filtrates were combined and washed with Et_2O and CH_2Cl_2 to remove neutral impurities. NaOH (50%, 40 ml) was added to the aqueous layer to precipitate IV. The white solid was filtered off with suction, washed with a little H_2O, and dried (4.29 g): mp 195° dec; ir (KBr), 3470 (m), 3300 (s), and 3150 (s) (NH), 2900 (s) and 2850 (m) (CH), 1600 (s) (broad, CN and NH), 1200 (m) cm^{-1}. The aqueous layer was neutralized with 65% HNO_3 and concentrated. The nitrate of IV crystallized upon cooling. The substance melted at 80–85°, solidified, and melted again at 140–145°. The total yield of IV was 80%. It was crystallized from EtOH–Et_2O: mp 151–153°. *Anal.* ($C_{11}H_{20}N_4O_3$) C, H, N, O.

dl-**2-Bornylcyanamide** was prepared from *dl*-2-bornylamine analogous to II. The Et_2O solution of the cyanamide was freed from dissolved bornylamine by washing with 2 *N* HCl; yield 97%; mp 40–48°; nmr ($CDCl_3$), δ 0.80–0.92 (9 H, CH_3, four signals), 0.98–1.90 (7 H, protons at C-3, 4, 5, and 6), 3.02 and 3.30 (1 H, proton at C-2 of the two isomers), 6.38 and 6.67 (1 H, NH of the two isomers). The isomer ratio was 2:3.

dl-**2-Bornylguanidine** (V).—*dl*-2-Bornylcyanamide (2.56 g, 14.4 mmol) and NH_4Cl (3.26 g, 61 mmol) were mixed and heated in an oil bath at 185° for 15 min. Upon cooling, the mixture was powdered and extracted with EtOH. The excess of NH_4Cl was filtered off and the filtrate was concentrated to dryness. The foamy residue (3.30 g) was dissolved in CH_2Cl_2 with a few drops of EtOH and remaining NH_4Cl was removed. The filtrate was extracted with H_2O and the colorless aqueous layer was concentrated to about 10 ml. Crystals of V·HCl separated (1.09 g), mp 270–274°. From the mother liquor a second crop was obtained (0.59 g): mp 268–275°; total yield 50%; nmr (TFA), δ 0.92–1.05 (9 H, CH_3, four signals), 1.10–2.10 (7 H, H at C-3, 4, 5, and 6), 3.38 and 3.72 (1 H, H at C-2, α to NH), 6.0 and 6.3 (NH). The two separate signals for the proton at C-2 indicate that both the isomers (substituent axial or equatorial) were present. The intensity ratio of these signals is 3:5. *Anal.* ($C_{11}H_{22}N_3Cl$) C, H, N, Cl.

t-**Butylguanidine** (VI).—*t*-Butylcyanamide[15] (5.15 g, 52.5 mmol) was mixed with finely divided NH_4Cl (8.27 g, 155 mmol) and heated at 200° for 15 min. The product was isolated as described for V. Attempts to crystallize VI·HCl were unsuccessful. After addition of an equivalent amount of $AgNO_3$, filtration, and concentration to dryness, a clear and colorless syrup of VI·HNO_3 (7.56 g) resulted, that solidified completely upon cooling; yield 81%; crystallization from H_2O and from MeOH by addition of Et_2O gave crystals with mp 128–129°. *Anal.* ($C_5H_{14}N_4O_3$) C, H, N, O.

VI·Picrate had mp 205–208° (from H_2O–EtOH, 1:1), yield 70%.

VI·3,5-Dinitrobenzoate had mp 185–187° (from H_2O–EtOH 9:1), yield 71%.

Acknowledgments.—The cooperation of Mr. K. Lundahl is gratefully acknowledged. We are indebted

(10) T. Tsuji and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **12**, 946 (1964).

(11) J. L. M. A. Schlatmann, C. A. de Bock, and W. T. Goedemans, Proceedings of the Vth International Congress of Chemotherapy, Vienna, 1967, Vol. IV, Verlag der Med. Akademie, Vienna, 1967, p 323.

(12) W. T. Goedemans and A. Peters, ref 11, Vol. II/1, p 1; C. E. Hoffmann, E. M. Neumayer, R. F. Haff, and R. A. Goldsby, *J. Bacteriol.*, **90**, 623 (1965).

(13) Melting points were measured in an electrically heated aluminum block. Temperature indication was given by a chromel-alumel couple on a Philips G.M. 6020 tube voltmeter. Nmr spectra were measured on a Varian HA spectrometer; chemical shifts are reported in parts per million from TMS. Ir spectra were recorded on a Perkin-Elmer Model 337. Mass spectral data were obtained from an AEI-MS 9 double-focusing mass spectrometer. Ir, nmr, and mass spectra were as expected. Elemental microanalyses were done by A. Bernhardt, Mikroanalytisches Lab, Elbach über Engelskirchen, West Germany, or by the Analytical Department of the Organic Chemistry Laboratory, State University, Groningen, The Netherlands. Where analyses are indicated only by symbols of the elements, analytical results of those elements were within ±0.4% of the theoretical values. Tlc was performed on Merck DC-Fertigplatten Kieselgel F254, solvent AcOEt–MeOH–AcOH (50:45:5 v/v). The spots were detected with the highly sensitive NaOCl–KI–benzidine reagent.[14]

(14) F. Reindel and W. Hoppe, *Naturwissenschaften*, **40**, 221 (1953); H. Zahn and E. Rexroth, *Z. Anal. Chem.*, **148**, 181 (1955).

(15) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960).

(16) H. Stetter and C. Wulff, *ibid.*, **95**, 2302 (1962).

(17) T. Mukaiyama, S. Ohishi, and H. Takamura, *Bull. Chem. Soc. Japan*, **27**, 416 (1954); *Chem. Abstr.*, **49**, 10210*h* (1955); see ref 18.

(18) After completion of this manuscript, the synthesis of *t*-butylguanidine was described: J. H. Short, C. W. Ours, and W. J. Ranus, Jr., *J. Med. Chem.*, **11**, 1129 (1968).

to Dr. C. A. de Bock and Dr. W. T. Goedemans for supplying and discussing the biological data and to colleagues and coworkers of the analytical department, especially to Miss M. E. van der Heeden, for measurements and interpretation of the spectra.

1-Adamantanecarboxylic Acid Ester of Scopolamine

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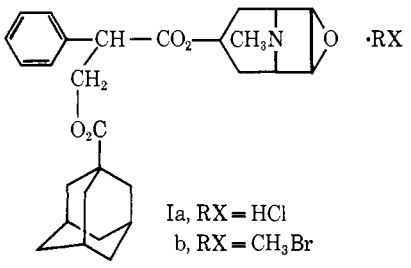
A few years ago it was found[1] that the esters of scopolamine were powerful anticholinergics. One of these, scopolamine pivalate hydrochloride, was found to be very effective as a topical antiperspirant.[2] In order to assess the influence of the rigid structure the 1-adamantanecarboxylic acid ester of scopolamine (I) has now been made.



Ia, RX = HCl
b, RX = CH_3Br

Both the hydrochloride (Ia) and the methobromide (Ib) were found to be powerful anticholinergics. They markedly dilated mouse pupils when injected intraperitoneally at doses of 20% of their LD_{50}'s. Ia had an LD_{50} of 562 mg/kg and Ib, 56 mg/kg.[3] Further testing is desirable to determine their minimum effective doses and to evaluate the degree of usefulness of Ia as an antiperspirant.

Experimental Section[4]

1-Adamantanecarboxylic Acid Ester of Scopolamine Hydrochloride (Ia).—1-Adamantanecarbonyl chloride was prepared from 12.6 g (0.07 mole) of the acid and 30 ml of $SOCl_2$. After removing the excess $SOCl_2$ under reduced pressure and purging with C_6H_6, the crude acid chloride was dissolved in 10 ml of C_6H_6 and added to a suspension of 19.22 g (0.05 mole) of dried scopolamine hydrobromide in 50 ml of dry pyridine under N_2. The solid was dissolved by warming and the mixture was allowed to stand overnight at room temperature. The mixture was basified with aqueous Na_2CO_3 and extracted (Et_2O). The Et_2O solution was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and evaporated under reduced pressure. The gummy free base was dissolved in 500 ml of absolute Et_2O and acidified with ethereal HCl giving 27.5 g of white solid hydrochloride. Recrystallization from 150 ml of *i*-PrOH yielded 19.6 g (78%) of white crystals, mp 218–221° dec. *Anal.* ($C_{28}H_{36}ClNO_5$) C, H, Cl, N.

The Methobromide Ib.—Free base was liberated from 5.02 g (0.01 mole) of the above hydrochloride with Na_2CO_3 and extracted (Et_2O). The Et_2O solution was washed (H_2O, saturated NaCl) and evaporated under reduced pressure. To the gummy free base in 25 ml of cold EtCOMe was added 10 ml of cold MeBr. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The quaternary salt was collected, washed (EtCOMe and Et_2O), and dried yielding 5.5 g (98%) of white crystals, mp 226.5–227.5° dec. *Anal.* ($C_{29}H_{38}BrNO_5$) C, H, Br, N.

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(3) For the method see R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964), Table I, footnote *a*.

(4) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir spectra were obtained on both compounds and nmr on the hydrochloride. These were in accordance with the proposed structures. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical.

Structure-Activity Studies of 3,4,5-Trimethoxybenzamides. I. Variation of the Amine Function

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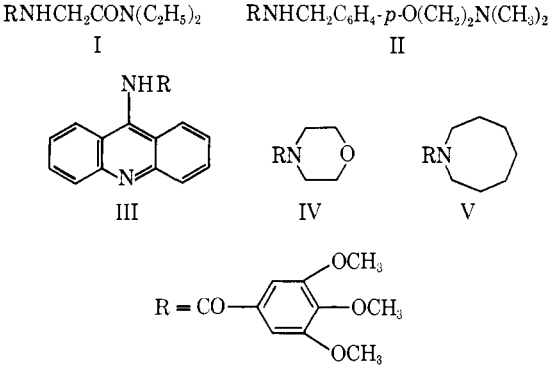
Various types of biological activity have been reported for 3,4,5-trimethoxybenzamides. The simplest member of the series, 3,4,5-trimethoxybenzamide, was found to have hypotensive effects and to potentiate the effects of phenobarbital.[1] Trimeglamide[2] (I) has been reported to possess hypnotic activity. Tigan (II) is well known as an antiemetic. Compound III has been reported[3] to have hypotensive activity and to potentiate muscle contraction. Vargha, *et al.*,[4] have synthesized a series of trimethoxybenzamides. A study[5] on one of these, N-(3,4,5-trimethoxybenzoyl)tetrahydro-1,4-oxazine (IV), has shown it to possess interesting tranquilizing properties. Compound V, however, reportedly possesses antidepressant activity.[6] The effect of IV on spontaneous activity of mice was compared with its effect on muscle function using the rotarod.[5] A comparison of the effective dose for depression of activity to that required for rotarod effects gives a measure of the selectivity of drug action. One would want to



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