ful for the small-scale synthesis of phenoxybenzamine-C^{14}. The key to the success of this synthetic method lies in the separation of N-(phenoxyisopropyl)ethanolamine (I) from the product, N-benzyl-N-(phenoxyisopropyl)ethanolamine (II). Nikawitz and coworkers[4] achieved separation of I and II by fractional distillation *in vacuo*. This mode of separation proved unsuccessful in our hands because of the small quantities that were involved. It was found that I and II could be separated by utilization of Hinsberg's method[5] since the reaction product of benzenesulfonyl chloride with I can be separated from II by solvent extraction.

Experimental Section[6]

H^3-Labeled N-Benzyl-N-(phenoxyisopropyl)ethanolamine (II).—A mixture of 1.114 g (5.71 mmoles) of I, 360 mg (2.86 mmoles) of benzyl-H^3 chloride,[7] 333 mg (3.14 mmoles) of powdered anhydrous Na_2CO_3, and 8.6 ml of absolute ethanol was heated under reflux for 21 hr. The ethanol was then distilled at reduced pressure and 0.73 ml (5.71 mmoles) of benzenesulfonyl chloride and 8.0 ml of 2.5 *N* aqueous NaOH were added. The mixture was mechanically shaken for 30 min and then extracted three times with 6-ml portions of anhydrous ether. The basic aqueous layer was discarded and the combined ethereal extracts were shaken with three 6-ml portions of 1 *N* HCl. The pooled acid layers were extracted with 2 ml of ether, which were discarded. The pooled acid solutions were made basic with 1.72 ml of 10 *N* NaOH and extracted with three 6-ml portions of ether. After pooling of the combined phases and drying (Na_2SO_4), distillation of the ether solution yielded II as a yellow oil.

H^3-Labeled Phenoxybenzamine Hydrochloride (III).—The conversion of II to III was accomplished by converting it to the salt form with 2 ml of $CHCl_3$ previously made acid by saturation with anhydrous HCl. A mixture of $SOCl_2$ (0.417 ml, 5.74 mmoles) in 2 ml of $CHCl_3$ was then added and heated under reflux for 2 hr. Distillation of the chloroform under reduced pressure left a yellow oil which was induced to crystallize by trituration with ether. Three recrystallizations from ethanol and ether gave 376 mg of pure white crystals of III. The overall yield was 39% based on benzyl-H^3 chloride. The melting point was 137–138°, identical with nonradioactive material, and the melting point of a mixture of the two was not depressed. Comparison of the infrared spectra of III and the nonradiomer showed them to be essentially identical. Chromatography on silica gel G (Stahl) with a solvent system composed of heptane–chloroform–methanol (140:65:25) showed III to be homogeneous and have an identical R_f with nonlabeled material (average R_f of II, 0.47; average R_f of III, 0.90). III was found to have a specific activity of 36.3 mcuries/mmole and reverse isotope dilution analysis showed it to be radiochemically pure.

Pharmacology.—Tritium-labeled phenoxybenzamine hydrochloride (III) was found to possess the expected adrenergic blocking activity. Incubation of III (concentration 0.1 μg/ml) for 5 min produced an almost complete blockade of the response to norepinephrine in preparations of the seminal vesicle of the rat according to Leitch.[8] Preliminary results of the use of III for labeling receptors based on the concept of receptor protection[9] have been presented.[10]

Acknowledgments.—The authors wish to thank Smith Kline and French Laboratories for a generous supply of the necessary precursor, I. This work was supported by Grant No. HD 00443 from the U. S. Public Health Service.

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(6) Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained between NaCl plates (for II) or as KBr pellets (for III) using the Perkin-Elmer Model 137B Infracord. Radioactive measurements were done using a Packard Tri-Carb liquid scintillation system.

(7) Obtained from New England Nuclear Corp., Boston, Mass., with a specific activity of 35 mcuries/mmole.

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New Compounds

Silicon-Substituted Medicinal Agents. Phenyl-Substituted Silacarbamates[1]

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Received November 4, 1965

In the course of our work on silacarbamates related to meprobamate,[3] it was convenient to prepare some phenyl-substituted silacarbamates. The synthetic reaction and the biological screening procedures were similar to those described in our previous publication[3] and will not be repeated in detail in this report. In general, these new carbamates showed muscle relaxant activity of short duration.

$$C_6H_5(CH_2)_n\text{—}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{Si}}}}\text{—}CH_2OCONH_2$$

$n = 0, 1, 2$

(1) This research was supported by Public Health Service Research Grant GM 10122 from the National Institute of General Medical Sciences.

(2) Alfred P. Sloan Fellow, 1965–1967.

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Experimental Section[4]

(Hydroxymethyl)dimethylphenylsilane Carbamate.—The reaction of 21.1 g (0.093 mole) of (bromomethyl)dimethylphenylsilane with 19.7 g (0.20 mole) of KOAc and 65 ml of acetic acid, after a 24-hr reflux, work up, and distillation, gave (hydroxymethyl)dimethylphenylsilane acetate, bp 91–105° (3.0 mm), $n^{24}D$ 1.5087, in 69% yield. The product was not purified further, but was carried directly into the next step. (Hydroxymethyl)-dimethylphenylsilane, bp 123–124° (5.0 mm), $n^{22}D$ 1.5241 [lit.[5] bp 130–135° (30 mm), $n^{20}D$ 1.5220], was obtained in 75% yield by the $LiAlH_4$ reduction of the acetate. Treatment of 25.9 g (0.143 mole) of the hydroxymethyl compound with 25.0 g (0.16 mole) of phenyl chloroformate and 60 ml of pyridine, followed by reaction of the carbonate intermediate (not isolated) with liquid NH_3,[3] yielded 17.2 g (53%) of the carbamate, bp 147–150° (2.2 mm), $n^{24}D$ 1.5265.

Anal. Calcd for $C_{10}H_{15}NO_2Si$: C, 57.37; H, 7.24; N, 6.69; Si, 13.41. Found: C, 57.25; H, 7.19; N, 6.84; Si, 13.27.

The infrared spectrum (thin film) was consistent with the structure assignment and showed bands at 2.9 (doublet, NH_2), 5.85 (CO), 7.0 and 9.0 (SiC_6H_5), 8.0 ($SiCH_3$), and 9.4 (COC) μ.

The LD_{50} was assayed to be 400 mg/kg, and the ED_{50} in the rotating rod test was determined to be 111 (103–120) mg/kg.

(4) All melting points (Fisher-Johns melting point apparatus) are corrected. The carbon, hydrogen, and nitrogen analyses were performed by the Berkeley Microanalytical Laboratory. Silicon analyses were performed in this laboratory using the wet ash method.

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At the ED_{50} in the rotating rod test, the duration of activity was determined to be about 15 min.

(Hydroxymethyl)benzyldimethylsilane Carbamate.—(Chloromethyl)benzyldimethylsilane, bp 89–90° (4 mm), $n^{29}D$ 1.5175, was prepared in 74% yield from 100 g (0.70 mole) of (chloromethyl)dimethylchlorosilane and 1.1 moles of benzylmagnesium chloride.

Anal. Calcd for $C_{10}H_{16}ClSi$: Si, 14.05. Found: Si, 14.18.

From 65 g (0.32 mole) of the (chloromethyl)silane, there was obtained 65.5 g (90%) of the acetate, bp 108° (2.0 mm), $n^{26}D$ 1.4972.

Anal. Calcd for $C_{12}H_{18}O_2Si$: Si, 12.62. Found: Si, 12.71.

The preparation of the hydroxymethylsilane was accomplished by hydrolysis.[6] To 39.3 g (0.18 mole) of the acetate was added 300 ml of aqueous methanol and 4 drops of concentrated H_2SO_4. The mixture was heated at reflux for 24 hr. Fractional distillation gave 28.8 g (90%) of the crude material. After repeated distillation, an analytical sample was obtained.

Anal. Calcd for $C_{10}H_{16}OSi$: Si, 15.55. Found: Si, 15.37.

Using 18.9 g (0.105 mole) of the hydroxymethyl compound, the carbamate, bp 170° (5.5 mm), $n^{25}D$ 1.5240, was obtained in 43% yield. The product solidified, and crystallization from acetone yielded 5.3 g, mp 65–66°.

Anal. Calcd for $C_{11}H_{17}NO_2Si$: C, 59.14; H, 7.69; Si, 12.57. Found: C, 59.30; H, 7.5; Si, 12.63.

The LD_{50} of this carbamate was found to be greater than 1000 mg/kg; the ED_{50} for the rotating rod was 318 (294–344) mg/kg. The duration of activity was observed to be 10 min at the ED_{50} level.

Hydroxymethylphenethyldimethylsilane Carbamate.—(Chloromethyl)phenethyldimethylsilane, bp 113–115° (5 mm), $n^{25}D$ 1.5100, was obtained in 50% yield from phenethylmagnesium bromide and (chloromethyl)dimethylchlorosilane. No attempt was made to obtain an analytical sample. From 70.1 g (0.046 mole) of the (chloromethyl)silane, there was obtained 70.4 g (90%) of the acetate, bp 128–130° (4.2 mm), $n^{24}D$ 1.4939.

Anal. Calcd for $C_{13}H_{20}Si$: Si, 11.87. Found: Si, 11.88.

Hydrolysis[6] of 43.4 g (0.19 mole) of the acetate yielded 18.4 g (50%) of the crude (hydroxymethyl)silane. Repeated redistillations gave a pure sample, bp 130–131° (6 mm), $n^{23}D$ 1.5141.

Anal. Calcd for $C_{11}H_{18}OSi$: Si, 14.41. Found: Si, 14.27.

From 10.7 g (0.058 mole) of the (hydroxymethyl)silane was obtained 7.7 g (58%) of the carbamate, bp 174–176° (4 mm), $n^{23}D$ 1.5170. When chilled, the carbamate solidified; mp 36–37°.

Anal. Calcd for $C_{12}H_{19}NO_2Si$: C, 60.70; H, 8.09; N, 5.90; Si, 11.82. Found: C, 60.70; H, 7.94; N, 5.85; Si, 11.98.

The infrared spectrum, consistent with the expected structure, showed a doublet in the 2.9-μ region and the expected bands at 5.7, 6.23, 8.0, and 9.4 μ.

The LD_{50} was observed to be greater than 1000 mg/kg; the ED_{50} for the rotating rod was 308 (290–326) mg/kg. The duration of activity at the ED_{50} level was 20 min.

Acknowledgment.—The authors are indebted to Mr. J. Dias for aid in the synthetic work.

(6) It should be noted that this procedure, which is in deviance with our usual procedure of reduction, gave inferior results when the purity of the product and the difficulty in obtaining an analytical sample are considered. Although never applied to the preparation of this particular compound, the authors consider the $LiAlH_4$ reduction procedure superior to this method.

Isomeric Estranes

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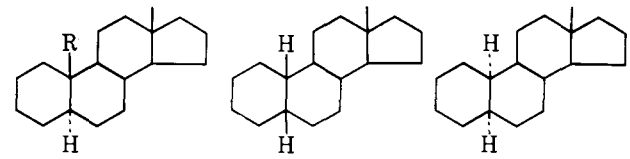
Received October 28, 1965

In 1960, Segaloff and Gabbard[2] demonstrated that 5α-androstane (Ib) was able to stimulate the seminal vesicles and prostate of the castrated rat. This indicated that oxygenated funtions at the 3- and 17-positions of androstanes was not obligatory for androgenic activity. For spectroscopic reasons, 5α-estrane (Ia), the 19-nor analog of Ib, as well as 5β- (II) and 5α,10α-estrane (III) have now been prepared. These isomers were readily obtained by Wolff–Kishner reduction of the previously described 3,17-diketones.[3] Intramuscular administration of Ia in castrated male rats showed it to have less than 1% of the androgenic activity of testosterone propionate.[4]



Ia, R = H
b, R = CH_3 II III

Experimental Section[5]

5α-Estrane (Ia). General Method.—A solution of 5α-estrane-3,17-dione[3] (2.7 g), 100% hydrazine hydrate (3 ml), and KOH pellets (2.0 g) in diethylene glycol (20 ml) was refluxed for 1 hr. The condenser was removed and the external temperature was raised. A stream of nitrogen was passed into the vessel for 20 min. The external temperature was raised to 230° and the mixture refluxed for 2 hr. The solution was allowed to cool and was poured into ice water (100 ml). The mixture was extracted with three 50-ml portions of ether and the extract was washed successively with two 25-ml portions of 2 *N* HCl and water (25 ml). The ether phase was dried (Na_2SO_4 and Darco) and the solvent was removed by distillation. The residual oil (1.6 g) was distilled *in vacuo* to afford pure Ia (see Table I).

TABLE I

Estrane	Bp, °C (mm)	$[\alpha]^{25}D$, deg	$n^{25}D$	18-H, δ (ppm)	% found[a] C	% found[a] H
5α	133–135(4)	+20	1.517	0.692	88.22	12.19
5β	102–103 (0.05)	+15	1.514	0.700	87.63	12.02
5α,10α	83–85(0.03)	−15.5	1.524	0.675	87.95	12.42

[a] *Anal.* Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27.

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(4) The author is grateful to Dr. F. J. Saunders for providing the biological information.

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Synthesis of Arysulfonyl-1-methyl-S-isothiosemicarbazides

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Received October 23, 1965

Lora-Tamayo,[1] *et al.*, and Hoggarth[2] have reported syntheses of a number of aroyl-1-methyl-S-isothiosemicarbazides. These compounds, as well as the related aroylthiosemicarbazides, show antimicrobial activity. The preparation of the bioisosteric arylsulfonyl-1-methyl-S-isothiosemicarbazides (I) from the corresponding arylsulfonylthiosemicarbazides is given here as a further utilization of the latter compounds, whose preparation and evaluation were reported[3] elsewhere. While the experi-

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