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

R. E. COUNSELL[1]

Division of Chemical Research, G. D. Searle and Company, Chicago, Illinois 60680

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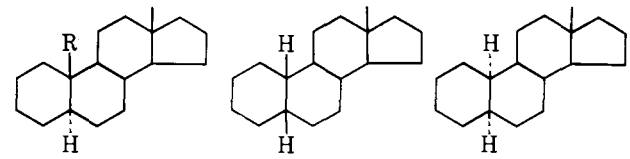
In 1960, Segaloff and Gabbard[2] demonstrated that 5α-androstane (Ib) was able to stimulate the seminal vesicles and prostate of the castrated rat. This indicated that oxygenated funtions at the 3- and 17-positions of androstanes was not obligatory for androgenic activity. For spectroscopic reasons, 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.

(3) R. E. Counsell, *Tetrahedron*, **15**, 202 (1961).

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

(5) Optical Rotations and analytical data were furnished by Dr. R. T. Dillon of our Analytical Department. The optical rotations were obtained in $CHCl_3$. The nmr spectra were obtained in $CDCl_3$ with a Varian high-resolution Model V-4300B using tetramethylsilane as the internal standard. These spectra were kindly provided by Dr. McNiven, Worcester Foundation for Experimental Biology.

Synthesis of Arysulfonyl-1-methyl-S-isothiosemicarbazides

CARLOS SUNKEL AND SONIA ERAZO

Department of Organic Chemistry, Institute of Research, Universidad Católica de Valparaiso, Valparaiso, Chile

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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-

(1) Laboratory of Medicinal Chemistry, College of Pharmacy, The University of Michigan, Ann Arbor, Mich. 48104

(2) A. Segaloff and R. B. Gabbard, *Endocrinology*, **67**, 887 (1960).

(1) M. Lora-Tamayo, G. Alonso, and R. Madronero, *Bull. Soc. Chim. France*, 259 (1964).

(2) E. Hoggarth, *J. Chem. Soc.*, 1918 (1949).

(3) M. Lora-Tamayo, C. Sunkel, and R. Madronero, *Bull. Soc. Chim. France*, 248 (1964).

TABLE I[a]

ARYLSULFONYL-1-METHYL-S-ISOTHIOSEMICARBAZIDES

XSONHNHC(=NH)SCH$_3$

I

X	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
C_6H_5	124–125 dec	95	$C_8H_{11}N_3O_2S_2$	39.18	4.49	39.49	4.63
p-$CH_3OC_6H_4$	141–142 dec	91	$C_9H_{13}N_3O_3S_2$	39.31	4.72	39.36	4.70
p-$C_2H_5OC_6H_4$	157–158 dec	99	$C_{10}H_{15}N_3O_3S_2$	41.52	5.19	41.48	5.40
p-*n*-$C_3H_7OC_6H_4$	151–152 dec	93	$C_{11}H_{17}N_3O_3S_2$	43.59	5.61	43.50	5.32
p-*n*-$C_4H_9OC_6H_4$	132–133 dec	70	$C_{12}H_{19}N_3O_3S_2$	45.42	5.99	45.72	6.01
$C_6H_5CH_2$	142	62	$C_9H_{13}N_3O_2S_2$	41.69	5.01	41.79	4.8

[a] Melting points were taken in open capillary tubes. The yields reported are those after one recrystallization. Elemental analyses were made by Dr. J. Calderón, of Instituto "Alonso Barba" of Madrid, Spain.

mental conditions of Lora-Tamayo, *et al.*, were also tried, those of Hoggarth gave much better results. The formulas and experimental data for the compounds prepared are presented in Table I.

Experimental Section

The arysulfonylthiosemicarbazide (5 mmoles) was suspended in 5 ml of 1 *N* NaOH. Several minutes of vigorous stirring produced a clear yellow solution. To this was added 0.78 g (5.6 mmoles) of methyl iodide in 1 ml of 95% ethanol. Precipitation of the white, crystalline product was complete in 15–20 min. Samples for analysis were recrystallized from ethanol–water.

A New Naphthylacetamide Derivative

TIBERIO BRUZZESE AND CARLA TURBA

Research Laboratories, Istituto De Angeli S.p.A., Milan, Italy

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Our interest in antiinflammatory drugs derived from naphthalene, of which thus far α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (**I**)[1] has been the best representative, has led us to synthesize the 4-isobutyl derivative in analogy with 4-isobutylphenylacetic acid (ibufenac), a product known to exert a marked analgesic and antiinflammatory action.[2] The new compound, α-isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetamide, possesses an analgesic action distinctly superior to that of I.

Experimental Section[3]

The 1-isobutylnaphthalene required was obtained by a new general method for preparing 1-alkylnaphthalenes, which will be described in a later paper.

1-Chloromethyl-4-isobutylnaphthalene.—A mixture of trioxymethylene (8.5 g, 0.283 mole), glacial acetic acid (110 g), and anhydrous HCl (11.7 g, 0.321 mole) was gently heated until the trioxymethylene dissolved, and then 1-isobutylnaphthalene (40 g, 0.217 mole) was added and the flask carefully was closed and heated for 20 hr at 65–70°. After cooling, the mixture was poured into water, the separated oil was extracted with benzene, and the resulting solution was washed with water and Na_2CO_3 and then dried (Na_2SO_4). The benzene was removed *in vacuo* and the product was distilled, bp 135–137° (0.3 mm), giving a colorless oil (35.2 g, 69.8% yield).

Anal. Calcd for $C_{15}H_{17}Cl$: C, 77.40; H, 7.36; Cl, 15.23. Found: C, 77.24; H, 7.28; Cl, 14.95.

4-Isobutyl-1-naphthylacetonitrile.—A mixture of 1-chloromethyl-4-isobutylnaphthalene (46.5 g, 0.2 mole), KCN (17.8 g, 0.274 mole), ethanol (77 ml), and water (30 ml) was refluxed for 1 hr. The alcohol was distilled, the residue was extracted with ether, and the solution was washed with water and then dried (Na_2SO_4). After distilling the solvent, the residue was purified by distilling at 145–147° (0.4 mm), and the oily product then was treated with petroleum ether (bp 40–70°) to give colorless crystals (18.3 g, 41% yield). On recrystallization from petroleum ether, the compound melted at 78–79° (cor).

Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.48; H, 7.73; N, 6.18.

α-(2-Dimethylaminoethyl)-4-isobutyl-1-naphthylacetonitrile.—This procedure follows the method previously described.[4] 4-Isobutyl-1-naphthylacetonitrile (26.8 g, 0.12 mole) was alkylated with 2-(*N*,*N*-dimethylamino)-1-chloroethane (13.55 g, 0.126 mole), refluxing for 5 hr in benzene (400 ml) in the presence of sodamide (4.9 g, 0.126 mole). The product obtained was distilled at 170–173° (0.4 mm) to give a colorless oil (22.9 g, 65% yield).

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.04; H, 9.01; N, 9.30.

α-Isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetonitrile.—Alkylation of the above nitrile (22.9 g, 0.078 mole) with 2-bromopropane (12.4 g, 0.101 mole) was performed by refluxing for 18 hr in benzene (500 ml) and in the presence of sodamide (3.94 g, 0.101 mole). The distilled product, bp 174–176° (0.6 mm), was a colorless oil (17.6 g, 67.1% yield).

Anal. Calcd for $C_{23}H_{32}N_2$: C, 82.09; H, 9.59; N, 8.33. Found: C, 81.16; H, 9.40; N, 8.17.

α-Isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetamide.—The hydrolysis was performed according to the general method recently reported.[1b] α-Isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetonitrile (33.6 g, 0.1 mole) was refluxed for 120 hr with a 1:1:1 mixture (131 ml) of concentrated H_2SO_4, glacial acetic acid, and water. The crude product was distilled at 188–191° (0.25 mm) to give a viscous oil (12.05 g, 34% yield).

Anal. Calcd for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90. Found: C, 78.52; H, 9.59; N, 7.73.

(1) α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide, naphthypramide. (a) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964); (b) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 594 (1965); (c) G. Pala, S. Casadio, T. Bruzzese, E. Crescenzi, and E. Marazzi-Uberti, *ibid.*, **8**, 698 (1965).

(2) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, *Nature*, **200**, 271 (1963).

(3) The boiling points are uncorrected.

(4) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 589 (1965).

Derivatives of 2-Azabicyclo[2.2.2]octane. II[1,2]

FRANK J. VILLANI AND CLAIRE A. ELLIS

Medicinal Chemical Research Department, Schering Corporation, Bloomfield, New Jersey

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Amides of formula I, related to the respiratory stimulant, diethylnicotinamide, were prepared. Reduction of these compounds gave a series of compounds represented by formulas II–V.

(1) Part I of this series: F. J. Villani and C. A. Ellis, *J. Med. Chem.*, **9**, 185 (1966).

(2) Isoquinuclidine, the common name of this ring system, is used throughout this manuscript.