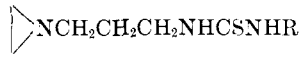
TABLE I

1-(3-ETHYLENIMINOPROPYL)-3-SUBSTITUTED THIOUREAS



R	Yield, %	Mp, °C	Recrystn solvent	Calcd, % C	H	N	S	Found, % C	H	N	S
C_6H_5	72	107–109	Ethyl acetate	61.24	7.28	17.85	13.63	61.36	7.20	17.92	13.79
$C_{10}H_7$	66	129.5–130.5	Benzene	67.33	6.71	14.72	11.23	67.54	6.64	14.59	11.41

TABLE II

1-[3-(2-MERCAPTOETHYLAMINO)PROPYL]-3-SUBSTITUTED THIOUREAS

$HSCH_2CH_2NHCH_2CH_2CH_2NHCSNHR$

R	Yield, %	Mp, °C	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
C_6H_5	100	77–79.5	$C_{12}H_{19}N_3S_2$	53.49	7.10	15.60	23.80	53.62	7.10	15.51	23.80
$C_{10}H_7$	100	106–108	$C_{16}H_{21}N_3S_2$	60.15	6.30	13.15	20.07	60.13	6.38	13.09	20.29

filtration. After a recrystallization from benzene, an analytical sample of 1-(3-ethyleniminopropyl)-3-(1-naphthyl)thiourea was obtained, mp 129.5–130.5°.

1-[3-(2-Mercaptoethylamino)propyl]-3-phenylthiourea.—Hydrogen sulfide was bubbled into absolute ethanol at −60° for 1 hr; approximately 12.0 g of H_2S was absorbed. This solution was cautiously added to 2.5 g (0.01 mole) of analytically pure 1-(3-ethyleniminopropyl)-3-phenylthiourea dissolved in 150 ml of a 1:1 mixture of chloroform and anhydrous ethanol. The solution was allowed to stand for 3 hr, then additional hydrogen sulfide was bubbled through the solution for 15 min. The solution was concentrated *in vacuo* on a rotary evaporator to afford a clear oil which, on rubbing with a glass rod, gave 2.5 g (quantitative yield) of snow white solid, mp 77.5–80°. The infrared spectrum showed a mercaptan peak at 2550 cm^{-1}.[13]

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 350.

Some Bridgehead-Substituted Tetrahydroacenaphthenones[1a]

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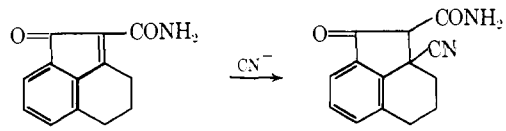
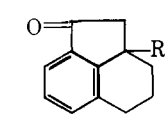
Attention has recently been called to the importance of rigid molecules, commonly possessing quaternary or bridgehead carbon atoms, in developing biologically active molecules of high potency.[2] A series of 2-dialkylaminoalkyl-2a,3,4,5-tetrahydroacenaphthen-1-ones has been reported,[3] some of which had analgesic activity. The ready availability of 2-carboxamido-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (**2**),[4] *via* the Michael addition of cyanide ion to 2-carboxamido-3,4-trimethyleno-1-indenone (**1**),[5] led to the preparation of several tetrahydroacenaphthene derivatives of **2** for pharmacological screening. These compounds are rigid molecules containing a quaternary carbon atom at a bridgehead, and hence might have enhanced biological activity.

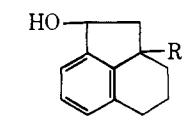


1 2

Hydrolysis of **2** with aqueous sulfuric acid (5–35%) led to 2a-carboxy-2a,3,4,5-tetrahydroacenaphthen-1-one (**3a**), while hydrolysis using 20% phosphoric acid gave a mixture of 2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (**3b**) and **3a**. The structure of **3a** is indicated by its stability (not a β-keto acid) and by the hydrolysis of **3b** with 50% aqueous sulfuric acid to a keto acid shown to be identical with **3a**. The acid **3a** was converted to β-diethylaminoethyl (**3c**), γ-dimethylaminopropyl (**3d**), and β-1-piperidinoethyl 1-oxo-2a-3,4,5-tetrahydroacenaphthene-2a-carboxylate hydrochloride (**3e**) by treatment with the appropriate dialkylaminoalkyl chloride hydrochloride and potassium carbonate in dimethylformamide. Treating the acid chloride of **3a** with the appropriate alcohol led to the formation of **3c** and **3d**. β-Chloroethyl 1-oxo-2a,3,4,5-



3a, R = CO_2H
b, R = CN
c, R = $CO_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$
d, R = $CO_2(CH_2)_3N(CH_3)_2 \cdot HCl$
e, R = $CO_2CH_2CH_2N(CH_2)_5 \cdot HCl$
f, R = CH_2CH_2Cl
g, R = $CONH_2$



4a, R = CO_2H
b, R = CN
c, R = $CO_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$

tetrahydroacenaphthene-2a-carboxylate (**3f**) was formed when a mixture of **3a**, ethylene chlorohydrin, and concentrated sulfuric acid was heated in benzene. Treatment of **3b** with concentrated sulfuric acid af-

(1) (a) Contribution No. 1391. This work was supported by a grant from the Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y., and is taken in part from theses submitted to Indiana University for the degree Doctor of Philosophy by W. L. Roelofs, June 1964, and by R. F. Weddleton, June 1965. Presented in part before the Division of Medicinal Chemistry, 148th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) Bristol Laboratories Predoctoral Fellow, 1962. (c) Bristol Laboratories Predoctoral Fellow, 1962–1965.

(2) E. L. May, *J. Med. Chem.*, **6**, 322 (1963); L. H. Sarett, Award Address for Creative Work in Synthetic Organic Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

(3) H. J. Glenn and B. W. Horrum, *J. Am. Chem. Soc.*, **76**, 3640 (1954).

(4) E. Campaigne and W. L. Roelofs, *J. Org. Chem.*, **30**, 2610 (1965).

(5) (a) E. Campaigne and G. F. Bulbenko, *ibid.*, **26**, 4703 (1961); (b) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and D. R. Maulding, *ibid.*, **27**, 4428 (1962).

TABLE I

PROPERTIES OF COMPOUNDS PREPARED

Product	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
3a	175.5–176.5	$C_{13}H_{12}O_3$	72.21	5.60	72.50	5.86
3b	123–124	$C_{13}H_{11}NO$	79.16	5.62	79.34	5.68
3c	205–206	$C_{18}H_{26}ClNO_3$[a]	64.85	7.45	64.95	7.36
3d	183–184	$C_{18}H_{24}ClNO_3$[b]	63.99	7.16	63.70	7.23
3e	170.5–171.5	$C_{20}H_{28}ClNO_3$[c]	66.01	7.20	65.82	6.97
3f	56–57	$C_{15}H_{13}ClO_3$	64.63	5.42	65.42	5.75
3g	208–209	$C_{32}H_{32}NO_2$[d]	72.54	6.09	72.54	6.04
4a	172–174	$C_{13}H_{14}O_3$	71.55	6.47	71.79	6.78
4b	64–65	$C_{13}H_{13}NO$	78.36	6.58	78.30	6.64
4c	180.5–181.5	$C_{20}H_{28}ClNO_3$[e]	64.48	7.97	63.95	8.24

[a] *Anal.* Calcd: Cl, 10.08. Found: Cl, 10.18. [b] *Anal.* Calcd: Cl, 10.09. Found: Cl, 10.13. [c] *Anal.* Calcd: Cl, 9.74. Found: Cl, 9.72. [d] *Anal.* Calcd: N, 6.51. Found: N, 6.40. [e] *Anal.* Calcd: N, 3.06. Found: N, 4.13.

forded 2a-carboxamido-2a,3,4,5-tetrahydroacenaphthen-1-one (**3g**).

Reduction of **3a** and **3b** with sodium borohydride in base afforded 2a-carboxy-2a,3,4,5-tetrahydroacenaphthen-1-ol (**4a**) and 2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-ol (**4b**), respectively; **4a** was converted to β-diethylaminoethyl 1-hydroxy-2a,3,4,5-tetrahydroacenaphthene-2a-carboxylate hydrochloride (**4c**). Melting points and analyses of the compounds prepared are summarized in Table I.

Compounds **2–4** were evaluated for the following actions: central nervous system,[6,7] hypotensive,[6] analgesic,[6] anticoagulant, antiinflammatory,[8] autonomic,[9] antiallergic, endocrine,[10] reticuloendothelial,[11] antimicrobial,[12] and antifungal. The anticoagulant activity was determined from coagulation time in a capillary tube of blood obtained by retroorbital puncture in treated mice. Antifungal tests were modified from methods for the examination of specimens for evidence of mycotic disease of the New York State Department of Health. The activities observed were the following: **3b** was a mild protectant against pentylenetetrazole-induced convulsions and a weak smooth muscle relaxant; **3c** protected mice from both electrically induced and pentylenetetrazole-induced convulsions; **3d** exhibited analgesic activity. The pharmacological screening data, summarized in Table II, are through the courtesy of Dr. M. L. Pindell, of the Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y.

TABLE II

SUMMARY OF PHARMACOLOGICAL SCREENING RESULTS[a]

Structure	Activity[b]	MED, mg/kg	Toxic dose, mg/kg
2	*c*	...	>500
3a	*c*	...	>300
3b	CNS[d]	300	>300
	Autonomic[e]		
3c	CNS[f]	300	>300
3d	Analgesic	150[g]	>300
3e	*h*	...	<300
3f	*c*	...	>300
3g	Analgesic	100	>300
4a	*c*	...	>300
4b	*c*	...	>300
4c	*c*	...	>300

[a] The pharmacological screening data are through the courtesy of Dr. M. H. Pindell, of Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, N. Y. [b] The activities observed are listed together with the minimal effective dose (MED) for oral administration. These compounds were evaluated for the following actions: central nervous system (CNS), hypotensive, analgesic, anticoagulant, antiinflammatory, autonomic, antiallergic, endocrine, reticuloendothelial, antimicrobial, and antifungal. [c] Devoid of significant pharmacological activity at 300 mg/kg. [d] A mild protectant against pentylenetetrazole-induced convulsions. [e] A weak smooth-muscle relaxant, *in vitro* (50 μg/ml, bath concentration). [f] Protected mice from both electrically induced and pentylenetetrazole-induced convulsions; when dose was reduced to 150 mg/kg, there was no protection. [g] At 300 mg/kg strongly depressed spinal transmission; no CNS activity at a lower dose. [h] Devoid of significant pharmacological activity at 50 mg/kg.

Experimental Section[13]

2a-Carboxy-2a,3,4,5-tetrahydroacenaphthen-1-one (3a).—A solution of 5 g of 2-carboxamido-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (**2**)[4] in 100 ml of 10% H_2SO_4 (5, 20, or 35%) was heated on the steam bath for 20 hr. It was then cooled and 4.3 g (98%) of **3a**, mp 153–166°, was collected. Recrystallization of the crude **3a** from water yielded colorless plates: λ_{max}^{KBr} 3.6, 3.8, and 3.9 (bonded OH), 5.8 (CO), 5.93 μ (COOH).

2a-Cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (3b).—A mixture of 1 g of the cyano adduct **2** in 40 ml of 20% H_3PO_4 was heated on the steam bath for 12 hr. The resulting solution was poured into 100 ml of water and cooled in the refrigerator. The white solid collected was extracted with 5% $NaHCO_3$ leaving 0.2 g (25%) of **3b**, mp 110–112°. Recrystallization from 95% ethanol gave colorless crystals: mp 123–124°; λ_{max}^{KBr} 4.5 (CN), 5.85 μ (CO); mol wt ($CHCl_3$) 204 (calcd 197.2).

A **2,4-dinitrophenylhydrazone** was recrystallized from 95% ethanol to give red crystals: mp 267–268°; λ_{max}^{KBr} 3.0 (NH), 4.5 μ (CN).

Anal. Calcd for $C_{19}H_{15}N_5O_5$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.64; H, 4.29; N, 19.08.

Acidification of the $NaHCO_3$ extracts gave 0.15 g (4%) of the keto acid **3a**, mp 159–163°.

Dialkylaminoalkyl Esters of 3a. Method A.—A mixture of 4.55 g (0.021 mole) of **3a**, 4.27 g (0.031 mole) of K_2CO_3, and 25 ml of dimethylformamide was stirred in an ice bath while 0.021 mole of a dialkylaminoalkyl chloride hydrochloride was added in por-

(6) Y. G. Perron, W. F. Minor, M. E. Bierwagen, S. A. Ridilon, and M. H. Pindell, *J. Med. Chem.*, **9**, 136 (1966).

(7) J. H. Nodine and P. E. Siegler, Ed., "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," Year Book Medical Publishers, Inc., Chicago, Ill., 1964, pp 348–352.

(8) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(9) R. Magnus, *Arch. Ges. Physiol.*, **102**, 123 (1904).

(10) M. N. Zarrow, J. M. Jochim, and J. L. McCarthy, "Experimental Endocrinology: A Source Book of Basic Techniques," Academic Press Inc., New York, N. Y., 1964, pp 44–46.

(11) B. N. Halpern, B. Benacerraf, and G. Biozzi, *Brit. J. Exptl. Pathol.*, **34**, 426 (1953).

(12) A. Gourevitch, G. A. Hunt, J. R. Lattinger, C. C. Carmack, and J. Lein, *Proc. Soc. Exptl. Biol. Med.*, **107**, 455 (1961).

(13) Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord. Molecular weights were determined on a Mechrolab vaporphase osmometer in chloroform.

tions. The mixture was then stirred at room temperature for 20 hr and poured into 250 ml of ice and water, yielding either an oil or white precipitate. This material was extracted from the aqueous phase with three 50-ml portions of chloroform, and the $CHCl_3$ extracts were dried and evaporated. The resulting oil or solid was dissolved in 2-propanol and the solution was cooled in an ice bath while 2.1 ml (0.021 mole) of 37% aqueous HCl was added. Ether was added to precipitate all of the hydrochloride salt, which was filtered and crystallized from 2-propanol. The yields of once recrystallized products were the following: **3c**, 33%; **3d**, 7.3%; and **3e**, 34%. Further crystallization from 2-propanol afforded analytical samples.

Method B.—A quantity of 5.0 g (19 mmoles) of **3a** was dissolved in a minimum amount of boiling dry benzene, 4.55 g (38 mmoles) of $SOCl_2$ (distilled from quinoline then redistilled from linseed oil) was added dropwise over a period of 10 min from a pressure-equalizing separatory funnel, and the mixture refluxed on a steam bath for 1 hr. The excess $SOCl_2$ was removed as an azeotrope with benzene, 2 l. of benzene being distilled. The reaction mixture was cooled in an ice bath and 19 mmoles of dialkylaminoalkanol was added dropwise over a period of 20 min. The mixture was stirred in an ice bath for 1 hr, then at room temperature for 1 hr; the solvent was removed by a stream of air. The resulting oil was dissolved in a small amount of 1-propanol and dry HCl was added, yielding a white solid, which was filtered and recrystallized from 2-propanol. The yields of **3c** and **3d** obtained by this method were 33 and 17%, respectively.

β-Chloroethyl 1-Oxo-2a,3,4,5-tetrahydroacenaphthene-2a-carboxylate (3f).—A mixture of 2.16 g (0.01 mole) of **3a**, 1.6 g (0.02 mole) of ethylene chlorohydrin, 30 ml of benzene, and 5 drops of concentrated H_2SO_4 was refluxed under a Dean–Stark water trap for 20 hr. The solvent was evaporated, the resulting oil was dissolved in $CHCl_3$, and the $CHCl_3$ solution was washed with three 25-ml portions of 5% aqueous Na_2CO_3, dried, and evaporated, yielding an oil which solidified upon standing. Recrystallization first from 95% ethanol, then from ethyl acetate–hexane, afforded 0.18 g of long colorless needles, mp 53–55°. Condensation of the filtrate afforded an additional 0.75 g of material melting at 49–52°; over-all yield 0.93 g (33%). An additional recrystallization from ethyl acetate–hexane yielded an analytical sample melting at 56–57°, λ_{max}^{KBr} 5.9 μ (CO_2R and CO).

2a-Carboxamido-2a,3,4,5-tetrahydroacenaphthen-1-one (3g).—A mixture of 1.0 g of **3b** and 10 ml of concentrated H_2SO_4 was stirred at room temperature for 6 hr and then poured into 100 ml of ice water, yielding 0.92 g (85%) of a white precipitate, mp 206–208°. Two recrystallizations from 95% ethanol afforded colorless prisms: mp 208–209°; λ_{max}^{KBr} 2.94 and 3.2 (NH), 3.44 (CH), and 5.86–6.1 μ (CO and $CONH_2$).

2a-Carboxy-2a,3,4,5-tetrahydroacenaphthen-1-ol (4a).—A solution of 1 g of the keto acid **3a** in 10 ml of 2 *N* NaOH was stirred during the dropwise addition of 0.2 g of $NaBH_4$ in 10 ml of 2 *N* NaOH. The resulting solution was stirred for 5 hr and acidified with 20% H_2SO_4. Cooling caused the precipitation of 0.76 g (75%) of white crystals, mp 166–167°. Recrystallization from water gave white crystals of **4a**: λ_{max}^{KBr} 3.0 (OH), 3.75–3.9 (COOH), 5.9 μ (COOH). Thin layer chromatography using benzene–methanol (6:1) produced two spots to give evidence for the presence of two isomers.

2a-Cyano-2a,3,4,5-tetrahydroacenaphthen-1-ol (4b).—A solution of 1 g of ketonitrile **3b** in 10 ml of methanol was stirred during the dropwise addition of 0.1 g of $NaBH_4$ dissolved in 5 ml of 1% NaOH. The solution was stirred at room temperature for 2 hr and then acidified with dilute H_2SO_4. The aqueous layer was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallization of the residue from aqueous ethanol yielded 1.02 g (100%) of **4b**, mp 57–60°. Further recrystallization gave an analytical sample: λ_{max}^{KBr} 2.81, 2.95, and 3.15 (OH), 4.5 μ (CN).

β-Diethylaminoethyl 1-Hydroxy-2a,3,4,5-tetrahydroacenaphthene-2a-carboxylate Hydrochloride (4c).[14]—The method employed is similar to that of Campaigne and Bourgeois[15] for preparing hydroxy esters. To a solution of 1.7 g of β-chloroethyldiethylamine in 17 ml of anhydrous isopropyl alcohol was added 2.78 g of **4a** in 17 ml of anhydrous isopropyl alcohol, and the mixture refluxed for 10 hr. The solvent was condensed under aspirator vacuum, and the resulting white solid crystallized from ethanol and then 2-propanol, yielding 1.8 g (40.3%) of colorless crystals: λ_{max}^{KBr} 3.00 (OH), 3.34 (CH), 3.80 and 4.02 (NH^+), and 5.88 μ (CO_2R).

(14) We are indebted to Sister M. M. Christine, of Clarke College, Dubuque, Iowa, National Science Foundation Research Participant, summer 1963, for the preparation of this compound.

(15) E. Campaigne and R. C. Bourgeois, *J. Am. Chem. Soc.*, **75**, 2702 (1953).

The Synthesis of Some 2,3-Epithio-5α-pregnanes

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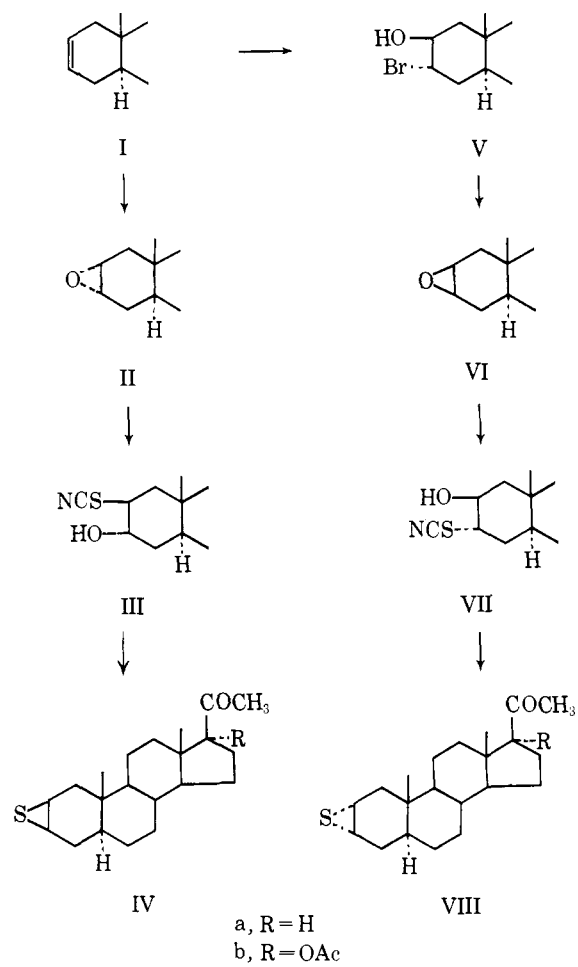
Received March 17, 1966

The recent observation of the potent anabolic activity of some 2,3-epithioandrostane derivatives[1] prompted the synthesis of some similar compounds in the 5α-pregnane series.

The episulfide derivatives (Table I) were prepared by a procedure similar to that reported earlier[2] for episulfides in the cholestane series. When the 2,3-dehydro analogs (I)[3,4] were treated with perbenzoic acid, the 2,3α-epoxides II were obtained (Chart I). Subsequent

CHART I



treatment with thiocyanic acid afforded the thiocyanohydrins III. Treatment with an alcoholic solu-

(1) P. D. Klimstra, E. F. Nutting, and R. E. Counsell, *J. Med. Chem.*, **9**, 693 (1966).

(2) K. Takeda and T. Komeno, *Chem. Ind.* (London), 1793 (1962).

(3) J. A. Edwards and A. Bowers, *ibid.*, 1962 (1961).

(4) M. M. Janot, H. Q. Khuong, and R. Goutard, *Bull. Soc. Chim. France*, 1640 (1960).