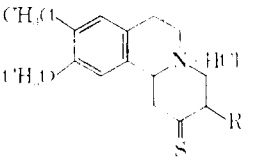
TABLE I

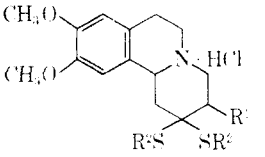
2-THIO-1,3,4,6,7,11b-HEXAHYDRO-9,10-DIMETHOXY-2H-BENZO[*a*]QUINOLIZINE HYDROCHLORIDES



No.	R	Mp, °C	Yield, %	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
1	$CH_2CH(CH_3)_2$	216–217	73.3	$C_{19}H_{27}NO_2S \cdot HCl$	61.7	7.6	3.8	8.7	61.5	7.5	3.8	8.8
2	$CON(C_2H_5)_2$	176–178	35.8	$C_{20}H_{28}N_2O_3S \cdot HCl$	58.2	7.1	6.8	7.9	58.4	7.0	6.9	7.8

TABLE II

2,2-BIS(ALKYLTHIO)- AND 2,2-BIS(ARYLTHIO)-1,3,4,6,7,11b-HEXAHYDRO-9,10-DIMETHOXY-2H-BENZO[*a*]QUINOLIZINE HYDROCHLORIDES



No.	R^1	R^2	Mp, °C	Yield, %	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
3	$CH_2CH(CH_3)_2$	CH_3	226–227	86.4	$C_{21}H_{33}NO_2S_2 \cdot HCl$	58.4	7.9	3.2	14.8	58.2	8.2	3.3	15.0
4	$CON(C_2H_5)_2$	CH_3	197–200	99.4	$C_{22}H_{34}N_2O_3S_2 \cdot HCl$	55.6	7.4	5.9	13.5	55.8	7.4	5.9	13.4
5	$CH_2CH(CH_3)_2$	C_2H_5	222–224	98.0	$C_{23}H_{37}NO_2S_2 \cdot HCl$	60.0	8.3	3.0	13.9	60.2	8.4	3.1	14.1
6	$CON(C_2H_5)_2$	C_2H_5	177–179	85.9	$C_{24}H_{38}N_2O_3S_2 \cdot HCl$	57.3	7.8	5.6	12.7	57.1	8.0	5.3	12.8
7	$CH_2CH(CH_3)_2$	$(CH_2)_3CH_3$	171–173	78.1	$C_{27}H_{45}NO_2S_2 \cdot HCl$	62.8	9.0	2.7	12.4	62.8	9.3	2.5	12.2
8	$CH_2CH(CH_3)_2$	$CH_2CH{=}CH_2$	142–145	74.0	$C_{25}H_{37}NO_2S_2 \cdot HCl$	62.0	7.9	2.9	13.3	62.2	8.0	2.7	13.4
9	$CH_2CH(CH_3)_2$	C_6H_5	216–218	46.3	$C_{31}H_{37}NO_2S_2 \cdot HCl$	66.9	6.9	2.5	11.5	66.9	7.1	2.6	11.5
10	$CH_2CH(CH_3)_2$	CH_2CH_2OH	217–219	30.4	$C_{23}H_{37}NO_4S_2 \cdot HCl$	56.1	7.8	2.9	13.0	56.3	8.0	3.0	13.2

TABLE III[a]

Compd	Min dose (mg/kg) causing signif CNS depres[b] IP	Oral	Approx LD_{50}, mg/kg IP	Oral
1	100	100	500	1000
2	200	200	500	>1000
3	50	50	300	1000
4	200	200	200	500
5	100	100	500	>1000
6	50	200	300	500
7	100	100	500	500
8	300	1000	500	>1000
9	300	>1000	300	>1000
10	200	500	500	>1000
Tetrabenazine	50	300	500	750

[a] We are grateful to Mrs. I. M. Cole for biological data. [b] The minimum dose causing the same degree of loss of the spontaneous motor activity as an intraperitoneal dose of 20 mg/kg of pentobarbital.

centrated at reduced pressure. The 2-thio-3-isobutyl derivative was purified by trituration of the residue with water (50 ml) and reprecipitation of the solid thus obtained from MeOH with ether. The 2-thio-3-(N,N-diethylcarboxamido) compound (**2**) was obtained as a yellow solid on treatment of the residue with ether (50 ml) and recrystallized from EtOH.

2,2-Bis(alkylthio)- and 2,2-Bis(arylthio)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine Hydrochlorides.—A solution of the ketone hydrochloride (5.0 g) and the appropriate thiol (50 ml) in saturated EtOH–HCl (250 ml) was allowed to stand at room temperature for 2 days and then concentrated at reduced pressure. The water-insoluble 3-isobutyl derivatives (**3**, **5**, and **7**–**10**) were purified by trituration of the residue with water (50 ml) and recrystallization of the solid thus obtained from benzene or benzene–ether mixtures. 3-(N,N-Diethylcarboxamido) compounds (**4** and **6**) were recrystallized from EtOH.

Infrared Data.—The infrared absorption spectra[5] were in full accordance with the proposed structures. The ketone C=O stretching bands present at 1720 cm^{-1} in the spectrum of tetrabenazine hydrochloride and at 1730 cm^{-1} in that of 1,3,4,6,7,11b-hexahydro-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-2H-benzo[*a*]quinolizin-2-one hydrochloride were not present in the spectra of the products **1**–**10**. The amide C=O stretching band at about 1640 cm^{-1} was, however, present in the spectra of the compounds with the carboxamido substituent (**2**, **4**, **6**).

Biological Data.—The compounds were administered as 2% suspensions in 3% tragacanth to albino Swiss–Webster mice by both intraperitoneal and oral routes.

(5) Determined as Nujol mulls by Mr. W. Washburn.

Some 2,6-Methanonaphth[1,2-*d*]azocines

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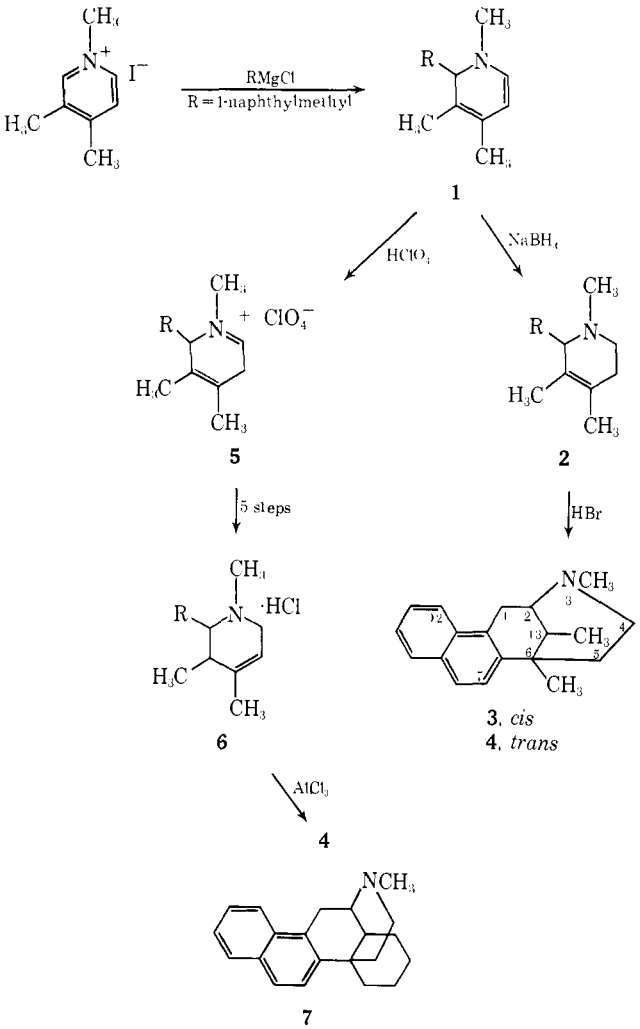
The development by May and co-workers of a convenient synthesis of the benzomorphan or, more properly, the 2,6-methano-3-benzazocine ring system[1] has made possible the synthesis of compounds exhibiting a variety of biological activities. In an attempt to improve certain parameters, some 2,6-methanonaphth[1,2-*d*]azocines were prepared by the same route.

Both the *cis* isomer **3** with 6-quasi-equatorial (with respect to the hydroaromatic ring) and 13-axial methyl groups and the *trans* isomer **4** with 6-quasi-equatorial and 13-equatorial methyl groups were obtained. These could be separated by recrystallization or chromatography on silica. Addition of the dihydropyridine **1**

(1) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); N. B. Eddy, J. G. Murphy, and E. L. May, *ibid.*, **22**, 1370 (1957). The synthetic route was originally developed by R. Grewe and A. Mondon [*Chem. Ber.*, **81**, 279 (1948)] for the morphinans.

to perchloric acid gave the perchlorate **5**. By addition and loss of hydrogen cyanide to **5** according to the procedure developed by Fry,[2] the *trans*-tetrahydropyridine **6** was obtained. Cyclization of **6** with aluminum chloride gave almost exclusively **4** (see Scheme I).

SCHEME I



The assignment of configuration of the 6,13-methyl groups was based upon nmr data. The downfield shift in going from the axial to the equatorial 13-methyl reported for the 5,9-dimethylbenzomorphans[3] is quite characteristic for all the benzomorphans. The possibility of cyclization of **2** to the 8 position of the naphthalene ring rather than to the 2 position was excluded on the basis of infrared and nmr investigations of acenaphthene, naphthalene-1,8-dicarboxylic acid, 1,8-naphthalenedimethanol, 1,2-dimethylnaphthalene, and 1-chloromethyl-2-methylnaphthalene as model compounds. The related N-methylbenzo[*a*]morphinan **7** has recently been reported.[4] This synthesis also involves cyclization into the 2 position of naphthalene.

The pure *cis*- and *trans*-N-methyl-2,6-methanonaphth-[1,2-*d*]azocines (**3**, **4**) were converted to the norbases with cyanogen bromide. These norbases were acylated with cyclopropylcarbonyl chloride, and the resulting N-acyl derivatives were reduced with lithium aluminum hydride to the cyclopropylmethyl analogs. In the *cis* series the N-cyclobutylmethyl and N-phenethyl compounds were also prepared. In the *trans* series the N-(3-methyl-2-butenyl) compound was made.

Pharmacology.—Although, in the benzazocine series, the N-cyclopropylmethyl derivatives bearing either an 8-hydroxyl, 8-methoxyl, or 8-hydrogen and the N-cyclobutylmethyl derivative bearing an 8-hydroxyl were active as meperidine antagonists at doses of less than 1 mg/kg,[5] and the N-(3-methyl-2-butenyl) derivative was active at 3.3 mg/kg,[6] the naphthazocines reported here were all inactive at doses of 40 mg/kg ip. All naphthazocines were also inactive on the D'Amour–Smith rat tail flick test at doses of 120 mg/kg sc and/or ip. Some activity was noted on the inclined screen, but this activity was lower than that seen in the benzazocine series.[7] The *cis*- and *trans*-N-cyclopropylmethylnaphthazocines both had ED_{50} values of 55 mg/kg ip, and the cyclobutylmethyl had an ED_{50} of 80 mg/kg ip on the inclined screen.

Experimental Section

1,3,4-Trimethyl-2-(1-naphthylmethyl)-1,2,5,6-tetrahydropyridine.—The Grignard reagent from 37.2 g of Mg and 274 g of 1-chloromethylnaphthalene was added to 376 g of **1** suspended in 1500 ml of ether. The mixture was poured onto ice and about 50 g of NH_4Cl. NH_4OH was added to make the mixture basic, and the ether layer was separated and concentrated to give 267 g of red oil. This was dissolved in 1 l. of ethanol and reduced at 15–20° with 28 g of $NaBH_4$ in 240 ml of H_2O. Work-up gave 181 g of orange-red oil. This was distilled to give 148 g boiling at 148–156° (0.5 mm).

1,2,3,4,5,6-Hexahydro-3,6,13-trimethyl-2,6-methanonaphth-[1,2-*d*]azocines.—The above 148 g of oil was refluxed for 24 hr with 1500 ml of 48% HBr. The mixture was concentrated *in vacuo* and partitioned between 2 l. of H_2O and 400 ml of ethyl acetate. The H_2O layer was made basic with K_2CO_3 and the liberated oil was extracted with ether. Concentration gave 135 g of dark oil. This was dissolved in 100 ml of acetone and cooled in a Dry Ice–methanol bath. After 1 hr, the product was filtered and washed with a little cold acetone to give 90.5 g, mp 55–73°. This consists of a mixture of the *cis* isomer, mp 78–81°, R_f 0.16–0.19 on silica (benzene–isopropylamine, 99:1), and *trans* isomer, mp 133–135.5°, R_f 0.53–0.56, in a ratio of 4 parts of *cis* (**3**) to 1 part of *trans* (**4**). Two recrystallizations from acetone gave 9 g of pure **4**. The mother liquors afforded additional crops of **3** and **4**. The last, weighing 13.5 g and melting at 67–75°, was recrystallized from 25 ml of acetone (seeded with **4**) and refrigerated overnight. Upon filtration of 1.0 g of **4**, 2.8 g of pure **3** separated as needles. Further crops of crystals were mixtures of **3** and **4**. Additional supplies of the pure isomers were obtained by chromatography on silica.

A suspension of 250 g of SiO_2 in 400 ml of benzene and 75 ml of isopropylamine was stirred by hand and transferred to a column. The column was washed with benzene. A crude mixture of 12.9 g of **3** plus **4** was placed on the column and eluted with benzene containing 1% isopropylamine by volume. When material appeared at the bottom of the column, 50-ml fractions were collected. Fraction 1 gave 0.9 g of **4**, fractions 2–6 gave a total of 7.4 g of mixture, and fractions 7–10 gave 4.0 g of **3** showing one spot on tlc. The latter was recrystallized from ether (cooling in Dry Ice) to give 3.5 g, mp 76–78°.

Anal. Calcd for $C_{19}H_{23}N$: C, 85.98; H, 8.73; N, 5.28. Found (*trans*): C, 86.26; H, 8.55; N_D, 5.82. Found (*cis*): C, 85.93; H, 8.60; N_D, 5.06.

(2) E. M. Fry, *J. Org. Chem.*, **28**, 1869 (1963).
(3) S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).
(4) T. Takahashi and K. Okamura, *J. Pharm. Soc. Japan*, **82**, 1667 (1962).
(5) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).
(6) B. F. Tullar, L. S. Harris, R. L. Perry, A. K. Pierson, A. E. Soria, W. F. Wetteran, and N. F. Albertson, *ibid.*, **10**, 383 (1967).
(7) *Cf.* S. Archer, L. S. Harris, N. F. Albertson, B. F. Tullar, and A. K. Pierson, Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 162.

The nmr spectra, obtained at room temperature from about 20% solutions in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard, were recorded on a Varian A-60 instrument. The *trans* isomer (**4**) showed an N-methyl at 141, a C-methyl at 83, and a split methyl at 77 cps with $J = 7$ cps. The *cis* isomer (**3**) had an N-methyl signal at 145, a C-methyl at 86, and a split methyl at 52 cps with $J = 7$ cps.

***trans*-1,3,4-Trimethyl-2-(1-naphthylmethyl)-1,2,3,6-tetrahydropyridine Hydrochloride (6).**—The Grignard reagent from 97 g of 1-chloromethylnaphthalene and 13.3 g of Mg in 500 ml of ether was added to 1,3,4-trimethylpyridinium bromide under 500 ml of ether. After 1 hr, the mixture was filtered, and the filtrate was added to 300 g of ice and 105 ml of 60% $HClO_4$ with stirring. The inorganic salts were removed by filtration and the filter cake (53 g) was washed with ether to give, from the filtrate, 65.4 g of white crystals (**5**) melting at 103–119° dec. This perchlorate (55 g) was stirred with 60 ml of H_2O and 300 ml of ether, while a solution of 35 g of NaCN in 50 ml of H_2O was added to give 1,3,4-trimethyl-2-(1-naphthylmethyl)-6-cyanopyridine as a solution in ether. The ether layer was separated and concentrated to a small volume. Then, 80 ml of H_2O was added, followed by the slow addition of 80 ml of concentrated HCl. This caused vigorous evolution of HCN; the temperature rose to 70°. When the reaction had moderated, 320 ml of $CHCl_3$ was added, and the mixture was warmed 3 hr on the steam bath under reflux. The $CHCl_3$ and some of the H_2O were removed *in vacuo* to give *trans*-2,3-dihydro-1,3,4-trimethyl-2-(1-naphthylmethyl)pyridinium chloride as an orange oil suspended in H_2O. Fifty grams of NaCN were added, and the resulting *trans*-1,2,3,6-tetrahydro-1,3,4-trimethyl-2-(1-naphthylmethyl)-6-cyanopyridine was extracted with ether. Removal of the ether left 46 g of orange-brown syrup. This, in 250 ml of ethanol, was reduced with 12 g of $NaBH_4$ in 50 ml of H_2O. Work-up in the usual way gave 27.5 g of product which readily gave a crystalline hydrochloride **6**, mp 250–252° after one recrystallization from 2-propanol.

Anal. Calcd for $C_{19}H_{23}N \cdot HCl$: C, 75.61; H, 8.02; N, 4.64. Found: C, 75.54, 75.88; H, 7.91, 7.79; N, 4.55, 4.53.

The nmr spectrum of a 20% trifluoroacetic acid solution, using an external TMS standard, showed seven aromatic hydrogens at 435–470, one vinyl hydrogen at 325, a methyl singlet at 109, and a doublet at 74 cps.

Cyclization of 5 g of **6** with 5 g of $AlCl_3$ in 25 ml of CS_2 gave a 66% yield of crude material melting at 117–123°. Tlc showed that this was almost all **4** with a few per cent of **3** and a small amount of another material.

1,2,3,4,5,6-Hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine Hydrochloride.—Compound **3** (42 g) was treated with 17 g of BrCN in $CHCl_3$ and the resulting N-cyano compound was hydrolyzed in the usual manner with 640 ml of 6% HCl to give 30.5 g of crude norbase. This was distilled to give 28.1 g (71%) of product boiling at 154° (0.6 mm). The hydrochloride, after recrystallization from ethanol, melted at 286–290°.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: C, 75.11; H, 7.71; N, 4.87. Found: C, 74.86; H, 7.52; N, 5.04.

In like manner, 20 g of **4** gave 15.1 g (80%) of norbase boiling at 162–166° (0.9 mm). This gave a hydrochloride showing only one spot on tlc and decomposing at 330–337°.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: N, 4.87; Cl, 12.32. Found: N, 5.02; Cl, 12.54.

3-Cyclopropylcarbonyl-1,2,3,4,5,6-hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine.—A solution of 7.6 g of *cis*-norbase in 50 ml of $CHCl_3$ and 4.6 ml of Et_3N was treated with 3.2 g of cyclopropanecarbonyl chloride in 25 ml of $CHCl_3$. The resulting solution was washed with H_2O, dilute HCl, and aqueous $NaHCO_3$. Concentration gave 9.8 g of light orange oil. Distillation of 7.7 g of this gave 0.3 g boiling at 60–192° (0.1 mm) and 6.0 g boiling at 192–197° (0.1 mm).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 82.63; H, 7.61; N, 4.53.

In like manner, the *trans* isomer was prepared. The product, after recrystallation from ethyl acetate–hexane, melted at 139.0–140.8° (cor).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 82.82; H, 7.97; N, 4.64.

3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine.—Reduction of 10.0 g of the *cis*-cyclopropylcarbonyl compound with 3 g of $LiAlH_4$ gave 9.6 g of clear, viscous oil which crystallized on standing. Three recrystallizations from aqueous ethanol gave 5.3 g melting at 78–81° (cor).

Anal. Calcd for $C_{22}H_{27}N$: C, 86.50; H, 8.91; N, 4.59. Found: C, 86.43; H, 8.74; N, 4.54.

In like manner the *trans* isomer was prepared. The base did not crystallize, but was converted to the hydrochloride. This was recrystallized from 2-propanol to give the pure product in 73% over-all yield from the amide. The hydrochloride melted at 248.5–251.5° (cor).

Anal. Calcd for $C_{22}H_{27}N \cdot HCl$: C, 77.28; H, 8.25; N, 4.10. Found: C, 77.09; H, 8.32; N, 4.07.

3-Cyclobutylmethyl-1,2,3,4,5,6-hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine.—To 8.5 g of *cis*-norbase in 50 ml of $CHCl_3$ and 5.1 ml of Et_3N was added 4.3 g of cyclobutylcarbonyl chloride in 25 ml of $CHCl_3$. Work-up as for the cyclopropyl analog gave 11.3 g of amide as a viscous oil. This was reduced in tetrahydrofuran (THF) with 3.5 g of $LiAlH_4$ to give 11.0 g of oil which was dissolved in 20 ml of ethanol, diluted with 15 ml of H_2O, and refrigerated to give 9.4 g of crude product. Two recrystallizations from aqueous ethanol gave 6.6 g, mp 81–84°.

Anal. Calcd for $C_{23}H_{29}N$: C, 86.46; H, 9.16; N, 4.38. Found: C, 86.63; H, 9.51; N, 4.44.

1,2,3,4,5,6-Hexahydro-*cis*-6,13-dimethyl-3-phenethyl-2,6-methanonaphth[1,2-*d*]azocine Hydrochloride.—Reaction of 7.6 g of *cis*-norbase with 4.7 g of phenylacetyl chloride in the usual manner gave a quantitative yield of crude amide as an oil. This was reduced with 2 g of $LiAlH_4$ in THF to give 9.8 g of crude product as a yellow oil. The oil was dissolved in 50 ml of acetone and 3.5 g of oxalic acid dihydrate in 20 ml of acetone was added to give 10.1 g of oxalate melting at 220–225° dec. Recrystallization from 400 ml of 75% ethanol gave 7.1 g of white crystals, mp 232–234° dec, showing one spot on tlc. These were converted to the hydrochloride, mp 270–273°.

Anal. Calcd for $C_{26}H_{29}N \cdot HCl$: C, 79.66; H, 7.72; N, 3.57. Found: C, 79.34; H, 7.52; N, 3.56.

1,2,3,4,5,6-Hexahydro-*trans*-6,13-dimethyl-3-(3-methyl-2-butenyl)-2,6-methanonaphth[1,2-*d*]azocine Hydrochloride.—A mixture of 6.3 g of *trans*-norbase, 5.5 g of $NaHCO_3$, 55 ml of dimethylformamide, and 3.9 g of dimethylallyl bromide was stirred and refluxed for 4 hr, filtered, and concentrated *in vacuo*, and the residue was partitioned between H_2O and ethyl acetate. The ethyl acetate was dried, treated with charcoal, filtered, and concentrated to give 6.8 g of oil. This was converted to the hydrochloride, 5.0 g, mp 248–245° dec. Tlc indicated one impurity which was removed by recrystallization from ethanol; mp 266.8–268.0° dec (cor).

Anal. Calcd for $C_{23}H_{29}N \cdot HCl$: C, 77.61; H, 8.50; N, 3.94. Found: C, 77.55; H, 8.50; N, 4.00.

Acknowledgment.—We are indebted to a number of our colleagues for technical assistance: to Mr. K. Fleischer and staff for microanalyses, to Dr. L. S. Harris and staff for biological testing, and to Drs. R. K. Kullnig, F. C. Nachod, and Miss K. Martini for nmr data.

Effect of Organic Compounds on Reproductive Processes. VII. Bis-N,N′-carbamoylaziridines

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Previous results from this laboratory have shown that certain N,N′-bis(aziridineacetyl)-α,ω-diamines were effective chemosterilants for houseflies.[1,2] Borkovec and Woods[3] reported that certain N-carbamoylaziri-

(1) W. A. Skinner, H. C. Tang, T. E. Shellenberger, and G. W. Newell, *J. Med. Chem.*, **8**, 617 (1965).

(2) W. A. Skinner, M. Cory, T. E. Shellenberger, and J. I. DeGraw, *ibid.*, **9**, 520 (1966).

(3) A. B. Borkovec and C. W. Woods, *ibid.*, **8**, 545 (1965).